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UROONCOLOGY

Original Article

Applicability of the EORTC risk tables to predict outcomes in non-muscle-invasive bladder cancer in Turkish patients

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ABSTRACT

Objective: To evaluate the consistency of the results of patients who were treated for non-muscle-invasive bladder cancer (NMIBC) in our clinic with the European Organization for Research and Treatment of Cancer (EORTC) risk table.

Material and methods: Data were retrospectively analyzed from 452 patients who had undergone transurethral resection of bladder tumor (TUR-BT) between the years 2002, and 2010 for primary or recurrent NMIBC. Our study had a retrospective design but based on prospective cohort study. Patients were staged according to the 2002 Tumor Node Metastasis (TNM) classification and the 1973 World Health Organization grading system. Recurrence was defined as non-muscle-invasive or muscle-invasive and progression as muscle-invasive tumor determined based on following cystoscopy and TUR-BT results, and confirmed by histopathologic analysis. Patients in the current study were classified into four groups according to the EORTC risk tables. Time to first recurrence and progression was determined for each risk group.

Results: Of the 452 patients, 348 were enrolled in this study. The overall mean follow-up period was 55.25 months of all patients. Of 348 patients, 130 (37.4%) and 258 patients (74.1%) had recurrence after treatment at the 1 and 5 year follow-up period, respectively. While 35 (10.1%) and 99 patients (28.4%) progressed to muscle-invasive cancer at the 1 and 5 year follow-up period, respectively. In the multivariate analysis, grade, number, size of the tumor size, and concomitant carcinoma in situ were found to be statistically significant for disease progression and recurrence.

Conclusion: When EORTC risk tables were comparatively evaluated in our patient population, we can say that EORTC tables predict nearly accurately the clinical course of patients with NMIBC.

Keywords: Disease recurrence; EORTC; progression; urinary bladder neoplasm.

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Introduction

Approximately 80% of the cases with transitional cell carcinoma of the bladder present as non-muscle-invasive bladder cancer (NMIBC). Although 70-80% of the cases with NMIBC recur after transurethral resection of bladder tumor (TUR-BT), 20-30% of the patients progress into muscle-invasive cancer.[1]

The prediction of recurrence and progression of patients with NMIBC is very important, and helpful for the selection treatment strategies after TUR, therefore the European Organization for Research and Treatment of Cancer (EORTC) have developed a risk table, which provides a scoring system for the risk of recurrence and progression.[2]

The EORTC scoring system and risk tables were used to determine actual recurrence and progression rate of patients with NMIBC at 1 and 5 years.[2] Six clinical and pathological factors according to the EORTC risk table, which are number, and size of tumor, prior recurrence rate, T category, presence of carcinoma in situ and pathologic grade features, are known to be prognostic factors in NMIBC. Different scores are used and according to these summed scores, the patients are divided into low, intermediate, and high risk groups to predict the recurrence and progression rates. Recently, this

prediction model has been implicated in the European Association of Urology (EAU) guidelines.

The current study was aimed to compare and investigate the consistency of the results of patients of a single center with EORTC risk tables.

Material and methods

The study was performed in compliance with the ethical principles of the Declaration of Helsinki. All patients provided their informed consents concerning the risks of the procedure. The data were retrospectively analyzed from 452 patients who had undergone TUR-BT for primary or recurrent bladder cancer and received a histopathological diagnosis as NMIBC at a single institution between 2002 and 2010. Our study had retrospective design but based on prospective cohort study. We screened patients' databases prospectively from the beginning of 2002. Patients who were primarily carcinoma in situ (CIS) but upgraded to muscle-invasive disease after second-look TUR-BT, those who were unable to get in contact with their physicians due to unknown reasons were excluded from the study. Patients were followed up for at least 60 months, if disease progression was not assessed.

Patients who were diagnosed with primary or recurrent bladder cancer were treated with TURBT and 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 whenever any contraindication was not observed by the operating urologist. Patients were evaluated every 3 months during the first 2 years, and every 6 months thereafter with cystoscopies, cytology, and if necessary, TURBT. Pathological investigations were made by uropathologists at a single center. Pathological reports were not reviewed by other pathologists. Recurrence was defined as non-muscle-invasive or muscle-invasive disease and progression as muscle-invasive tumor determined based on cystoscopy and TUR-BT, and confirmed by histopathologic analysis.

Primary end point for recurrence was defined as the occurrence of the first recurrence or progression. Primary end point for progression was defined as disease progression. We performed our study with patients whose tumors recurred in terms of progression. Surveillance data were also obtained, including pathologically proven recurrence or progression, and time to first recurrence or occurrence of muscle-invasive cancer, which was defined as the time period between the date of initial diagnosis and the date of recurrence or progression.

Patients whose death was known to be unrelated to bladder cancer were excluded from the analysis. Patients in the current study were classified into four groups according to the EORTC risk tables.[2]

Statistical analysis

Time to first recurrence and progression was determined for each risk group. A Kaplan - Meier plot was generated and survival analysis was performed. Cox- regression and multivariate analysis were conducted for each prognostic factor. Concordance index was performed after multinomial logistic regression analyze. Receiver operating characteristic (ROC) curve analysis was performed for testing reliability of EORTC scale. A p value of <0.05 was accepted as statistically significant. Tests were conducted within a 95% confidence interval.

Results

Of the 452 patients, 348 were enrolled in this study. The overall median follow-up period was 55.25 months of the all patients. Median follow-up period was 68.9 months in patients in whom progression was not assessed. The median age of the patients was 63.60 (31-91) years. Characteristics of the study patients were given in Table 1. Immediate post-operative instillation of a single dose mitomycin-C was performed in 312 (89.7%) patients. One hundred and fifty-seven patients (45.1%) who were in the high risk group for recurrence or progression received six weekly intravesical instillations of bacillus Calmette-Guérin (BCG) therapy. None of the patients were treated by maintenance BCG therapy. One hundred, and eleven patients (31.9%) in the intermediate risk group or patients in the high risk group who had intolerance to BCG therapy received six weekly intravesical instillations of mitomycin-C. Eighty patients (23%) had not received any intravesical therapy except single dose mitomycin-c (Table 1).

Of 348 patients, 130 (37.4%) and 258 patients (74.1%) had recurrence after treatment at the 1- and 5-year follow-up periods, respectively. Figure 1 shows the time to first recurrence for patients in all risk groups. Thirty five patients (10.1%) and 99 patients (28.4%) progressed to muscle-invasive cancer at the 1- and 5- year follow-up periods, re-

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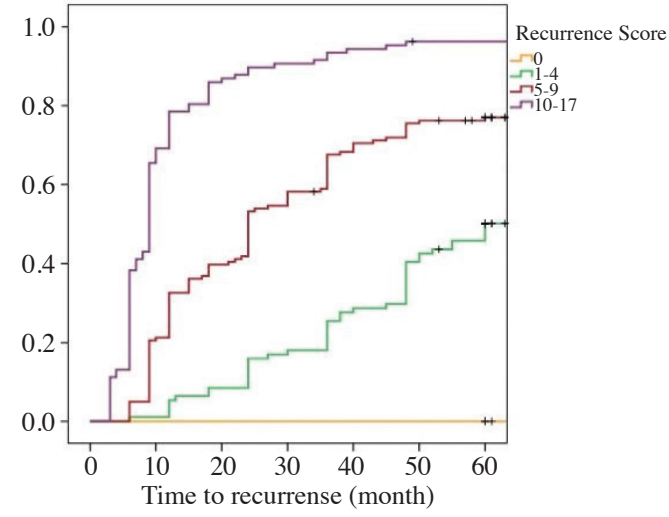
Table 1. Characteristics of the study patients

	Number	Value (%)
Age (yrs)		
≤65	197	56.6
>65	151	43.4
Sex		
Men	285	81.9
Women	63	18.1
Tumor size		
≥3 cm	194	55.7
<3 cm	154	44.3
Number of tumors		
1	195	56.0
2 to 7	84	24.1
≥8	69	19.8
Prior recurrence rate		
Primary	178	51.1
≤1/year	88	25.3
>1/year	82	23.6
Concomitant CIS		
No	316	90.8
Yes	32	9.2
Stage		
Ta	144	41.4
T1	204	58.6
Grade		
1	29	8.3
2	156	44.8
3	163	46.8
Immediate post-operative instillation of mitomycin-C		
Yes	312	89.7
No	36	10.3
Intravesical therapy		
No	80	23.0
Mitomycin-C	111	31.9
BCG	157	45.1

CIS: carcinoma in situ; BCG: Bacille Calmette-Guérin



Number of patients at risk

Recurrence Score	n	%	Time (Months) 10	20	30	40	50	60
0	6	1.7	6	6	6	6	6	6
1-4	94	27.0	93	86	78	68	57	47
5-9	141	40.5	112	85	64	44	35	33
10-17	107	30.7	37	15	10	6	4	4

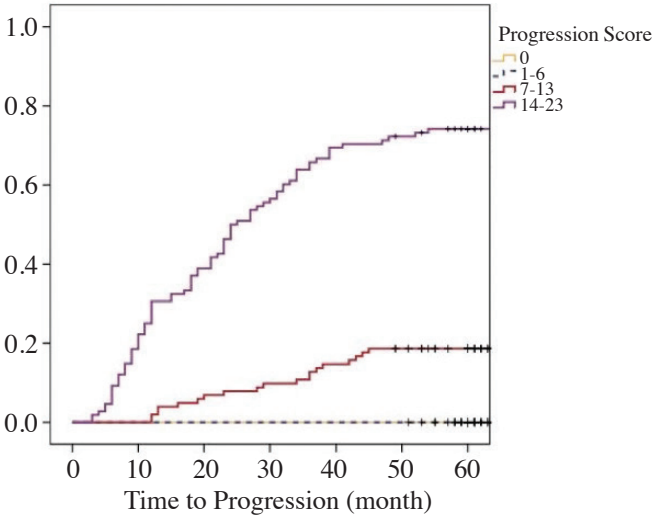
Figure 1. Five--year disease- specific survival of patients with EORTC progression scores (Kaplan-Meire curve) (p<0.05). Median disease-specific survival time in patients with all risk groups have not been obtained

spectively. Figure 2 shows the time to progression for each risk group. The probability rates of recurrence and progression of the study risk group were compared with those indicated in EORTC risk tables (Table 2 and 3).

Concordance index was 0.939 and 0.817 for progression and recurrence, respectively. In ROC curve analysis, area under curve (AUC) was 0.901 for progression and 0.773 for recurrence. These test results accurately validated the outcomes of our patients based on EORTC risk classification table. In the univariate analysis, age, presence of T1G3, grade, number, size, and stage of the tumor, concomitant CIS, instillation of intravesical therapy, and prior recurrence rate were statistically significant for the prediction of recurrence and disease progression (p<0.05).

In the multivariate analysis, age, number, and size of the tumor, and concomitant CIS were statistically significant

for the prediction of disease progression (p<0.005). Number, grade, and size of the tumor, and concomitant CIS were statistically significant for the prediction of recurrence (p<0.05) (Table 4).



Number of patients at risk

Progression Score	n	%	Time (Months) 10	20	30	40	50	60
0	30	8.6	30	30	30	30	30	30
1-6	108	31.0	108	108	108	108	108	108
7-13	102	29.3	102	96	92	87	83	83
14-23	108	31.0	88	66	48	32	30	28

Figure 2. Five- year progression-free survival of the patients with EORTC progression score (Kaplan-Meier curve) (p<0.05). To date Median progression-free survival times in patients with all risk groups have not been obtained.

Discussion

Bladder cancer has higher lifetime treatment costs per patient due to the high recurrence rate and ongoing invasive monitoring requirement.[3]

Individualized management for each patient, predicting the risk of recurrence and progression in NIMBC is a crucial point. For example, fulguration,[4] adjuvant chemotherapy,[5] or active surveillance alone[6] could be adequate treatment modalities for patients with low potential of recurrence and progression. Controlled, prospective, randomized multicenter studies are required for the selection of appropriate treatment modality. Recently, the EORTC-Genitourinary group developed a risk table using prognostic factors for the recurrence and progression of bladder cancer.[2] Nevertheless, currently it is widely used, and several trials are ongoing to evaluate the external validity of the EORTC risk tables in patients with NMIBC. Despite the fact that the smoking rate in Turkey is higher than in developed countries,[7] the results of local cohort with NMIBC were comparable to the results indicated in EORTC risk tables.

A scoring model for patients with NMIBC treated with BCG that predicts risks of recurrence and progression has been published by the Club Urológico Español de Tratamiento Oncológico (CUETO) (Spanish Urological Oncology Group).[8] Using these tables, probability of recurrence among our patient population was lower than that indicated in the EORTC risk tables. For progression, because of a more effective instillation therapy in the CUETO, calculated risk was lower only in high-risk patients.

No maintenance BCG therapy or second TUR were performed in these patients in the EORTC study. However,

Table 2. Comparison of the results of our study, and EORTC risk tables regarding groups with risk of recurrence

Recurrence risk group	First year	First year	Fifth year	Fifth year	Recurrence risk group according to EAU
	Predicted recurrence rates according to EORTC risk tables % (95% CI)	The results of the study group % (95% CI)	Predicted recurrence rates according to EORTC risk tables % (95% CI)	The results of the study group % (95% CI)	
I (0)	15 (10-19)	0 (0)	31 (24-37)	0 (0)	Low risk
II (1-4)	24 (21-26)	9.2 (7.4-11.1)	46 (42-49)	53.9 (43-64.8)	Intermediate risk
III (5-9)	38 (35-41)	39.5 (33-6.1)	62 (58-65)	77.9 (65.1-90.8)	High risk
IV (10-17)	61 (55-67)	84.9 (69-100)	78 (73-84)	96.4 (78.1-100)	High risk

EAU: European Association of Urology; EORTC: European Organisation for Research and Treatment of Cancer; CI: confidence interval

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Table 3. Comparison of the results of our study, and EORTC risk tables regarding groups with risk of progression

Progression risk group	First year	First year	Fifth year	Fifth year	Progression risk group according to EAU
	Predicted progression rates according to EORTC risk tables % (95% CI)	The results of the study group % (95% CI)	Predicted progression rates according to EORTC risk tables % (95% CI)	The results of the study group % (95% CI)	
I (0)	0.2 (0-0.7)	0 (0)	0.8 (0-1.7)	0 (0)	Low risk
II (2-6)	1 (0.4-1.6)	0 (0)	6 (5-8)	0 (0)	Intermediate risk
III (7-13)	5 (4-7)	3.8 (3.1-4.6)	17 (14-20)	18.6 (15-22.2)	High risk
IV (14-23)	17 (10-24)	35.3 (28.7-42)	45 (35-55)	74 (60.3-88.4)	High risk

EAU: European Association of Urology; EORTC: European Organisation for Research and Treatment of Cancer; CI: confidence interval

Table 4. Multivariate analysis (Cox regression analysis)

	Progression				Recurrence			
		95% CI				95% CI		
Multivariate analysis	p	HR	Low	High	p	HR	Low	High
Age (≤65/>65) yrs	0.010	1.70	1.14	2.55	0.027	1.33	1.03	1.71
Tm Size (<3/≥3) cm	0.000	4.12	2.18	7.80	0.000	2.19	1.65	2.90
CIS (Yes/No)	0.000	4.86	3.09	7.65	0.006	1.73	1.17	2.57
Tm Number (Single/Multiple)	-	-	-	-	0.009	1.41	1.09	1.83
Stage (Ta/T1)	0.000	8.78	5.60	13.7	0.068	2.09	0.88	3.28
Grade (1-2/3)	-	-	-	-	0.000	1.72	1.49	1.98
Prior recurrence rate	-	-	-	-	-	-	-	-
Recurrence (yes/no)	0.009	14.18	1.95	102.92	-	-	-	-

EAU: European Association of Urology; EORTC: European Organisation for Research and Treatment of Cancer; CI: confidence interval

evaluation of the trials performed with BCG maintenance therapy has indicated that BCG therapy prevents, or at least delays, the risk of progression of NMIBC.[9,10] Second-look TUR has gained attention because of the inaccuracy of the pathological diagnosis.[11-13]

Hernandez et al. [14] and Pillai et al.[15] conducted different trials to evaluate external validity and applicability of the EORTC risk tables. Due to the sample size of the trial, Hernandez et al.[14] could only validate the recurrence model of the EORTC algorithm and Pillai et al.[15] were not able to validate the proposed algorithm in their patients.

Some of the differences in patient characteristics (tumor size (>3 cm), tumor number (>8), concomitant CIS, presence of T1G3) may be observed compared to EORTC's patient group. However, the patient characteristics of other trials were similar to the current study's patient characteristics. [14,15] In contrast to Sylvester's study which had been done in industrialized world, Turkey which is included among the developing countries, has lack of organized health care and a large portion of the patients have significant socioeconomic problems in accessing a convenient health center. As such, increase in the cases with histopathological diagnosis of high grade bladder tumor and concomitant CIS were observed with time.

While the actual recurrence rates for 1 and 5 years were 37.4% and 74.1%, respectively, the actual progression rates for 1 and 5 years were 10.1% and 28.4%, respectively. The

median time to the first recurrence and disease -progression could not be determined in our study.

Because of small sample size, risk groups for recurrence, and groups without any risk for disease progression or those carrying low risk could not be determined in our study. For recurrence, the majority of patients were placed in Group III and IV, and Group IV in particular showed a higher rate of probability of recurrence than the corresponding EORTC group (Table 2). We can say that recurrence rate is increasing by increased risk. In some of our study groups risk rates were similar to those indicated in EORTC risk tables, while in the other groups they were different, but not extremely. For progression, there were relatively equal number of patients in Groups II, III, and IV and only in Group III probability of progression was comparable that indicated in EORTC risk tables. However results in other groups were not extremely different from those indicated in EORTC risk tables (Table 3). We think this difference is result of small sample size and heterogeneity of study population. So results of our study are not the same but parallel to EORTC results.

Some limitations of the present study are the smaller sample size, and inter-observer variations among uropathologists,[16] subjectivity and variance between different operators, and missing patient records.

In conclusion, when the rates of recurrence, and progression in EORTC risk tables are compared with those of our patient population, we can say that EORTC tables predict nearly accurately the clinical course of the patients with NMIBC. EORTC is an helpful nomogram for the prediction of recurrence and progression of NMIBC.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Written informed consent was obtained from all patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.F.K.; Design – G.B., S.G.; Supervision – A.D.; Resources – N.C.S., S.A.; Data Collection and/or Processing – G.B.; Analysis and/or Interpretation – A.D.; Literature Search – S.G., S.A.; Writing Manuscript – M.F.K., G.B.; Critical Review – A.D., N.C.S.; Other – S.G., S.A.

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