

## Performance of the EORTC and CUETO Models to Predict Recurrence and Progression in High-risk Non-muscle-invasive Bladder Cancer Patients

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**Purpose:** To evaluate the performance of the European Organization for Research and Treatment of Cancer (EORTC) and the Spanish Urological Club for Oncological Treatment (CUETO) risk scoring models in non-muscle-invasive bladder cancer (NMIBC) patients defined as high risk according to European Association of Urology guidelines and managed based on current recommendations.

**Material and Methods:** Data from 187 high-risk NMIBC patients treated at a tertiary center between July 2010 and November 2021 were analyzed retrospectively. One- and five-year recurrence- and progression-free survival were assessed for each patient using the EORTC and CUETO risk scores. The patients were divided into four risk groups according to their risk scores as low, medium-low, medium-high and high risk, as indicated in the models. Discriminative ability was evaluated with the Harrell's concordance index (c-index).

**Results:** Both risk scoring models overestimated the risk of recurrence and progression at one and five years. Only the prediction of recurrence at five years in the high risk group according to the CUETO model was compatible with our cohort. CUETO (c-indices for recurrence and progression were 0.802 and 0.834, respectively) exhibited better discrimination than EORTC (0.722 for recurrence and 0.752 for progression) in the prediction of disease recurrence and progression.

**Conclusion:** The CUETO model was superior to the EORTC model in predicting recurrence and progression and stratifying patients with different prognoses in our high-risk NMIBC patient population treated according to current guideline recommendations. However, both models overestimated the probability of disease recurrence and progression. Only the probability of recurrence at five years in the high-risk group of the CUETO model was compatible with our cohort.

**Keywords:** bladder cancer; cueto; eortc; progression; recurrence

### INTRODUCTION

Bladder cancer is the most common malignant disease of the urinary system, and about 75% of patients at the time of diagnosis have non muscle invasive bladder cancer (NMIBC).<sup>(1,2)</sup> The prognosis of NMIBC cases is highly variable. In the 5-year follow-up after diagnosis, 50-70% recurrence and 10-20% progression to muscle-invasive disease have been reported.<sup>(3,4)</sup> Moreover, patients with progression to muscle-invasive disease have a worse prognosis compared to patients with primary muscle-invasive bladder cancer.<sup>(5)</sup> This highlights the need to identify patients at high risk of progression to consider early cystectomy or other intravesical approaches. Therefore, an accurate prognostic estimation is important to determine the optimal patient-specific follow-up and adjuvant treatment scheme. For this purpose, the European Organization for Research and Treatment of Cancer (EORTC) and the Spanish Urological Club for Oncological Treatment (CUETO) models have been developed to estimate one- and five-year recurrence and progression rates.<sup>(3,4)</sup> The EORTC model was established in 2006, based on the analysis of data from seven studies and a total of 2596 NMIBC cases.<sup>(4)</sup> The major drawback of the

EORTC model is that while the study cohort received mostly chemotherapy as adjuvant intravesical therapy, only 6.6% received Bacillus Calmette-Guerin (BCG) induction therapy without maintenance. To overcome this limitation, CUETO proposed a new model in 2009 by analyzing data from 1062 cases treated with adjuvant intravesical BCG.<sup>(3)</sup> In the BCG protocol employed in the CUETO study, six additional maintenance instillations were administered at 2-week intervals after a 6-week induction cycle. However, this protocol was much shorter than the long-term (1-3 years) BCG maintenance protocol recommended by current guidelines.<sup>(6)</sup> In addition, repeat transurethral resection (Re-TUR), which is recommended for high-risk disease (T1 and/or high grade), was not performed in either model. Therefore, the applicability of these models specifically to high-risk NMIBC patients treated according to current guideline recommendations needs to be evaluated. We hypothesize that current EORTC and CUETO risk scoring models will overestimate the risk of recurrence and progression in high-risk NMIBC patients followed and treated according to current guideline recommendations. Therefore, in the present study, we aimed to evaluate the performance of the EORTC and CUETO models in high-risk NMIBC cases.

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**Table 1.** Demographic and clinicopathological characteristics of the study cohort

	Current Study (n, %) N = 187	EORTC (%) N = 2596	CUETO (%) N = 1296
<b>Age (years)</b>			
≤ 60	66 (35.3%)	33.1	31.2
61-70	66 (35.3%)	34.3	37.6
71-80	47 (25.1%)	26.6	28.3
> 80	8 (4.3%)	4.5	2.9
<b>Sex</b>			
Male	176 (94.1%)	78.7	90
Female	11 (5.9%)	19.8	10
<b>Recurrence rate<sup>a</sup></b>			
Primary	126 (67.4%)	54.1	66.5
≤ 1 recurrence/year	44 (23.5%)	19.5	33.5
> 1 recurrence/year	17 (9.1%)	24.8	
<b>Pathologic stage</b>			
Ta	60 (32.1%)	55.9	19.4
T1	127 (67.9%)	42.7	77.2
<b>Grade<sup>b</sup></b>			
1	22 (11.8%)	43.2	15.2
2	0 (0%)	43.9	57.9
3	165 (88.2%)	10.4	23.5
<b>Tumor number</b>			
1	113 (60.4%)	56.4	49.2
2-3	54 (28.9%)	32.2	26.9
4-7	16 (8.6%)		15.0
≥ 8	4 (2.1%)	9.8	8.9
<b>Tumor size (cm)</b>			
< 3	59 (31.5%)	80.4	54.2
≥ 3	128 (68.5%)	17.9	45.8
<b>Concomitant CIS</b>			
No	165 (88.2%)	94.0	89.7
Yes	22 (11.8%)	4.4	10.3

a. When we translated tumor grade from the 2004 WHO system used within our study population to the 1973 WHO tumor grading system used in EORTC and CUETO models, no patients were mapped to G2 because it corresponds to both high and low grade in the 2004 system.

b. Prior bladder cancer history is reported by CUETO as either Primary or Recurrent—a Recurrent patient could be either (≤ 1 rec/y) or (>1 rec/y) in EORTC.

## MATERIALS and METHODS

### Study design and population

The data of high risk NMIBC patients in accordance with the European Association of Urology (EAU) guidelines, who were followed up and treated at a tertiary center between July 2010 to November 2021, were analyzed retrospectively.<sup>(6)</sup> Patients with no regular follow-up, incomplete data, non-urothelial cell carcinoma or variant pathology, primary CIS, a follow-up period of less than one year, muscle-invasive disease after re-TUR, and inadequate BCG treatment (at least five instillations in the induction cycle and at least two instillations in the maintenance cycle) were excluded from the study. Thus, 187 high-risk NMIBC patients who met the study criteria were included.

### Procedures and follow-up

Visible tumor suspicious lesions of all patients were completely resected via transurethral route. In the absence of contraindications such as bleeding, extensive resection or suspected perforation, a single intravesical instillation of Mitomycin-C (MMC) was applied within the first two hours after TUR. Tumor stage and grade of specimens were diagnosed by experienced pathologists at our institution in accordance with the 2002 TNM classification and the 2004 World Health Organization (WHO) system, respectively. Patients with histopathologically diagnosed T1 and/or high grade NMIBC or patients without muscle tissue in the sample underwent re-TUR within 2-6 weeks.

In the follow-up, urine cytology and cystoscopy were performed every three months for the first two years after the TUR. If no recurrence was detected, the same procedures were repeated every six months for the next

three years, and then once a year. In the presence of a suspicious lesion, it was resected. Only in case of cytology positivity, mapping biopsy of the prostatic urethra and bladder urothelium was performed. Also, the upper urinary system was evaluated annually by computed tomography urography.

All patients were scheduled for one to three years of full-dose intravesical BCG therapy recommended by EAU guidelines in high-risk NMIBC. The BCG protocol consisted of a six-week induction cycle followed by three-week maintenance cycles of 3, 6, 12, 18, 24, 30 and 36 months. However, some patients did not receive all scheduled instillations due to adverse effects, patient preference, or BCG shortage.

Detection of NMIBC at any stage or grade during follow-up was considered as recurrence, and detection of muscle invasive disease was considered as progression. The time from the date of first diagnosis of NMIBC to first recurrence or progression was calculated. Follow-up was calculated as the time from the date of first diagnosis to the date of the last available follow-up cystoscopy or TUR.

The clinicopathological data of the patients (age, sex, tumor size, number of tumor, tumor grade and stage, prior recurrence rate, and presence of concomitant CIS) were entered into the EORTC and CUETO models. We translated the low- and high-grade tumors in our cohort graded according to the 2004 WHO system into the 1973 WHO system used in the EORTC and CUETO models as grade 1 and grade 3, respectively. Therefore, no patients were mapped to grade 2, as grade 2 in the WHO 1973 system corresponds to both low- and high-grade in the WHO 2004 system. Estimated one- and five-year recurrence and progression rates were calcu-

**Table 2.** One- and five-year recurrence and progression probabilities according to the EORTC and CUETO scoring systems

	N:187	Probabilities at 1 year (%)		Probabilities at 5 years (%)	
		Current study	Reference	Current study	Reference
<b>EORTC Recurrence</b>					
0	0 (0%)	-	15 (10-19)	-	31 (24-37)
1-4	37 (19.8%)	-	24 (21-26)	13 (2-24)	46 (42-49)
5-9	123 (65.8%)	4 (3-5)	38 (35-41)	23 (17-29)	62 (58-65)
10-17	27 (14.4%)	16 (9-23)	61 (55-67)	45 (35-55)	78 (73-84)
<b>EORTC Progression</b>					
0	0 (0%)	-	0.2 (0-0.7)	-	0.8 (0-1.7)
2-6	12 (6.4%)	-	1 (0.4-1.6)	-	6 (5-8)
7-13	109 (58.3%)	-	5 (4-7)	2 (1-3)	17 (14-20)
14-23	66 (35.3%)	3 (1-5)	17 (10-24)	12 (6-18)	45 (35-55)
<b>CUETO Recurrence</b>					
0-4	74 (39.6%)	-	8 (6-11)	-	21 (17-25)
5-6	41 (21.9%)	6 (2-10)	12 (8-16)	6 (2-10)	36 (29-42)
7-9	58 (31.0%)	8 (5-11)	25 (20-31)	38 (30-46)	48 (41-55)
10-16	14 (7.5%)	23 (12-34)	42 (28-56)	70 (55-85)	68 (54-82)
<b>CUETO Progression</b>					
0-4	10 (5.3%)	-	1.2 (0.2-2.2)	-	3.8 (1.9-5.6)
5-6	31 (16.6%)	-	3 (0.8-5.2)	-	12 (7.6-16)
7-9	82 (43.9%)	-	5.6 (2.7-8.4)	-	21 (16-27)
10-14	64 (34.2%)	3 (1-5)	14 (6.6-21)	14 (7-21)	34 (23-44)

lated for each patient. In addition, the recurrence and progression risk scores of the patients were calculated, and the patients were stratified into four risk groups according to their risk scores as low, medium-low, medium-high and high risk, as indicated in the EORTC and CUETO models.

This study was conducted in accordance with the Declaration of Helsinki and institutional ethics committee approval was obtained (No. 2022-178).

**Statistical analysis**

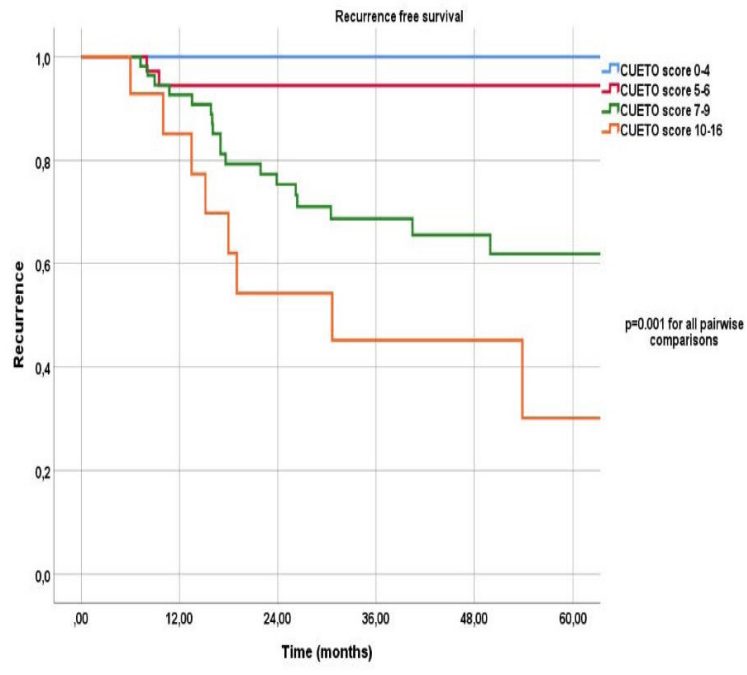
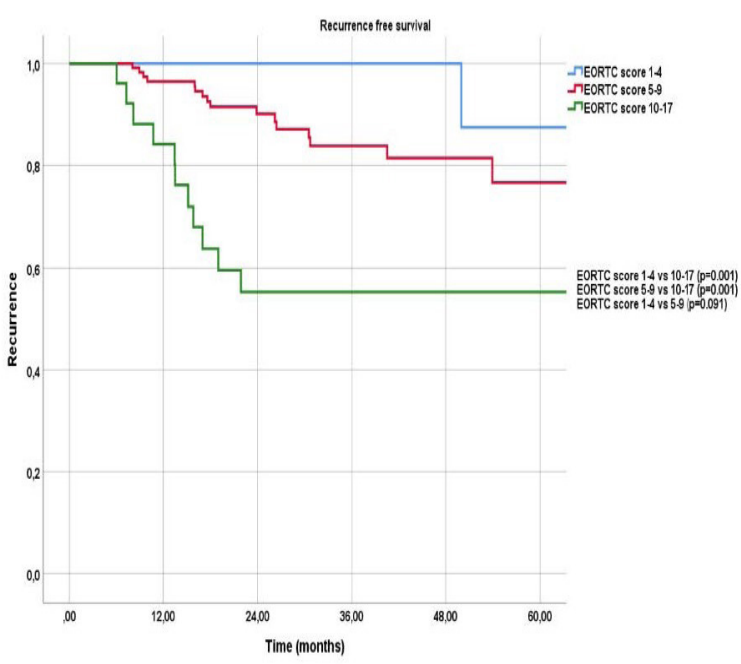
Statistical analysis were performed using the Statistical Package for the Social Sciences version 25 (SPSS IBM Corp., Armonk, NY, USA) program. One- and five-year probability of recurrence and progression were assessed using Kaplan-Meier analysis. The starting date for survival analysis was the date of the first TUR. The

end time of PFS was the date of detection of progression by performing TUR or the date of last available cystoscopy. The end time of RFS was the date of recurrence detection or last available cystoscopy.

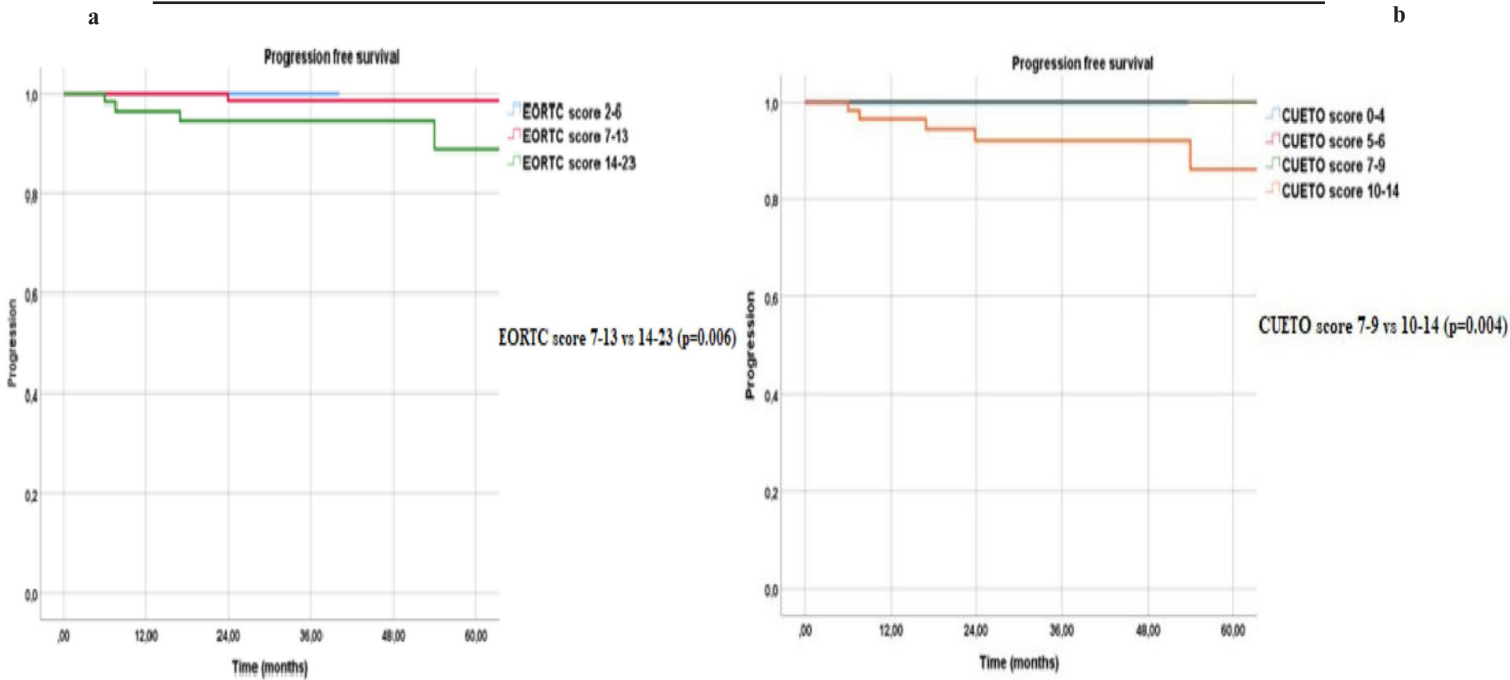
The Kaplan-Meier method was used to estimate the survival curves and the log-rank test was calculated to compare groups according to the risk groups. Cox proportional hazard regression models were used to estimate hazard ratios (HR) according to the risk groups. There were 48 patients censored in our study, accounting for 25.6% of all 187 patients with survival data. Reasons for censoring include patients being lost to follow-up or death from a cause other than bladder cancer. Compliance of recurrence and progression data with scoring systems was assessed with Harrell's concordance index (c-index).

a

b



**Figure 1a:** Recurrence free survival analysis according to EORTC classification. **b:** Recurrence free survival analysis according to CUETO classification.



**Figure 2a:** Progression free survival analysis according to EORTC classification. **b:** Progression free survival analysis according to CUETO classification.

Study sample size analysis was calculated using the G\*Power program (effect size 0.5, alpha error 0.05, power 0.80).<sup>(7)</sup> In the power analysis performed by evaluating the data in the reference literature on the subject, it was calculated that at least 148 patients should be included in the study.<sup>(8)</sup>

## RESULTS

The mean age and median follow-up of 187 high risk NMIBC patients were  $64.1 \pm 10.3$  years and 29.7 (IQR 18.3 - 48.4) months, respectively. Clinicopathological features of the study cohort are presented in **Table 1**. Thirty-three (17.6%) patients received a single dose of intravesical MMC after TUR. None of the patients received maintenance intravesical MMC therapy. All patients underwent re-TUR, and all patients received at least five BCG instillations in the induction cycle and at least two BCG instillations in the maintenance cycle. 37.9% ( $n = 71$ ) of the patients received BCG maintenance immunotherapy for at least one year or longer. Six (3.2%) patients received all BCG instillations of three years full maintenance therapy. During the available follow-up period, 17.1% ( $n = 32$ ) of the patients had recurrence and 4.8% ( $n = 9$ ) had progression. In one (0.5%) patient, clinical T stage worsened from Ta to T1. According to the EORTC recurrence scoring system, 37 (19.8%), 123 (65.8%) and 27 (14.4%) patients were stratified as medium-low, medium-high and high-risk groups, respectively. Corresponding data in the EORTC progression scoring system were 12 (6.4%), 109 (58.3%), and 66 (35.3%) patients. Recurrence- (RFS) and progression-free survival (PFS) Kaplan-Meier curves were plotted for the risk groups, and a significant difference was detected between the groups with the log-rank test, except between the medium-low and medium-high risk groups (HR: 2.8, %95 CI: 0.6–12.2,  $P = .09$  for recurrence; HR: 1.1, %95 CI: 0.9-1.2,  $P = .75$  for progression) (Figure 1a, Figure 2a). The c-indices based on the EORTC model for recurrence and pro-

gression were 0.722 (0.646 - 0.798) and 0.752 (0.682 - 0.821), respectively.

According to the CUETO recurrence scoring system, 74 (39.6%), 41 (21.9%), 58 (31.0%) and 14 (7.5%) patients were stratified as low, medium-low, medium-high and high-risk groups, respectively. Corresponding data according to the CUETO progression scoring system were 10 (5.3%), 31 (16.6%), 82 (43.9%) and 64 (34.2%) patients. **Figures 1b and 2b** show the Kaplan-Meier curves of RFS and PFS according to the CUETO model, respectively. A statistically significant difference was found between the risk groups in terms of RFS (**Figure 1b**). All patients with progression were in the high risk group, and the difference between the high risk group and the other groups was significant (**Figure 2b**). The c-indices based on the CUETO model for recurrence and progression were 0.802 (0.745 - 0.859) and 0.834 (0.795 - 897), respectively.

The observed one- and five-year recurrence and progression rates for each risk group of our cohort and the estimated reference values according to the EORTC and CUETO risk tables are given in **Table 2**. Overall, the EORTC and CUETO models overestimated the risk of recurrence and progression at one and five years. Only the prediction of recurrence at five years in the high risk group according to the CUETO model was compatible with our cohort.

## DISCUSSION

This study provided external validation of the EORTC and CUETO models in NMIBC patients managed according to current guideline recommendations. In the present study, we tested the calibration (congruence between the predicted probability of an event and the observed) and discrimination (ability to stratify patients with different prognoses) of the EORTC and CUETO models in high-risk NMIBC patients who had received adequate BCG therapy and had undergone re-TUR. In our cohort, although the CUETO model showed better

performance than the EORTC model in terms of calibration, both models overestimated the risk of disease recurrence and progression. Only the prediction of recurrence at five years in the high risk group according to the CUETO model was compatible with our cohort. Similarly, CUETO demonstrated a better ability than EORTC model to discriminate disease recurrence and progression.

The major drawback of the EORTC and CUETO risk scoring models is that they were developed based on data from patients treated differently from current guideline recommendations. Re-TUR and long-term maintenance BCG therapy were not routinely administered. In eligible patients, the prognosis of the NMIBC has been shown to improve with the implementation of Re-TUR and a long-term BCG maintenance program.<sup>(9-13)</sup> Residual tumors can be found in 17-67% of Ta tumors and 20-71% of T1 tumors with Re-TUR. In addition, upstaging has been reported in 0-8% of Ta tumors and 0-32% of T1 tumors.<sup>(14)</sup> Therefore, in the EORTC and CUETO models, some patients may have been considered early recurrence or progression. Also, BCG is more effective than chemotherapy and other intravesical treatments in preventing disease recurrence and progression, especially in high risk NMIBC.<sup>(12,13)</sup> In addition, maintenance BCG instillations increase the effectiveness of the treatment. In the NIMBUS trial, the effectiveness of standard BCG therapy was compared with a reduced number of standard-dose BCG instillations during induction and maintenance in high-risk NMIBC patients. Overall 91% of the patients underwent re-TUR prior to BCG induction therapy. After a median follow-up of 12 months, a 60% relative reduction in the risk of recurrence in favor of the standard dose was reported.<sup>(15)</sup> In patients receiving the standard dose, the estimated recurrence rates at 12 and 24 months were 11% and 15%, respectively, similar to our results. Thus, as in our study, these models may tend to overestimate the risk of recurrence and progression, especially in high-risk patients managed with the current standard of care. Our findings are consistent with previous studies based on patients with similar characteristics.<sup>(16,17)</sup> Xylinas et al., in a large multicenter cohort, found that the EORTC and CUETO models overestimated the risk of disease recurrence and progression in high risk patients.<sup>(16)</sup> Holz et al found similar findings in their study of 123 high risk patients treated with BCG.<sup>(17)</sup>

All patients in our study received adequate BCG therapy, but only about one-third completed one year or more of maintenance BCG therapy. Still, both models overestimated the risk of recurrence and progression. Only, the CUETO model predicted a similar risk of recurrence in patients with a recurrence score of 10-16. However, the estimated probabilities of the CUETO model were closer than those of the EORTC. These results are not surprising considering that our study population is more similar to the CUETO cohort in terms of the clinicopathological features of the cases and the adjuvant intravesical treatment they received. Despite conflicting reports in the literature, in the majority of current studies, it has been reported that the CUETO model gives more accurate results in BCG-treated cohorts than the EORTC model.<sup>(16-19)</sup> Based on these findings, although the CUETO model seems more applicable than EORTC in BCG-treated NMIBC patients, it still overestimates recurrence and progression rates.

Our results showed that the CUETO model exhibited better discrimination than EORTC in predicting disease recurrence (0.722 for the EORTC model and 0.802 for the CUETO model) and progression (0.752 for the EORTC model and 0.834 for the CUETO model). Interestingly, similar to previous external validations regardless of cohort characteristics, both models showed better discrimination in estimating the risk of progression.<sup>(3,20-23)</sup>

The discriminative power of both models varied significantly among the prior external validations.<sup>(16,19,22,23)</sup> However, contrary to our findings, it has been reported that the models mostly showed moderate to poor performance. These variable results might be owing to differences in study population characteristics, experience of surgeons and pathologists, and treatment and follow-up strategies. In addition, ethnic and geographical differences may also have an effect.<sup>(24)</sup> Especially in multicenter studies, there may be significant differences between institutions on these issues. Higher c-indices were reported in single-center studies than in multicenter studies, confirming our assumptions.<sup>(16,19,22)</sup>

In terms of recurrence, the CUETO model was able to discriminate our BCG-treated cohort into different risk groups. However, the EORTC model could not discriminate between medium-low and medium-high risk groups. On the other hand, in terms of progression, progression was detected only in the intermediate and high-risk groups according to the EORTC model, and only in the high-risk group according to the CUETO model. However, we believe that both models can be helpful in individualizing patient management, as they can distinguish especially high-risk patients in terms of both recurrence and progression.

There are both strengths and limitations of our study. The strengths of the study are that the patients are evaluated by experienced surgeons and pathologists in a single tertiary center, and their follow-up and treatment regimen is standardized in line with current recommendations. The limitations of the study are the relatively small size of the study population and the retrospective nature of the study. Additionally, in this study, tumors were graded according to the WHO 2004 system, rather than the WHO 1973 system used in the EORTC and CUETO models. Moreover, the study cohort consisting only of well-treated patients who received adequate BCG therapy and excluding those who did not receive adequate treatment may have caused selection bias.

## CONCLUSIONS

The CUETO model was superior to the EORTC model in predicting recurrence and progression and stratifying patients with different prognoses in our high-risk NMIBC patient population treated according to current guideline recommendations. However, both models overestimated the probability of disease recurrence and progression. Only the probability of recurrence at five years in the high-risk group of the CUETO model was compatible with our cohort. Based on these findings, the EORTC and CUETO models should be updated based on data from a large series of NMIBC patients treated according to current standards.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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