A Comparison of EORTC And CUETO Risk Tables in Terms of the Prediction of Recurrence and Progression in All Non-Muscle-Invasive Bladder Cancer Patients

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Purpose: To compare the prediction accuracy of the European Organization for Research and Treatment of Cancer (EORTC) and the Spanish Urology Association for Oncological Treatment (CUETO) risk tables in all non-muscle invasive bladder cancer patients.

Material and Methods: Recurrence and progression-free survival of all patients were assessed according to the EORTC and the CUETO risk tables for each patient and the concordance index was used to indicate discriminative ability. Statistical analyses were performed, at 1 and 5 years, to the whole group and separately to those treated or not treated with bacillus Calmette-Guerin (BCG) .

Results: The study included 400 patients. One-year BCG maintenance therapy was applied to 181 patients (45.3%). The recurrence rate was higher than in CUETO, and similar to EORTC. The EORTC was determined to provide better discrimination than CUETO in the whole patient group and in those treated or not treated with BCG. The concordance indices for these groups were 0.777, 0.705; 0.773, 0.669; and 0.823, 0.758, respectively . The progression rate was similar in this study to the rate defined in both risk tables. The discrimination power was similar in EORTC and CUETO for all the groups. The concordance indices were 0.801, 0.881; 0.915, 0.930; and 0.832, 0.806, respectively.

Conclusion: The EORTC has more power than CUETO to discriminate each recurrence risk group and both risk tables can successfully discriminate progression risk groups in all patients.

Keywords: CUETO; EORTC; progression; recurrence; bladder cancer; non-muscle invasive

INTRODUCTION

In developed countries, bladder cancer is the sixth most common cancer in males and the seventeenth most common cancer in females [(1)]. It is the most common malignancy of the urinary tract[(2)]. Nearly 80% of urothelial carcinoma of the bladder presents as non-muscle-invasive bladder cancer (NMIBC). However, 70-80% of cases with NMIBC recur after transurethral resection of the bladder tumor (TURB), and 20-30% of patients progress to muscle-invasive cancer, despite additional intravesical chemotherapy or immunotherapy[(3)].

Risk tables can be used for the prediction of recurrence and especially progression[(4)]. The European Organization for Research and Treatment of Cancer (EORTC) developed a risk table, which provides a scoring system for recurrence and progression risk. The EORTC risk table includes these factors: number of tumors, tumor size, prior recurrence rate, T stage, presence of carcinoma in situ (CIS), and grade for NMIBC patients not treated by maintenance bacillus Calmette-Guerin (BCG) instillation therapy[(5)]. The Spanish Urology Association for Oncological Treatment (CUETO) later proposed a modified model to be used for patients only treated with BCG instillation. This risk tables includes these factors: age, gender, recurrent tumor, number of tumors, T stage, CIS, and grade[(6)].

Although there is a new EORTC risk table that can be used for NMIBC patients treated with BCG, it is not yet in routine use in general practice[(7)]. The rationale of this study was to evaluate the power of EORTC and CUETO risk tables on all patients who had undergone all the necessary stages in current practice, including maintenance BCG, single-dose immediate intravesical chemotherapy and second-look TURB.

The main aim of this study was to compare the utility of the EORTC and CUETO risk tables in all patients, and separately in patients treated or not treated with BCG.

PATIENTS AND METHODS

Study Population and Design

A retrospective analysis was made of data from 491 patients who had undergone TURB for primary or recurrent bladder cancer and received a histopathological diagnosis as non-muscle invasive bladder cancer, at a single institution between 2007 and 2016. The study

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Table 1. Patients' characteristics.

	All patients	Patients not treated with BCG	Patients treated with BCG	*P* value
Number of Patients (n)	400	219 (54.8%)	181 (45.2%)	
Age (years)				
<6	146 (36.5%)	84 (38.4%)	62 (34.2%)	0.366
60-70	142 (35.5%)	71 (32.4%)	71 (39.2%)	
>70	112 (28%)	64 (29.2%)	48 (26.5%)	
Gender				
Male	327 (81.7%)	179 (81.7%)	148 (81.8%)	0.993
Female	73 (18.3%)	40 (18.3%)	33 (18.2%)	
Prior Recurrence Rate				
Primary	223 (55.7%)	127 (58%)	96 (53%)	0.043
≤1/ year	95 (23.7%)	57 (26%)	38 (21%)	
>1/ year	82 (20.6%)	35 (16%)	47 (26%)	
Number of tumors				
1	231 (57.8%)	132 (60.3%)	99 (54.7%)	0.063
2-3	49 (12.3%)	28 (12.8%)	21 (11.6%)	
4-7	41 (10.2%)	25 (11.4%)	16 (8.8%)	
>7	79 (19.7%)	34 (15.5%)	45 (24.9%)	
Tumor size				
≤3 cm	183 (45.8)	109 (49.8)	74 (40.9%)	0.076
>3 cm	217 (54.2)	110 (50.2)	107 (59.1%)	
T Stage				
Ta	170 (42.5)	101 (46.1)	69 (38.1%)	0.107
T1	230 (57.5)	118 (53.9)	112 (61.9%)	
Grade				
1	36 (9%)	18 (8.2%)	18 (10%)	0.184
2	177 (44.3%)	106 (48.4%)	71 (39.2%)	
3	187 (46.7%)	95 (43.4%)	92 (50.8)	
Carcinoma in situ				
Yes	32 (8%)	9 (4%)	23 (12.8%)	0.002
No	368 (92%)	210 (96%)	158 (87.2%)	
Single dose Mitomycin-C				
Yes	365 (91.2%)	205 (93.6%)	160 (88.4%)	.066
No	35 (8.8%)	14 (6.4%)	21 (11.6%)	

was retrospective but was based on a prospective cohort study, which means that most patients underwent more than one TURB procedure between 2007-2016. The patient database screening was begun prospectively from January 2007. Therefore, TURB data which was closest to January 2007 were recorded as patient characteristics, and other TURB records (histopathologically proven) were accepted as recurrence or progression. Patients were excluded from the study if they had primary CIS, were upgraded to muscle-invasive disease after second-look TURB, had non-urothelial carcinoma of the bladder, concomitant upper urinary tract tumor, or could not be contacted for whatever reason. This trial is registered with ClinicalTrials.gov, number NCT03174912.

Surgery and After Surgery Procedure

Patients diagnosed with primary or recurrent bladder cancer were treated with TURB, and were staged according to the 2002 TNM classification and the 1973 World Health Organization grading system. One single immediate intravesical instillation of chemotherapy with mitomycin-C was administered in all cases by the operating urologist when there were no contraindications. Second-look TURB was performed 2-6 weeks after the first TURB to patients with pathological stage T1 or grade 3, or initial incomplete TURB. BCG induction and maintenance therapy of at least one year was applied to patients with one of T1, grade-3, or CIS or all the factors of multiple, recurrent, large tumor (>3cm). No intravesical induction or maintenance therapy was given to patients with no risk factors. Intravesical chemotherapy, mitomycin-C 6-weekly, were also applied to patients with one or two risk factors that were not high risk (large, multiple or recurrent tumor). BCG treatment was not applied to some patients who were high risk due to adverse effects, or had contraindications to BCG medication or on patient request. Patients were evaluated every 3 months during the first 2 years, and every 6 months thereafter with cystoscopies, cytology, and if necessary, biopsy or TURB. Upper urinary tract assessment was performed to all intermediate and high-risk patients annually. Pathological investigations were made by a uropathologist at a single-center and the review pathology investigation was made by the same pathologist. Patients were followed up for at least 60 months if progression was not determined.

Outcome Assessment

Recurrence was defined as non-muscle invasive or muscle invasive and progression as muscle-invasive tumor determined from cystoscopy and TURB and then proven histopathologically.

The primary end point for recurrence was accepted as the occurrence of the first recurrence or progression. The primary end point for progression was accepted as occurrence of progression. Follow-up was continued in terms of progression for patients with a recurrent tumor. Surveillance data were also obtained, including pathologically proven recurrence or progression, and the time to first recurrence or muscle-invasive cancer, which was defined as the time period between the date of initial diagnosis and the date of recurrence or progression. Patients without recurrence were evaluated at the time of the last cystoscopy for recurrence analysis and those without recurrence were evaluated at the time of the last cystoscopy for progression.

Patients known to have died from causes unrelated to

Table 2. Comparison of expected outcome in terms of recurrence according to the EORTC and CUETO risk tables scoring versus observed outcomes in the current study.

	Recurrence rate at 1 year (95% CI)				Recurrence rate at 5 years (95% CI)			
	Risk Tables	All patients	Patients not treated with BCG	Patients treated with BCG	Risk Tables	All patients	Patients not treated with BCG	Patients treated with BCG
EORTC Recurrence Groups								
I (0)	15 (10-19)	0	0	*	31 (24-37)	11 (4-17)	22 (18-26)	*
II (1-4)	24 (21-26)	19 (15-24)	19 (15-24)	19 (15-24)	46 (42-49)	60 (54-65)	52 (47-57)	69 (63-75)
III (5-9)	38 (35-41)	47 (42-52)	48 (44-52)	46 (41-51)	62 (58-65)	80 (72-87)	76 (70-81)	85 (75-94)
IV (10-17)	61 (55-67)	76 (70-81)	81 (74-88)	70 (62-77)	78 (73-84)	94 (88-99)	92 (85-99)	97 (92-99)
	Concordance index					0.777	0.773	0.823
CUETO Recurrence Groups								
I (0-4)	8 (6-10)	27 (20-33)	29 (21-37)	24 (16-31)	21 (17-25)	63 (53-72)	60 (55-65)	66 (57-75)
II (5-6)	12 (8-16)	44 (36-51)	47 (37-57)	39 (33-45)	36 (29-42)	78 (69-77)	76 (70-81)	80 (72-88)
III (7-9)	25 (20-31)	64 (56-71)	67 (56-77)	62 (55-68)	48 (41-55)	85 (78-92)	76 (70-81)	93 (84-99)
IV (10-16)	42 (28-56)	46 (36-55)	60 (54-65)	38 (31-45)	68 (54-82)	85 (75-93)	80 (75-85)	88 (80-95)
	Concordance index					0.705	0.669	0.758

Green: Outcomes of reference studies, dark blue: outcomes are equal with one standard deviation, light blue: outcomes are equal with two standard deviations, red: outcomes are not equal with two standard deviations (*: There is no patient to analyze).

bladder cancer were excluded from the analysis. Statistical analysis was performed separately on the whole patient group, and patients treated or not treated with BCG. The patients in the current study were classified into four groups according to the EORTC and CUETO risk tables. This classification was performed by one urologist and confirmed by a different urologist. The time to first recurrence and progression was determined for each risk group. A Kaplan-Meier survival analysis plot was generated for cumulative recurrence and progression analysis. The probabilities of 1 and 5-year cumulative incidence were analyzed with a 95% confidence interval (CI). Cumulative incidence probability results were divided into three groups. The first group was the probability results equal to the original risk tables with one standard deviation (SD), the second group was with two SD. The third group was the probability results lower or higher than the risk tables with two SD. The concordance index (C index) was applied after multinomial logistic regression analysis. A value of $P < .05$ was accepted as statistically significant. SPSS 17 package software for Windows (Chicago, Il) was used for all statistical processes.

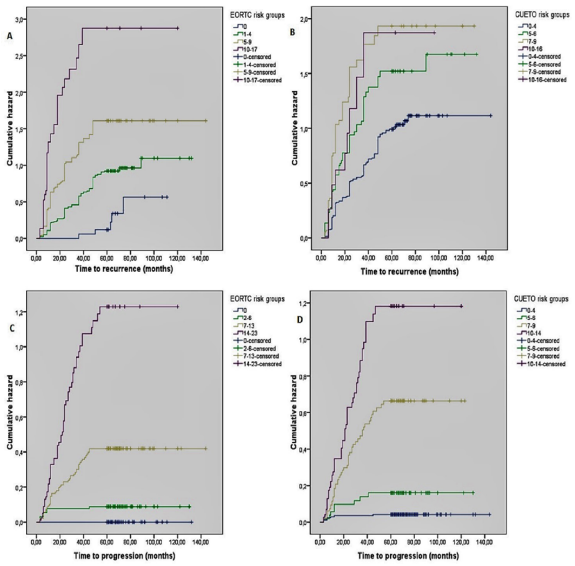

Figure 1. Kaplan-Meier survival curves of risk of recurrence according to the EORTC **(A)** and CUETO risk tables **(B)**, risk of progression according to the EORTC **(C)**, and CUETO risk tables **(D)** of all patients. In the recurrence analysis, the EORTC model **(1A)** showed a significant difference in all groups (P <.001), but in the CUETO model **(1B)**, the groups showed a significant difference except between groups with scores of 7-9 and 10-16 (P = .45). In the progression analysis, EORTC **(1C)** and CUETO **(1D)** showed a significant difference (P < .001).

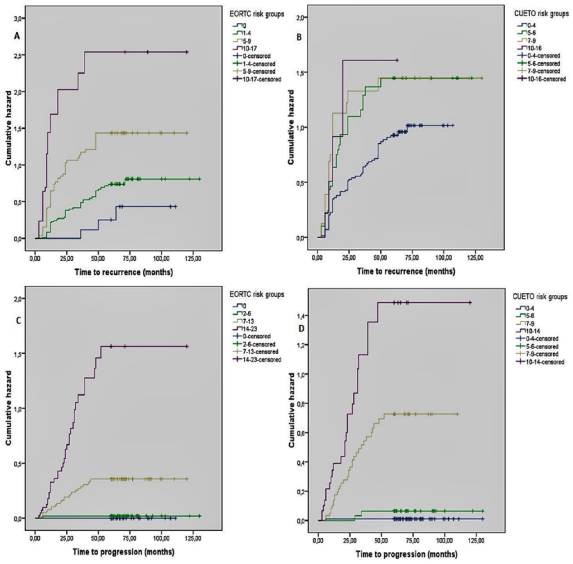

Figure 2. Kaplan-Meier survival curves of risk of recurrence according to the EORTC **(A)** and CUETO risk tables **(B)**, risk of progression according to the EORTC (C), and CUETO risk tables **(D)** of patients not treated with BCG. In the recurrence analysis, the EORTC model (**Fig 2A**) showed a significant difference in all groups (P < .001), but in the CUETO model (**Fig 2B**), a significant difference was seen only between patients with 0-4 score and the others (P < .001). In the progression analysis, both risk tables showed a significant difference (P < .001) in all groups except the groups with 0 and 2-6 scores for EORTC **(2C)** and groups with 0-4 and 5-6 for CUETO **(2D)**.

Table 3. Comparison of expected outcome in terms of progression.according to the EORTC and CUETO risk tables scoring versus observed outcomes in the current study

	Progression rate at 1 year (95% CI)				Progression rate at 5 years (95% CI)			
	Risk Tables	All patients	Patients not treated with BCG	Patients treated with BCG	Risk Tables	All patients	Patients not treated with BCG	Patients treated with BCG
EORTC Progression Groups								
I (0)	0.2 (0-0.7)	0	0	*	0.8 (0-1.7)	0	0	*
II (2-6)	1.0 (0.4-1.6)	7.4 (3-12)	2 (1-3)	14 (10-18)	6 (5-8)	8 (4-11)	2 (0.5-3.5)	16 (12-20)
III (7-13)	5 (4-7)	14 (6-22)	7 (4-10)	21 (16-26)	17 (14-20)	34 (29-39)	30 (26-34)	39 (30-47)
IV (14-23)	17 (10-24)	28 (20-36)	28 (21-35)	28 (22-34)	45 (35-55)	70 (60-79)	79 (70-87)	61 (50-71)
	Concordance index					0.801	0.915	0.832
CUETO Progression Groups								
I (0-4)	1.2 (0.2-2.2)	3.5 (2-5)	4.5 (3-6)	6.6 (5-8)	3.7 (1.9-5.6)	4 (2-6)	1 (0.5-1.5)	8 (4-12)
II (5-6)	3 (0.8-5.2)	9 (5-14)	3(2-4)	22 (17-27)	12 (7.6-16)	15 (10-20)	6 (3-9)	27 (20-34)
III (7-9)	5.5 (2.7-8.4)	17 (11-23)	13 (9-17)	23 (17-29)	21 (16-27)	48 (41-55)	51 (46-56)	44 (38-50)
IV (10-14)	14 (6.6-21)	29 (25-33)	32 (26-37)	27 (23-31)	34 (23-44)	69 (64-74)	77 (70-84)	64 (59-69)
	Concordance index					0.881	0.930	0.806

Green: Outcomes of reference studies, dark blue: outcomes are equal with one standard deviation, light blue: outcomes are equal with two standard deviations, red: outcomes are not equal with two standard deviations (*: There is no patient to analyze).

RESULTS

Of a total 491 patients, 400 patients were included in this study after exclusion of 91 patients because of lack of follow-up (n=14), incomplete data (n=16), concomitant upper urothelial tract carcinoma (n=6) or detection of invasive carcinoma on second-look TUT-BT (n=55). Second-look TURB was performed on 268 patients, and the final pathology was reported as non-invasive carcinoma in 55 patients who were then excluded from the study. The overall mean follow-up period of the whole patient group was 60.6 ± 27.6 months and for patients not determined with progression,70.2 ± 14.3 months. The mean age of the patients was 63.7 ± 10.8 years (range: 23-91 years). Immediate post-operative single dose mitomycin-C instillation was applied to 365 (91.2%) patients. BCG therapy of 6-week induction and 1-year maintenance was applied to 181 patients (45.3%). Intravesical instillation treatment of mitomycin-c was applied to 124 patients (31%) at 6-week intervals. No intravesical therapy except the single dose post-operative instillation of mitomycin-c was applied to 95 patients (23.8%). The distribution of the numbers of patients in terms of risk factors according to EORTC and CEUTO is shown in **Table 1**. The prior recurrence frequency (P = .043) and CIS (P = .002) rates were significantly different in the two groups of BCG treated or not treated. The number of the patients who did not receive single dose mitomycin-C was similar in the two groups.

The 1 and 5-year rates for recurrence and progression of the EORTC and CUETO risk tables and the results obtained in this study with these rates are shown in Tables 2 and 3. The tables are colored according to the proximity of the data obtained in this study with the data of the reference risk tables.

Recurrence Analyze

Recurrence occurred in 154 (38.5%) and 285 (71.3%) of all patients in the 1 and 5-year follow-up periods respectively. The recurrence rates of all the risk groups according to the EORTC and CUETO risk tables in all patients are shown in **Table 2**. **Figures 1A and 1B** show cumulative hazard curves for each of the four groups for the time to recurrence using EORTC and CUETO in all the patients.

The number of patients not treated with BCG was 219 (54.8%). Recurrence occurred in 88 (40.2%) and 147 (67.1%) of all patients not treated with BCG in the 1 and 5-year follow-up periods respectively. Figures 2A and 2B show cumulative hazard curves for each of the four groups for the time to recurrence using EORTC and CUETO in the patients not treated with BCG.

The number of patients treated with BCG was 181 (45.2%). Recurrence occurred in 66 (36.5%) and 138 (76.2%) of all patients treated with BCG in the 1 and 5-year follow-up periods respectively. Figures 3A and 3B show cumulative hazard curves for each of the four groups for the time to recurrence using EORTC and CUETO in the patients treated with BCG.

Progression Analyze

Progression occurred in 50 (12.5%) and 116 (29%) of all patients in the 1 and 5-year follow-up periods respectively. The progression rates of all the risk groups according to the EORTC and CUETO risk tables in all patients are shown in **Table 3**. Figures 1C and 1D show the cumulative hazard curves of each of the four groups for the time to progression using EORTC and CUETO in all the patients.

Progression occurred in 19 (8.7%) and 59 (26.9%) of all patients not treated with BCG in the 1 and 5-year follow-up periods respectively. **Figures 2C and 2D** show the cumulative hazard curves of each of the four groups for the time to progression using EORTC and CUETO in the patients not treated with BCG.

Progression occurred in 31 (17.1%) and 57 (31.5%) of all patients treated with BCG in the 1 and 5-year follow-up periods respectively. Figures 3C and 3D show the cumulative hazard curves of each of the four groups for the time to progression using EORTC and CUETO in the patients treated with BCG.

DISCUSSION

In the current study, the recurrence rates may be high, but when patients were grouped according to the points of the EORTC risk table, it was observed that as the risk increased so the recurrence rate directly increased (Figures 1A, 2A, 3A). In contrast, just as the recurrence predictions in the CUETO risk table were not compatible with those of the current study, no clear difference was observed between the four groups in the classification

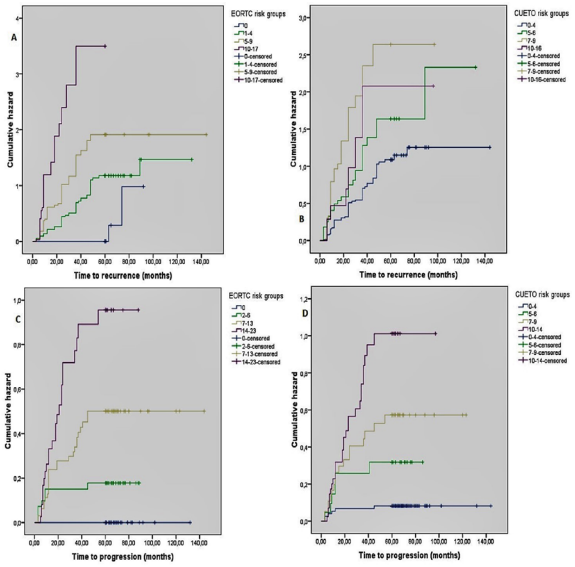

Figure 3. Kaplan-Meier survival curves of risk of recurrence according to the EORTC **(A)** and CUETO risk tables **(B)**, risk of progression according to the EORTC **(C)**, and CUETO risk tables **(D)** of patients treated with BCG. In the recurrence analysis, the EORTC model **(Fig 3A)** showed a significant difference ($P < .001$) in all groups, but in the CUETO **(Fig 3B)** model, a significant difference was seen only between patients with 0-4 score and the others ($P < .001$). In the progression analysis, EORTC **(Fig 3C)** and CUETO **(Fig 3D)** risk tables showed a significant difference ($P < .001$) in all groups.

made (Figures 1B, 2B, 3B). The CUETO risk table was considered to be insufficient in the risk classification and the prediction of recurrence in the current series.

In the progression rates, especially in the high-risk patients, the 5-year progression rates of the current study were seen to be higher than those of the risk tables. The C index values of the EORTC and CUETO tables for the whole patient group, those not receiving BCG and those receiving BCG were found to be 0.801, 0.881; 0.915, 0.930 and 0.832, 0.806, respectively. Although the progression rates were higher than those of the tables, when patients were grouped according to the points, the risk groups were significantly differentiated from each other in all 3 groups (the whole patient group, those not receiving BCG and those receiving BCG) of both the EORTC and CUETO (**Figures 1C, 1D, 2C, 2D, 3C, 3D**). Despite the higher progression rates determined in the current series compared to the reference risk tables, it can be considered that both the EORTC and the CUETO risk tables could be used for the prediction of progression and risk classification in patients treated and not treated with BCG.

The 5-year cancer specific survival in muscle-invasive bladder cancer patients with NMIBC history has been reported to be 35% and 60% in patients without NMIBC history[8,9]. A delay in definitive treatment, particularly in high-risk patients, could be a reason for missing the opportunity for treatment at the local stage of the disease. Risk tables can give an idea of the prediction of recurrence and especially progression. In the studies made when forming the EORTC risk table, approximately 78% of the patients received intravesical chemotherapy and 10% BCG therapy, while none received BCG maintenance[5]. In contrast, all the patients in the CUETO study received BCG therapy[6]. In NMIBC patients, BCG therapy is known to decrease recurrence and progression[4,10]. Therefore, while the EORTC prediction of recurrence and progression of high-risk patients receiving BCG is higher than normal, in the CUETO table, the prediction is lower than for high-risk patients not receiving BCG.

Previous studies have been published related to the compatibility of risk tables with local patient groups, the general accuracy and comparisons with each other. In two different studies of the validation of EORTC in a local patient group, the recurrence prediction accuracy rate was similar but there was not full compatibility in respect of progression[11,12].

There is no urology clinic in the world where no patient is given maintenance BCG treatment or all patients are given BCG maintenance treatment. Therefore, in addition to investigating the accuracy of the risk tables, comparisons with each other have been made and even the accuracy of EORTC for those receiving BCG and the accuracy of CUETO for those not receiving BCG have been examined[13,14]. In a study, which examined the accuracy of the EORTC risk tables in patients receiving maintenance BCG, there was high accuracy in respect of both recurrence and progression. However, as the maintenance BCG period was 3 months in that study, it has drawn criticism that the treatment period was not sufficient[13]. The reliability of the CUETO risk table for patients not receiving BCG has been examined and it was reported that the EORTC risk table predicted recurrence and progression with more accuracy than the CUETO in patients not receiving maintenance BCG following TURB[14].

In another comparative study of patients receiving maintenance BCG for at least 1 year and those not receiving maintenance BCG following TURB, both recurrence and progression were predicted to be higher in both risk tables, especially in high-risk patients, and this difference was seen to be more evident in patients receiving BCG especially in the EORTC risk table[15]. When the patients were grouped according to the risk points, there was seen to be no significant differentiation between the groups of the EORTC and CUETO risk tables in the prediction of recurrence and progression. That only 11% of the patients in that study were receiving BCG suggests that the treatment was not sufficient. The reason for this view is that it was a multi-center study and included the data of patients from the year 2000.

The recurrence rates obtained in the current study were similar to those of the EORTC table but higher than those of the CUETO risk table. The 5-year recurrence rates of the patients receiving BCG in both the EORTC and CUETO risk tables were lower than the 5-year recurrence rate results obtained in the current study. The C index values for EORTC and CUETO for the whole patient group, those not treated with BCG and those treated with BCG were 0.777, 0.705; 0.773, 0.699; and 0.823, 0.758, respectively. Although the recurrence rates of the patients receiving BCG were not similar to the risk tables, the high C index value is explained by the clear difference between the groups.

It has been previously reported in literature that insufficient intravesical treatment following TURB increases the recurrence and progression rates and this could be a cause of incorrect results in the risk table predictions [16]. In a study which included only primary NMIBC pa-

tients receiving and not receiving maintenance BCG, it was shown that the recurrence predictions of both the EORTC and the CUETO risk tables remained insufficient and only high-risk patients could be differentiated [17]. In the analysis of only the patients receiving BCG in that same study, the results were reported to be worse. While 36.8% of the patients were in the moderate and high-risk group, only 23% received maintenance BCG and approximately 50% of those receiving BCG were in the low risk group. It was a multi-center study and the patient data was from 1998-2001, again raising the question of whether standard and sufficient intravesical treatment was applied to patients following TURB[17]. The maintenance BCG therapy rate is known to be as low as it should be[18]. In the current study, some of the high-risk patients were not treated with BCG, for reasons of patient preference, adverse events, unavailability etc.

That this study was retrospective could be seen as a limitation, but retrospective data were obtained from both the EORTC and the CUETO risk tables[5,6]. Later validation studies were also conducted with a retrospective method[11-13]. As the primary outcome points were highly objective and all the patients were applied with the same treatment and follow-up plan, apart from the loss of data, the retrospective nature cannot be considered to have caused any limitation to the features of the study. That the study was conducted in a single-center and the intravesical instillation and follow-up protocol were standardized as a single type can be considered to have increased the power of the study. This is the first single-center study which has applied a standard intravesical treatment and follow-up protocol and performed an analysis of all patients and separately of those who received and did not receive BCG according to the EORTC and CUETO risk tables.

In conclusion, the EORTC risk table differentiated recurrence risk groups from each other more successfully than the CUETO risk table in patients receiving and not receiving BCG. Both risk tables yielded similar results in the prediction of progression. There is undoubtedly a need for a new risk table. When creating this table, the data should be used from centers where a current, standard treatment and follow-up protocol has been applied in the proper manner.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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