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External validation of European Association of Urology NMIBC risk scores to predict progression after transurethral resection of bladder tumor in Korean patients with non-muscle-invasive bladder cancer

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Purpose: This study aimed to validate the newly proposed risk model in Korean patients diagnosed with non-muscle-invasive bladder cancer (NMIBC).

Materials and Methods: A retrospective review was performed with 1,238 patients who underwent transurethral resection of bladder tumor from 2009 to 2020. We included 973 patients and categorized them into four risk groups according to the European Association of Urology (EAU) NMIBC risk stratification standards, which incorporate the World Health Organization 2004/2016 grading classification. Kaplan–Meyer survival analysis and multivariable analysis of time to progression were performed to calculate the probability of progression for all risk groups.

Results: A total of 973 patients were followed for 54.85 months. Patients were classified according to the risk factors proposed by the new NMIBC risk table and stratified into low, intermediate, high, and very high-risk groups based on the table. Cancer progression into muscle-invasive bladder cancer (MIBC) in each risk group was observed in 7 (4.4%), 24 (15.2%), 76 (48.1%), and 51 (32.3%) individuals, respectively. The progression rate was distinguishable between risk groups in the Kaplan–Meier progression-free survival analysis, and higher risk was associated with a higher rate of progression. The new NMIBC risk variables were demonstrated to have prognostic value in the multivariate analysis. The very high-risk group was associated with progression to muscle-invasive disease.

Conclusions: This study demonstrates that the new EAU NMIBC risk group categorization is feasible in predicting the progression of NMIBC into MIBC in the Korean population and thus should be applied to clinical practice in Korea.

Keywords: Disease progression; Prognosis; Risk factors; Urinary bladder neoplasm

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INTRODUCTION

Bladder cancer is the 10th most diagnosed cancer worldwide [1]. It is about four times as common in men as in women and primarily affects individuals over 55 years of age [2]. Staging of transitional cell carcinoma of the bladder uses the TNM system based on the degree of bladder muscle involvement [3,4]. Non-muscle-invasive bladder cancer (NMIBC) refers to stage Ta, T1, and carcinoma *in situ* (CIS) tumors and accounts for more than 70% of all bladder cancers [5,6]. The remaining patients have muscle-invasive bladder cancer (MIBC) or metastatic bladder cancer with extravesical invasion.

NMIBC is a disease with various risks for recurrence and progression. The survival rate for most patients with NMIBC is favorable, with a cancer-specific survival rate of 70% to 85% in patients with high-grade disease and a much higher rate for patients with low-grade disease [7]. Adjuvant therapy with bacillus Calmette-Guérin (BCG) or chemotherapeutic agents is often necessary after transurethral resection of bladder tumor (TUR-BT) to reduce the rate of recurrence [8].

Once the diagnosis is made, identifying the likelihood of progression of NMIBC to MIBC by risk stratification is critical to making treatment decisions based on short-term and long-term prognosis. Patients at risk for progression have life-long monitoring and treatment requirements, resulting in a low quality of life and high medical costs. Because the rate of progression depends on several clinical and pathological factors, estimating risk on the basis of these factors is essential in determining an optimal treatment strategy.

The European Organization for Research and Treatment of Cancer (EORTC) risk table was devised to accurately predict disease prognosis. However, the patient data on which this prediction model was based included a low number of patients treated with BCG [9]. On the other hand, the Club Urologico Espanol de Tratamiento Oncologico (CUETO) prediction model was based on patients who were treated with intravesical BCG instillations after TUR-BT. Additional studies from CUETO [10], EORTC [11], and others [12] have widened our understanding of the prognostic factors of NMIBC.

Since its publication in 2021 by Sylvester et al. [13], the European Association of Urology (EAU) NMIBC prognostic factor risk groups were updated according to the World Health Organization (WHO) 1973 [14] and the WHO 2004/2016 grading classification [15], both of which are recommended in clinical practice [8,16]. In the present study, we aimed to validate the newly proposed scoring system and to evaluate its applicability to the patients of our institution.

MATERIALS AND METHODS

1. Data collection

After obtaining written informed consent from the patients, we performed a retrospective review of patients admitted to Pusan National University Yangsan Hospital who underwent TUR-BT. The protocol was approved by the ethics committee at Pusan National University Yangsan Hospital (approval no. 06-2021-007), and the study was done in accordance with the principles of the Declarations of Helsinki.

From 2009 to 2020, the initial data set of 1,238 patients was collected. The following inclusion criteria were applied: a) the patients were diagnosed with urothelial cancer after TUR-BT; b) the patients underwent TUR-BT at least once; and c) the patients were followed for over 6 months. Exclusion criteria included patients diagnosed with MIBC or non-urothelial cancer types such as adenocarcinoma, squamous cell cancer, sarcomatoid cancer, and cancer with micropapillary features, and patients who were lost to follow-up.

Among the 1,238 patients, 163 were diagnosed with MIBC, 76 were identified with nonurothelial carcinoma or inflammatory lesions, and 26 were lost to follow-up. Thus, a total of 973 patients were retrospectively analyzed.

All surgical specimens were processed according to standard pathological procedures by the institute's department of pathology, and some specimens were reclassified. Tumors were graded according to the 2004 WHO/International Society of Urological Pathology classification of urothelial neoplasia. Tumors were classified as a papillary urothelial neoplasm of low malignant potential (PUN-LMP), low-grade urothelial carcinoma, and high-grade urothelial carcinoma [15]. After histopathological evaluation, tumors were staged according to the 2002 American Joint Committee on Cancer staging system [17]. The retrospective analysis of the patient data included age, sex, stage, grade, multifocality, concomitant CIS, tumor size, recurrence, and progression.

2. Patient follow-up

Patients were evaluated by urinary cytology and cystoscopy every 3 months for the first 2 years and every 6 months for 5 years thereafter. Repeat TUR-BT was not performed routinely. Extravesical surveillance strategies to detect metastasis or upper tract urinary cancer included annual imaging by chest and abdominal computed tomography.

The primary end point was time to progression, which

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Table 1. Clinical composition of the new European Association of Urology non-muscle-invasive bladder cancer prognostic factor risk groups based on the WHO 2004/2016 or WHO 1973 grading classification systems

Risk group	Clinical composition
Low risk	A primary, single, Ta LG/G1 tumor ≤3 cm in diameter without CIS in a patient ≤70 y
	A primary LG/G1 tumor with at most one of the following additional clinical risk factors:
	Age >70 y
	Multiple tumors
	Tumor diameter ≥3 cm
	Stage T1
Intermediate risk	Patients without CIS who are not included in either the low-, high-, or very high-risk groups
High risk	All T1 HG/G3 without CIS, except those included in the very high-risk group
	Stage, grade with additional clinical factors:
	Ta LG/G2 or T1 G1, no CIS with all 3 risk factors
	Ta HG/G3 or T1 LG, no CIS with at least 2 risk factors
	T1 G2 no CIS with at least 1 risk factor
Very high risk	Stage, grade with additional clinical risk factors:
	Ta HG/G3 and CIS with all 3 risk factors
	T1 G2 and CIS with at least 2 risk factors
	T1 HG/G3 and CIS with all 3 risk factors
	T1 HG/G3 no CIS with all 3 risk factors

WHO, World Health Organization; CIS, carcinoma *in situ*; LG, low grade; HG, high grade.
Patients with recurrent disease should be included in the intermediate-, high-, or very high-risk group according to their other prognostic factors.

was calculated from the time of initial diagnostic TUR-BT to the first progression. Progression was defined as development into muscle-invasive disease, metastasis into regional lymph nodes, or distant metastasis, either at follow-up TUR-BT or at the time of cystectomy [13].

Patients without any event during follow-up were censored at the time of their last visit. Patients with loss to follow-up because of death unrelated to bladder cancer were censored at their time of death. The cause of death was determined by the treating physician, medical record review, or death certificates alone.

3. Statistical analysis

Statistical analysis was performed based on the prognostic variables of the new NMIBC risk table. Patients were analyzed according to age (≤70 vs. >70 years), tumor grade, number of tumors (single vs multiple), tumor size (<3 cm vs. ≥3 cm), stage, concomitant CIS, and WHO grade 2004/2016 [13]. Patients were classified into four risk groups by applying the criteria used by Sylvester et al. [13] in 2021. The clinical composition of the new EAU NMIBC prognostic factor risk groups based on the WHO 2004/2016 or WHO 1973 grading classification systems is shown in Table 1. The WHO 2004/2016 PUN-LMP and low-grade tumors were combined into a single category because the PUN-LMP category accounts for a low percentage of tumors, and the prognosis of PUN-LMP and Ta–low-grade disease is similar [18].

The Kaplan–Meier method was used to analyze time to progression and to estimate the risk for progression. Multivariate Cox models were used to compare the predictive performance of the prognostic factors. For all statistical analyses, p-values of 0.05 or less were considered significant. SPSS 15.0 was used for these analyses.

RESULTS

A total of 973 patients with an initial diagnosis of NMIBC were analyzed. Table 2 shows the clinical and pathological characteristics of the patients. Our cohort consisted of 157 females (16.1%) and 816 males (83.9%). The patients' median age was 71 years (range, 18–95 years).

A total of 328 patients (33.7%) had a single tumor and 645 patients (66.3%) had multiple tumors. Concerning tumor size, 770 patients (79.1%) had tumors sized <3 cm and 203 (20.9%) had tumors sized ≥3 cm. The tumor stage was Ta in 530 (54.5%) and T1 in 443 (45.5%) patients. Of the total, 935 (96.1%) had no concomitant CIS. Recurrence of disease was seen in 400 patients (41.1%). Progression of disease was seen in 158 patients (16.2%), with a median time to progression of 20.6 months (range, 1–120 months).

Using the prognostic variables of the patients from our institution, we stratified the patients into risk groups according to the new EAU NMIBC risk table [13]. With use of this risk table, our study cohort comprised 155 low-risk (15.9%), 259 intermediate-risk (26.6%), 438 high-risk (45.1%), and 121 very high-risk (12.4%) patients (Table 3). Repeat TUR-BT was not performed routinely; a total of 96 (9.9%) patients underwent repeat TUR-BT (Table 2). In each risk category, cancer

Table 2. Patient and tumor characteristics

Parameter	Result
Age (y)	
Range	18–95
First quartile	62
Median	71
Third quartile	78
Sex	
Female	157 (16.1)
Male	816 (83.9)
Number of tumors	
Single	328 (33.7)
Multiple	645 (66.3)
Maximum diameter	
<3	770 (79.1)
≥3	203 (20.9)
Tumor stage	
Ta	530 (54.5)
T1	443 (45.5)
Concomitant CIS	
No	935 (96.1)
Yes	38 (3.9)
Recurrence	
No	573 (58.9)
Yes	400 (41.1)
Progression	
No	815 (83.8)
Yes	158 (16.2)
WHO grade 2004/2016	
PUN-LMP	25 (2.6)
Low grade	383 (39.4)
High grade	565 (58.1)
Repeat TUR-BT	
No	876 (90.0)
Yes	96 (9.9)
Unknown	1 (0.1)

Values are presented as number (%).
CIS, carcinoma *in situ*; WHO, World Health Organization; PUN-LMP, papillary urothelial neoplasm of low malignant potential; TUR-BT, transurethral resection of bladder tumor.

Table 3. New European Association of Urology non-muscle-invasive bladder cancer risk groups with WHO 2004/2016 classification

Risk group	No. of patients	Progression
Low	155 (15.9)	7 (4.4)
Intermediate	259 (26.6)	24 (15.2)
High	438 (45.1)	76 (48.1)
Very high	121 (12.4)	51 (32.3)

Values are presented as number (%).

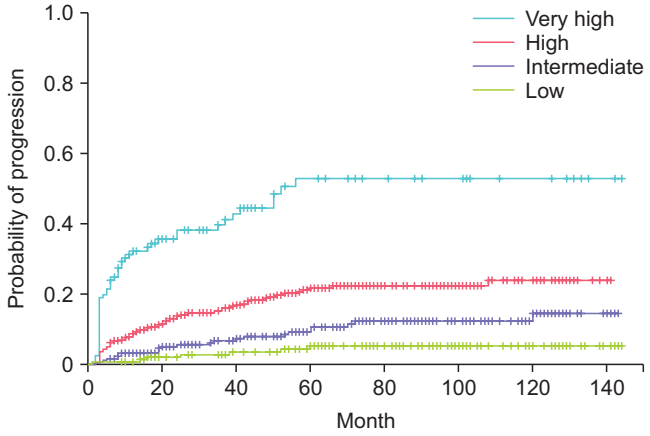

Fig. 1. Kaplan–Meier progression-free survival analysis shows progression curves of low-, intermediate-, high-, and very high-risk patients. A significant difference is seen between the high- and very high-risk curves. Higher risk was associated with a higher rate of progression.

progression into MIBC was observed in 7 (4.4%), 24 (15.2%), 76 (48.1%), 51 (32.3%) individuals, respectively. A higher risk for progression was associated with a higher rate of progression at 1, 5, and 10 years. In the very high-risk group, the probability was 31.40%, 41.14%, and 42.14% at 1, 5, and 10 years, respectively.

Kaplan–Meier time-to-progression curves are provided in Fig. 1. The probability of progression was distinguishable for each risk group. The median time to progression was 25, 20, 13, and 5 months for the low-, intermediate-, high-, and very high-risk groups, respectively. Higher risk was associated with a higher rate of progression, and the difference was particularly noticeable between the high- and very high-risk groups.

Multivariable analysis showed that age, the number of tumors, tumor size, stage, concomitant CIS, and tumor grade to be associated with the risk for progression. The hazard ratio was statistically significant for patient age, the number of tumors, tumor size, tumor stage, concomitant CIS, and WHO 2004/2016 grade (Table 4).

DISCUSSION

Stratification of patients into risk groups is essential in planning adjuvant treatment. The EAU NMIBC risk stratification as updated in 2021 is presently the best existing model for predicting progression and provides a straightforward scoring system.

The EORTC risk table was proposed in 2006 to estimate recurrence and progression in patients with NMIBC and included six clinicopathological factors: number of tumors, tumor size, prior recurrence rate, cancer stage, concomitant CIS, and WHO grade 1973 [9]. However, the rate of BCG treatment in the studied patients was low, and those who were treated with BCG had undergone an induction course

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Table 4. Results of multivariable analysis of time to progression: WHO 2004/2016 classification

Parameter	Multivariable WHO 2004/2016	
	HR (95% CI)	p-value
Age (y)		
≤70	1	
>70	1.65 (1.14–2.38)	0.008
Number of tumors		
Single	1	
Multiple	1.42 (1.12–2.19)	0.021
Maximum diameter (cm)		
<3	1	
≥3	1.76 (1.32–2.42)	0.027
Stage		
Ta	1	
T1	2.58 (1.72–3.87)	<0.001
Concomitant CIS		
No	1	
Yes	2.09 (1.55–3.20)	<0.001
WHO 2004/2016 grade		
PUN-LMP–low grade	1	
High grade	1.55 (1.03–2.33)	<0.001

WHO, World Health Organization; HR, hazard ratio; CI, confidence interval; CIS, carcinoma *in situ*; PUN-LMP, papillary urothelial neoplasm of low malignant potential.

only and had not received maintenance therapy, leading to an overestimation of recurrence and progression [19]. Also, the risk table included only three risk groups, making the system less accurate. The EORTC risk scoring system was then updated, using data from more recent trials and including patients treated with BCG maintenance therapy. A "highest-risk" subgroup was added, which helped to identify patients for whom radical cystectomy was indicated. However, the study cohort lacked patients with CIS and requires further evaluation [11].

In 2006, CUETO created its scale for assessing the oncological outcomes of BCG-treated patients. This model enabled the prediction of progression and recurrence after 12 BCG instillations following TUR-BT and included seven prognostic variables: tumor stage, tumor grade, number of tumors, concurrent CIS, presence of recurrent tumors, age, and sex [20]. Compared with the EORTC model, the CUETO model predicts lower recurrence risk for all risk groups, whereas the risk for progression is lower only for high-risk patients [21,22]. No immediate postoperative instillation or repeat TURB-BT was performed in the patients used to develop the model. Clinical use of the model is limited because of the small size of the study population (1,062 patients) and the short maintenance period of BCG therapy [20]. This system's practicality is thus uncertain, considering the heterogeneous treatment methods in real practice.

Thus, the EORTC and CUETO models have shortcomings. Even though both models can accurately predict which patients will not progress to MIBC, neither can accurately predict the progression of cancer [23]. In addition, both models overestimate the risk for progression and recurrence in high-risk patients [21,22].

The earlier EAU NMIBC model was inspired by the EORTC model and recommended stratification of patients into low-, intermediate-, and high-risk groups and utilized the WHO 1973 grading system [8]. The risk groups had prognostic value for predicting recurrence, especially progression [9]. Because both the WHO 1973 and WHO 2004/2016 criteria classifications have been proven to have prognostic value [24], the current EAU guidelines recommend the use of both grading systems [8]. More recently, the new NMIBC risk model was updated to take into account both grading systems and added a very high-risk group. The new scoring model predicts the rate of disease progression and calculates progression based on the WHO 1973 classification, as it has better prognostic value. In this model, PUN-LMP tumors were categorized as low-grade tumors.

In a 2021 study by Sylvester et al. [13], the prognostic accuracy of the risk factors was assessed to validate the new scoring model. The risk for progression at 1, 5, and 10 years was provided [8]. With data collected from 1990 to 2018, 3,401 patients with an initial diagnosis of NMIBC were analyzed. Individuals treated with BCG after TUR-BT were excluded from this study, as this reduces the risk for progression of NMIBC [13]. This may result in an overestimation of the risk for progression in BCG-treated patients [25].

The patient characteristics in our study were comparable to those in the study by Sylvester et al. [13], except for two factors (Table 2). Tumor composition differed, as shown by 36% more multiple tumors and 27% more high-grade tumors (WHO 2004/2016 criterion). The WHO 1973 criterion was not used in risk stratification compared with the Sylvester et al.'s series [9,13,23], and these factors may have resulted in an overall higher risk for progression. However, the difference in the number and size of tumors may not be a confounding factor because the 10-year rate of progression in all risk groups was alike in both studies.

In the present study, the patients were stratified into four risk groups, using only the 2004/2016 grading system (Table 3). Compared with the Sylvester et al.'s series [9,13,23], in which most patients were stratified into the low-risk group, the high-risk group accounted for the most significant portion of our study, which may have increased the total rate of progression. This may have resulted from the fact that our institution is a tertiary medical center where most

disease cases are relatively severe compared with those seen at smaller institutions.

A total of 158 patients (16.2%) experienced disease progression during follow-up. Both studies had the lowest number of patients in the very high-risk group. Despite the difference in the composition of the risk groups, the 5-year progression rate in the low-risk group was almost 99% in both studies. The 5-year progression rate in the very high-risk group was similar in our study and the Sylvester et al.'s series [9,13,23], with rates of 41.14% and 40%, respectively. Compared with the Sylvester et al.'s series [9,13,23], in which progression was seen in 16%, 40%, and 53% of patients in the very high-risk group at 1, 5, and 10 years, morbidity was higher in our study. In both studies, recurrence did not occur with a 99% probability in the low-risk group at 1 year.

The Kaplan–Meier analysis is presented in Fig. 1. Time to progression in the low-, intermediate-, high-, and very high-risk groups was distinct, and differences between curves were particularly noticeable between the high- and very high-risk groups. Therefore, the Kaplan–Meier analysis validates the risk model presented by Sylvester et al. [13] for the risk stratification of patients. Compared with our study, prognosis of the low- and intermediate-risk groups became almost equivalent after 10 years in the Sylvester et al.'s series [9,13,23]. In our data, however, patients were followed up for 12 years, which may be why the two risk groups did not converge after 10 years of surveillance.

The results of the multivariate analysis demonstrated the prognostic value of the variables presented in the Sylvester et al.'s series (Table 4) [9,13,23], including age, the number of tumors, tumor size, stage, concomitant CIS, and tumor grade. The hazard ratio for these factors was higher with patient characteristics of ≥70 years, multiple tumors, tumor size ≥3 cm, T1 stage, and WHO high-grade tumors with concomitant CIS. All variables were statistically significant and associated with the risk for progression.

The present study had several limitations. This was a single-institution study conducted in a retrospective fashion. Various surgeons performed the surgeries and follow-up studies, which may have resulted in heterogenous data. Our study findings could have been biased by the heterogeneous study population, as the study included patients treated with different BCG and intravesical chemotherapy treatment schedules. Because of various problems such as the BCG shortage and discontinuation of therapy prior to completion, we could not adhere to standardized BCG treatment schedules. Therefore, despite BCG treatment being widely used in the intermediate-risk group and above, we did not analyze the risk for disease progression according to BCG treatment as a variable. This would have underestimated progression risk in the intermediate-risk group and above. Likewise, intravesical chemotherapy was not analyzed as a variable for disease progression because various chemotherapy regimens were applied to patients with irregular treatment schedules. The follow-up period was shorter than in the study by Sylvester et al. [13], rendering the progression rate after 10 years relatively inaccurate. Another limitation was the use of a single grading system, the WHO grade 2004/2016 criterion of PUN-LMP, low-grade, and high-grade. Not enough patient data were classified into grades G1, G2, and G3 according to the WHO 1973 grade owing to a lack of histologic data. Finally, our institution is a tertiary medical center where most disease cases are relatively severe compared with the cases analyzed in the study by Sylvester et al. [13]. Therefore, there were more patients with higher risk than in the Sylvester et al.'s series [9,13,23]. However, the new NMIBC calculator will be helpful because progression was significantly higher in the very high-risk patients.

CONCLUSIONS

NMIBC is a challenging disease with a high rate of progression. This complicates treatment decisions after TUR-BT. This validation study of the new EAU NMIBC risk table demonstrates the accuracy of the prognostic factors proposed by Sylvester et al. [13]. In our study, the new NMIBC risk tables correlated with risk for progression in our study cohort. Thus, we conclude that the scoring system is an effective tool that should be applied to clinical practice.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Jong Kil Nam. Data acquisition: Jong Kil Nam. Statistical analysis: Jong Kil Nam. Data analysis and interpretation: Jong Kil Nam. Drafting of the manuscript: Jae Yeon Kim. Critical revision of the manuscript: Jong Kil Nam, Won Hoon Song, Seung Soo Lee, and Sung Woo Park. Obtaining funding: none. Administrative, technical, or material support: Jong Kil Nam. Supervision: Jong Kil Nam. Approval of the final manuscript: all authors.

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