Original Article

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The Effect of Second TURBT on Recurrence and Progression in Primary Ta High-grade Bladder Cancers: A Multicenter Clinical Trial Comparing Long-term Outcomes

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Abstract

Objective: To evaluate the potential significance of the second transurethral resection of a bladder tumor (TURBT) in a population of patients whose primary pathology was high-grade pTa (Ta/HG) and who had received Bacillus Calmette-Guérin (BCG) treatment for at least 12 on oncological outcomes, based on the presence or absence of detrusor muscle.

Materials and Methods: Patients with primary Ta/HG tumors (n=207) that met the inclusion criteria were grouped based on the presence of muscle tissue in the first TURBT and whether the secondary TURBT was performed. Progression, recurrence, and disease-free survival rates were compared between the groups.

Results: Median follow-up period was 24 (12-205) months. In cases with muscle in the first TURBT, a second TURBT significantly increased the median disease-free survival time compared with those that did not undergo the second TURBT [32 months (12-83) vs 12 months (6-67); p<0.005]. In cases without muscle in the first TURBT, the second TURBT significantly reduced the rate of progression (p<0.05). Regression analysis showed that tumor size >3 cm [95% confidence interval (CI)=1.09-2.96, hazard ratio (HR)=1.79, p=0.021], presence of muscle tissue (95% CI=0.35-0.92, HR=0.57, p=0.022), and multiple tumor (95% CI=1.06-2.90, HR=1.75, p=0.028) were independent factors affecting disease relapse in primary Ta/HG tumor.

Conclusions: In patients with primary Ta/HG tumors, if there was no muscle in the first TURBT, a second TURBT should be performed to achieve lower progression rates. If there is muscle in the first TURBT, the second TURBT will only increase the median disease-free survival time.

Keywords: Bladder cancer, second look, urothelial carcinoma, second TURBT, BCG, pTa, high grade

Introduction

Up to 70 to 80% of all bladder neoplasms are non-muscle invasive bladder cancers (NMIBC). While 70% of NMIBCs are limited to the mucosa (Ta), 30% occupy the lamina propria (T1) (1). High-grade pTa tumors (Ta/HG) have a 10-15% higher risk of progression than low-grade pTa tumors (Ta/LG), but this risk is still lower than that of T1 tumors (2). When the classification proposed by the World Health Organization (WHO)/International Society of Urological Pathology in 2004 was widely adopted, all grade three bladder tumors and some previously grade two bladder tumors in the 1973 WHO classification were reclassified as high grade (3). Consequently, the high-grade pTa group was more heterogeneous than the pTaG3 group (4). This may lead to some differences in terms of clinical management and therefore the treatment guidelines for pTaG3 (WHO classification of 1973) may not apply to the pTa/HG group (5).

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Data on the indications and results of a second transurethral resection of a bladder tumor (TURBT) in Ta/HG tumors are limited and different approaches have been described in the literature (6-9). When we look at the guidelines, both the European Association of Urology and the National Comprehensive Cancer Network guidelines both suggest the second TURBT for pTa/HG urothelial carcinoma if there is no muscle tissue in the biopsy (10,11). However, American Urological Association guidelines did not make any recommendations regarding the need for the second TURBT in cases that had muscle in their first TURBT (12). Similarly, whether the presence of muscle changes the approach was not specified by the National Institute for Clinical Excellence (13).

In the literature, there is no consensus on different clinical approaches and results in the second TURBT of Ta/HG (6,8,14). Herr (8) noted that Ta/HG tumors are as deadly as T1 tumors and therefore should be treated with transurethral resection, intravesical therapy, and cystectomy in case of recurrence or progression, however they did not make any comment on the second TURBT. Dangi et al. (6) reported that the second TURBT increased median recurrence-free survival in primary Ta/HG tumors, while Tinay et al. (14) found that the second TURBT performed in patients with Ta/HG tumors resulted in longer median time to recurrence and progression and lower recurrence rates if the muscle tissue was absent at the first TUR and longer median time until the first recurrence if the muscle tissue was present at the first TUR.

This study aimed to determine the potential significance of the presence of detrusor muscle tissue at first TURBT in a population of patients whose primary pathology was Ta/HG and who were treated with Bacillus Calmette-Guérin (BCG) for at least 12 months. Additionally, we wanted to assess the effect of a second TURBT, performed on the basis of the presence or absence of detrusor muscle tissue, on recurrence and/or progression rates.

Materials and Methods

Following University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Clinical Research Ethics Committee approval (decision number: 2021/01-28, date: 25.01.2021), the data of patients, whose primary TURBT pathology result was Ta/HG NMIBC (reported according to the WHO 2004 classification) between January 2004 and February 2021, were retrospectively collected from four centers participating in the study. Patients' demographic and clinical characteristics [age, sex, body mass index (kg/m^2)], smoking status, comorbidities (hypertension, diabetes mellitus, chronic obstructive pulmonary disease, cardiovascular disease), Charlson comorbidity index and occupational exposures were determined. The first TURBT features [number of tumors (single, multiple), tumor size, and pathological features], the second TURBT features (visual persistent tumor, pathological features), follow-up status, and relapse time (defined as recurrence or progression time) were recorded.

For patients who underwent a second TURBT, this procedure was performed between 2 and 6 weeks after initial TURBT. Follow-up visits occurred at three-monthly intervals during their first two years, and then biannually during their three subsequent years and then once a year afterwards by cystoscopy, cytology, and tumor resection, if any tumor was detected. Instances with Ta/HG in the first TURBT and T1/HG or T1/LG in the second TURBT were not evaluated as progression. The rates are expressed separately. Cases with Ta/LG or Ta/HG tumors in the bladder during the follow-up were considered recurrence, T1± CIS as progression, cases with recurrence ± progression were considered relapse. Pathologies seen in the second TURBT were also examined.

In total, the data of 4244 patients from 4 centers were evaluated. There were 372 patients whose primary pathology was Ta/HG. Among these, patients who received BCG induction therapy and at least 1-year BCG maintenance in accordance with the the Southwest Oncology Group (SWOG) protocol had a minimum 12-month follow-up, had no carcinoma *in situ* (CIS) in its primary pathology and had a complete first TURBT were included in the study. The flowchart is summarized in Figure 1. Those with variant histology (n=4) and tumor in the upper urinary tract (n=5) in the first TURBT, patients who did not receive at least 1 year of BCG maintenance therapy (n=64), and ones that did not meet the follow-up time (n=45) and other inclusion criteria [incomplete TURBT (n=47)] were excluded from the study. Two-hundred-seven patients who met the inclusion criteria were evaluated in 4 groups. Group 1 included patients who had detrusor muscle tissue at the first TURBT and underwent a second TURBT. Group 2 included patients who had detrusor muscle at the first TURBT but did not undergo a second TURBT. Group 3 consisted of patients that did not have detrusor muscle tissue at the first TURBT and did not undergo the second TURBT, while group 4 had patients that did not have detrusor muscle in the first TURBT, and underwent the second TURBT (Figure 1). Recurrence and progression rates, and time to progression were recorded in each group. The length of time that the patient survived without relapse after receiving BCG induction therapy and minimum 1 year maintenance BCG according to the SWOG protocol was evaluated as disease-free survival.

Statistical Analysis

The Kolmogorov-Smirnov test was used to analyze the normality of the data. The Pearson chi-square test and Fisher's exact test were used to compare categorical variables. Continuous variables with a normal distribution were presented as mean ± standard deviation and variables with non-normal distribution as median (range) for descriptive statistics in the study. Mann-Whitney U test was used for paired comparisons between groups. For quantitative data, one-way analysis of variance (ANOVA) is used for normally distributed variables and Kruskal-Wallis test with Bonferroni posthoc correction for others (15). For all tests, the likelihood of a type I error was α=0.05. Furthermore, Bonferroni adjustment was used to determine significant variants in the four groups. The Bonferroni cut value was calculated as 0.05/6.

We conducted univariable and multivariable Cox proportional hazard regression analysis to determine risk factors for recurrence in patients with pTaBG, calculating hazard ratios (HRs) and 95% confidence interval (CI). Kaplan-Meier survival curves with 95% CI determined the effect of a second TURBT and the presence of muscle tissue in the recurrent tumor specimen. Survival outcomes were compared between groups using the log-rank

test. IBM SPSS V.22 package software program was used for statistical analyses.

Results

The median follow-up was 24 (12-205) months. The primary pathology of 8.7% of patients was determined as Ta/HG. The demographic, clinical, and pathological characteristics of 207 patients who met the inclusion criteria are summarized in Table 1. Second TURBT was performed in 97 patients (46.8%) and persistent visual tumor was observed in the second TURBT in 15.4% in group 1 and in 55.6% in group 4 ($p<0.05$). The tumor detection rate in the second TURBT was significantly higher in group 4 than in group 1. Analysis of the bladder maps revealed a persistent tumor at the same site as the initial tumor in 61.6%, at other sites in 12.8% and both in 25.6%. In group 1, restaging after second TURBT indicated that there was no upstaging, whereas 3.8% of the patients had Ta/HG tumors, and 11.5% had Ta/LG tumors. The restaging in group 4 showed upstaging to T1/HG in 20% of patients, Ta/HG in 4 (8.8%) patients, and Ta/LG tumors in 18 (40%) patients ($p<0.05$) (Table 1).

During the follow-up among all groups, 11 patients (5.3%) had progression (T1/HG in 11 patients, concomitant CIS in 1 patient), but none progressed to muscle-invasive disease. The progression was significantly higher in group 3, which included patients that did not have muscle tissue involvement in primary TURBT and did not undergo second TURBT ($p<0.05$). When all groups were evaluated, the median relapse time was 17 (3-107) months. The time until the relapse was significantly longer in group 1 ($p<0.05$) (Table 1).

Multivariate Cox proportional hazards regression analysis showed that tumor size >3 cm (95% CI=1.09-2.96, HR=1.79, $p=0.021$), presence of muscle tissue (95% CI= 0.35-0.92, HR=0.57, $p=0.022$), and multiple tumors (95% CI=1.06-2.90, HR=1.75, $p=0.028$) were independent factors affecting disease relapse in primary Ta/HG tumor (Table 2).

Evaluation of the difference in disease-free survival between the groups showed a significant survival advantage in group 1, especially in the first 2 years. Group 3 was found to be the worst population in terms of disease-free survival ($p=0.015$, Figure 2a). The subgroup analysis of groups 1 and 2, both of which had the muscle tissue in the first TURBT, but had different status on the second TURBT, showed that the presence of muscle tissue positively affected disease-free survival, independently from the second TURBT ($p=0.008$, Figure 2b). When we examined whether the second TURBT, regardless of the presence of muscle tissue in the first TURBT (groups 1 and 4), provided the survival advantage, we saw that there was no statistically significant difference ($p=0.059$, Figure 2c).

Evaluation of difference in recurrence-free survival according to groups and all subgroups showed that there was no statistically significant difference. ($p>0.05$, Figure 3).

Assessment of difference in progression-free survival according to groups showed a significant survival advantage in group 1 and group 2. Group 3 was found to be the worst population in terms of progression-free survival ($p=0.004$, Figure 4a). The subgroup analysis of groups 1 and 2, both of which had the muscle tissue in the first TURBT, but had different status on the second TURBT, showed that the presence of muscle tissue positively affected

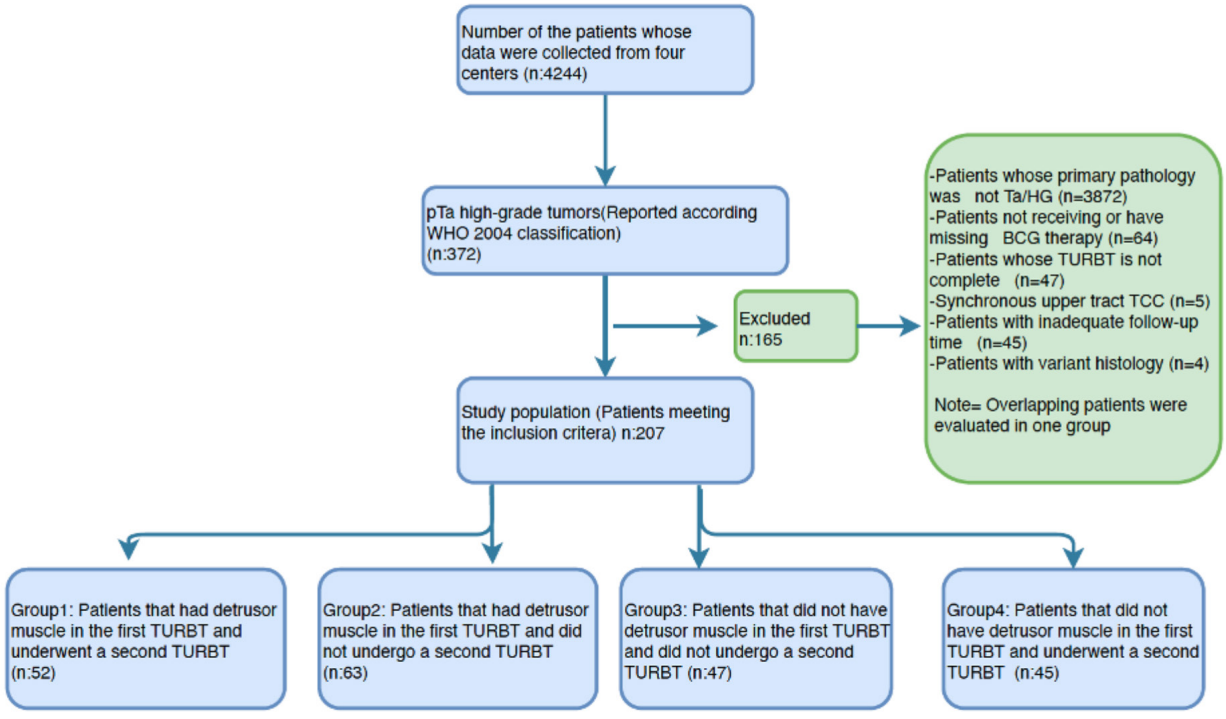

Figure 1. Study flow, detailing the process used to select cases for inclusion in the study

BCG: Bacillus Calmette-Guérin, WHO: World Health Organization, TURBT: Transurethral Resection of Bladder Tumor, TCC: Transitional cell carcinoma, Ta/HG: High-grade pTa tumors

progression-free survival, independently from the second TURBT (p=0.001, Figure 4b). When we examined whether the second TURBT, regardless of the presence of muscle tissue in the first TURBT (groups 1 and 4), provided the survival advantage, we saw that there was no significant difference (p=0.08, Figure 4c).

Discussion

There is uncertainty in the literature regarding the importance of detrusor muscle presence in the first TURBT, the need for the second TURBT, and data evaluating the effect of the second TURBT on tumor recurrence and progression in patients with maintenance BCG-treated primary Ta/HG (6,7,8,9). This study evaluated the potential significance of the second TURBT on oncological outcomes, based on the presence or absence of detrusor muscle in a population whose primary pathology was high-grade pTa (Ta/HG) and who had been treated with BCG for at least 12 months. Our results show that in patients with primary Ta/HG tumors, if there is no muscle in the first TURBT, a second TURBT should be performed to achieve lower progression rates. If there is muscle in the first TURBT, the second TURBT will only increase the median disease-free survival time.

Table 1. Distributions of diagnostic characteristics according to group

	Group 1 (n=52)	Group 2 (n=63)	Group 3 (n=47)	Group 4 (n=45)	p-value
Age, years (mean ± SD)	65.3±8.9	65.0±9.4	66.7±10.4	64.8±9.8	0.776[A]
Gender (M/F)	44/8	54/9	43/4	43/2	0.267[P]
BMI	25.9±4.7	26.6±4.3	25.3±4.4	25.3±2.9	0.356[A]
Charlson comorbidity index median (range)	3.2±1.5 3 (0-6)	3.0±1.8 3 (0-6)	3.2±1.9 3 (0-8)	3.0±1.4 3 (0-6)	0.911[A] 0.860[K]
Comorbidity number	1.1±0.8	1.1±1.2	1.0±1.1	1.0±0.8	0.839[A]
Smoking, n (%) Pack years (mean ± SD)	40 (76.9) 19.9±22.7	40 (63.5) 29.3±28.4	30 (63.8) 17.5±18.1	43 (95.6) 36.7±23.4	0.001[P] 0.001[A]
Comorbidity DM, n (%) HT, n (%) CVD, n (%) COPD, n (%)	 15 (28.8) 20 (38.5) 2 (3.8) 5 (9.6)	 17 (27) 22 (34.9) 6 (9.5) 8 (12.7)	 13 (27.7) 11 (23.4) 11 (23.4) 3 (6.4)	 14 (31.1) 16 (35.6) 4 (8.9) 6 (13.3)	 0.971[P] 0.412[P] 0.016[P] 0.664[P]
Occupational exposure, n (%) No Yes Unknown	 37 (71.2) 5 (9.6) 10 (19.2)	 36 (57.1) 3 (4.8) 24 (38.1)	 29 (61.7) 8 (17) 10 (21.3)	 28 (62.2) 4 (8.9) 13 (28.9)	0.138[P]
Number of tumors	1.9±1.4	2.0±1.5	1.5±0.7	2.2±3.3	0.284[A]
Tumor number, n (%) Single Multiple	 32 (61.5) 20 (38.5)	 39 (61.9) 24 (38.1)	 29 (61.7) 18 (38.3)	 24 (53.3) 21 (46.7)	0.793[P]
Tumor size, mm	3.0±1.8	3.1±2.2	2.5±1.6	3.3±1.5	0.154[A]
Visual persistent tumor, n (%)	8 (15.4)	-	-	25 (55.6)	0.004[P]
pT stage in the second TURBT, n (%) pT0 pTa pT1	 44 (84.6) 8 (15.4) 0	 - - -	 - - -	 14 (31.1) 22 (48.9) 9 (20)	<0.001[P]
Histological grade in the second TURBT, n (%) Benign Low grade High grade	 44 (84.6) 6 (11.5) 2 (3.8)	 - - -	 - - -	 14 (31.1) 18 (40) 13 (28.9)	<0.001[P]
Follow-up status, n (%) Disease-free Recurrence Progression	 39 (75) 13 (25) 0	 46 (73) 16 (25.4) 1 (1.6)	 26 (55.3) 14 (29.8) 7 (14.9)	 27 (60) 15 (33.3) 3 (6.7)	0.009[F] 0.094[P] 0.764[P] 0.016[F]
Follow-up total (months)	42 (12-83)[a,b,c]	20(12-62)[a,Ω,§]	24 (12-211)[b,Ω,q]	24 (12-132)[c,§,q]	0.023[K,M]
Relapse time (months)	32 (12-83)[†,‡,Δ]	16 (6-42)[†,ɣ,Σ]	15 (3-107)[‡,ɣ,ϕ]	12 (6-67)[Δ,Σ,ϕ]	<0.001[K,M]

[F]Fisher's exact test, [K]Kruskal-Wallis test, [M]Mann-Whitney U test, [P]Pearson chi-square test, [A]ANOVA.
[a]Group 1 vs group 2 p=0.005; [b]Group 1 vs group 3 p=0.014; [c]Group 1 vs group 4 p=0.292
[Ω]Group 2 vs group 3 p=0.932; [§]Group 2 vs group 4 p=0.146; [q]Group 3 vs group 4 p=0.257.
[†]Group 1 vs group 2 p<0.001; [‡]Group 1 vs group 3 p<0.001; [Δ]Group 1 vs group 4 p<0.001.
[ɣ]Group 2 vs group 3 p=0.338; [Σ]Group 2 vs group 4 p=0.672; [ϕ]Group 3 vs group 4 p=0.893.
[x]Group 2 vs group 3 p=0.854; [y]Group 2 vs group 4 p=0.033; [z]Group 3 vs group 4 p=0.102.
BMI: Body mass index, DM: Diabetes mellitus, HT: Hypertension, COPD: Chronic obstructive pulmonary disease, TURBT: transurethral resection of a bladder tumor, IVT: Intravesical treatment, M: Male, F: Female, SD: Standard deviation, CVD: Cardiovascular disease

In the literature, the pathology results of second TURBT after primary Ta/HG have been evaluated in various studies. In 2011, Herr (16) published a single-center study with 396 patients non-invasive grade 3 (TaG3) patients who underwent a second TURBT. Pathology results indicated pT0 in 35%, Ta/HG-CIS in 50%, pT1 in 10%, and pT2 in 5% of patients. In the study by Dangi et al. (6), 43 (38.3%) of 112 patients whose primary pathology was TaG3 underwent a second TURBT (only two of whom had no muscle in the first TURBT). In 7 of 37 patients whose first TURBT was complete, positive results (2 pTa LG lesions, 3 CIS, and 2 pTa HG lesions) were detected in the second TURBT, however no progression was found in any patient. Lazica et al. (7) performed a second TURBT in 61.3% of 142 patients with pTa/HG 97.1 days (the median) after the first TURBT and detected persistent tumors in 41.4%, progression to pT1/HG in 5.7%, and muscle-invasive tumors (T2) in none of the patients. Moreover, among 87 patients that had Ta/HG pathology, 38 had muscle tissue at the first TURBT, 5 did not have, and the presence of muscle at the first TURBT was not known in 44 patients (7). They recommended performing a second TURBT in these patients since the primary tumor site was the location for most of the persistent tumors (7). In another study by Hensley et al. (17), 104 of 209 patients with primary pathology Ta/HG underwent the second TURBT and residual disease was found in 39 patients (38%). The second TURBT was upstaged to pT1 in only one patient (1%). In our study, we found tumors in 39 (46.8%) of 97 patients who underwent the second TURBT, and this rate was significantly lower in group 1 than in group 4. During the second TURBT, a persistent visual tumor was observed in 8 (15.4%) patients in group 1, and 25 (55.6%) patients in group 4. Additionally, although there was no upstaging in group 1 with muscle involvement in the first round, we showed that there may be a tumor in the pathology specimen in the second TURBT, even with muscle involvement.

When considering the effect of the second TURBT on progression, recurrence and disease-free survival in primary TA/HG tumors, Dangi et al. (6) predicted median recurrence-free survival to be 76 months and 45 months for the groups that did and did not undergo second TURBT, respectively, and this difference was statistically significant. They suggested further large-scale studies investigating the second TURBT's role in this group (6). In a study by Tinay et al. (14) with 93 pTa/HG patients, they reported that in cases with muscle in the first TURBT, the median time to recurrence was increased significantly if the second TURBT was performed (77.6 vs 36.9 months, p=0.0086). Moreover, they reported that even in cases that did not have muscle at the first TURBT, the median time until recurrence (78.9 vs 42.7 months, p=0.0001) and median time until progression (22 vs 7 months, p=0.05) increased, while the recurrence rate (20% vs 66.7%, p=0.002) decreased in those that underwent a second round of TURBT compared to ones that didn't (14). Hensley et al. (17) reported that the second TURBT was associated with improved relapse-free survival (p=0.003) and progression-free survival (p=0.050) in all patients with non-stratified HG Ta. They noted that the second TURBT was associated with better results in all patients with Ta/HG, regardless of the stratified risk (17).

In our study, among all patients, 5.3% progressed to pT1 and none to pT2. Progression rates were significantly higher in group 3. Notably T1 pathology decreased in group 4 and progression was observed more in group 3, which emphasizing the importance of the second TURBT in cases without detrusor involvement in the first TURBT. Our results showed that having muscle tissue presence in the first TURBT significantly prolongs

Table 2. Univariate and multivariate Cox proportional hazards regression were performed to determine the factors that were associated with disease relapse

	Univariate model			Multivariate model		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age	1.011	0.986-1.036	0.406			
Gender (ref: male)	0.531	0.210-1.338	0.179			
BMI	0.989	0.938-1.043	0.683			
CCI	1.056	0.916-1.216	0.454			
Occupational exposure	1.110	0.845-1.459	0.452			
Smoking (years)	1.001	0.992-1.011	0.768			
Multiple tumor	2.142	1.318-3.480	0.002	1.756	1.062-2.903	0.028
Tumor size	1.228	1.095-1.378	<0.001			
Tumor size >3 cm	2.157	1.330-3.497	0.002	1.798	1.092-2.963	0.021
Immediately IVT	1.668	0.946-2.943	0.077			
Presence of muscle tissues	0.535	0.332-0.862	0.010	0.572	0.354-0.923	0.022
Second TURBT	0.632	0.387-1.032	0.067			
Visual tumor on Second TURBT	1.210	0.632-2.316	0.566			
Second TURBT pT stage	1.166	0.977-1.391	0.088			
Second TURBT grade	1.648	0.707-3.841	0.247			

HR: Hazard ratio, CI: Confidence interval, BMI: Body mass index, CCI: Charlson comorbidity index, TURBT: transurethral resection of a bladder tumor, IVT: Intravesical treatment

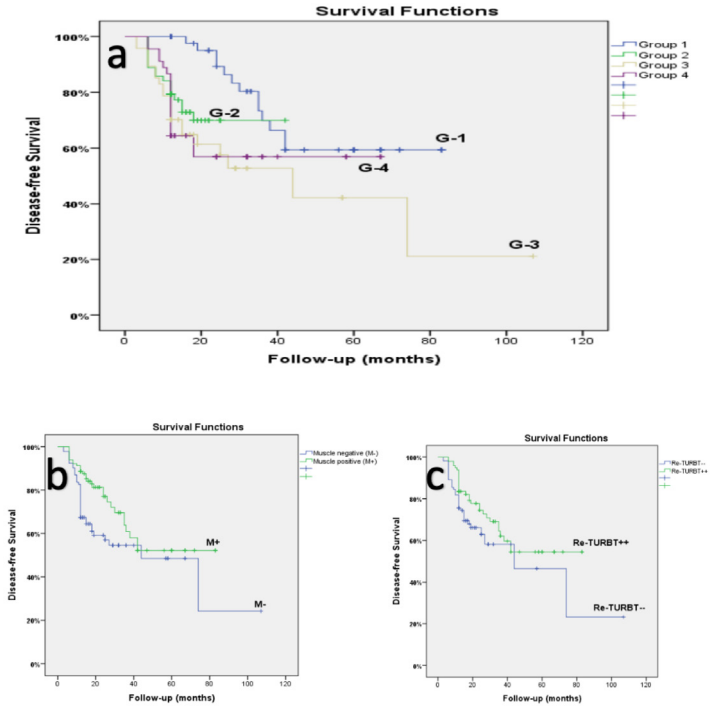

Figure 2. (a) Disease-free survival Kaplan-Meier curve according to groups. The log-rank method p-value was 0.015. The chi-square value was 10.455. **(b)** Disease-free survival Kaplan-Meier curve according to the presence of muscle in the specimen. The log-rank method p-value was 0.008. The chi-square value was 7.091, **(c)** Disease-free survival Kaplan-Meier curve according to the presence of the second TURBT. The log-rank method p-value was 0.059. The chi-square value was 3.558

TURBT: transurethral resection of a bladder tumor

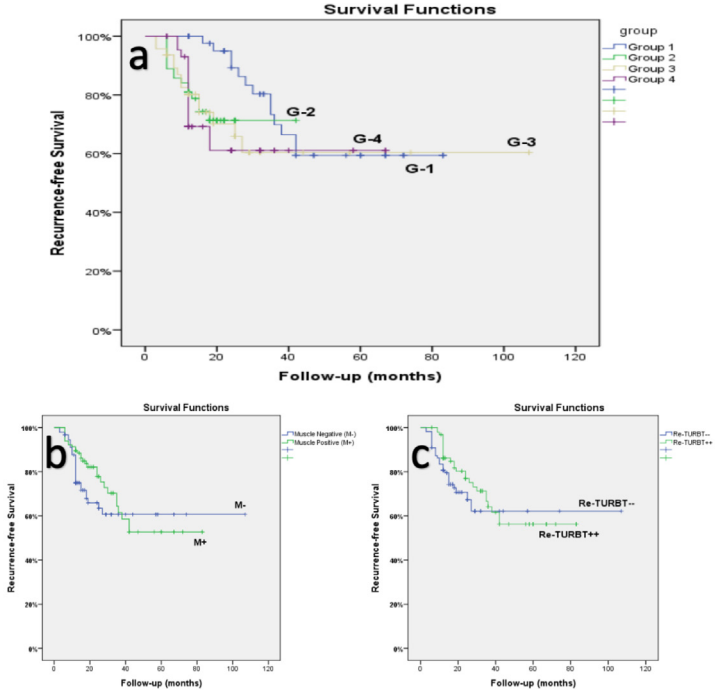

Figure 3. (a) Recurrence-free survival Kaplan-Meier curve according to groups. The log-rank method p-value was 0.157. The chi-square value was 5.217, **(b)** Recurrence-free survival Kaplan-Meier curve according to the presence of muscle in the specimen. The log-rank method p-value was 0.152. The chi-square value was 2.055, **(c)** Recurrence-free survival Kaplan-Meier curve according to the presence of the second TURBT. The log-rank method p-value was 0.202. The chi-square value was 1.631

TURBT: transurethral resection of a bladder tumor

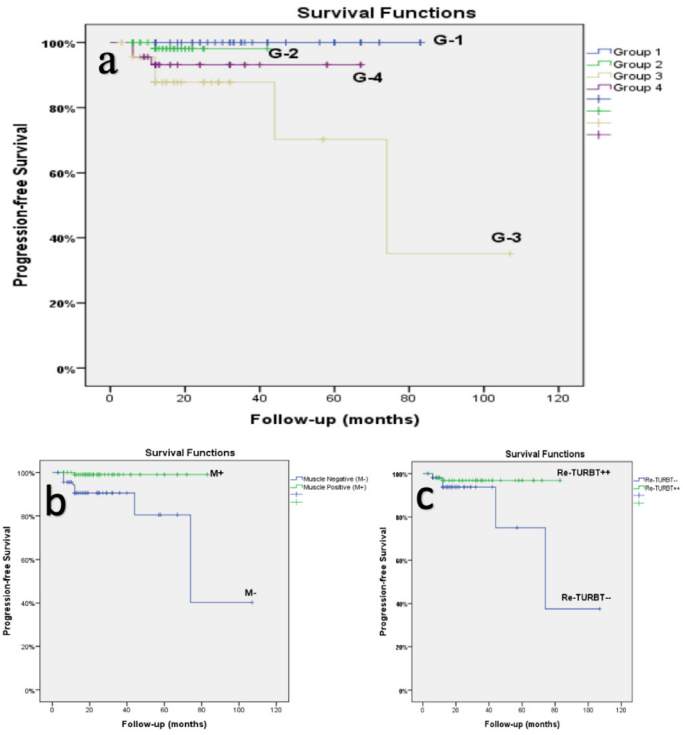

Figure 4. (a) Progression-free survival Kaplan-Meier curve according to groups. The log-rank method p-value was 0.004 the chi-square value was 13.342, **(b)** Progression-free survival Kaplan-Meier curve according to the presence of muscle in the specimen. The log-rank method p-value was 0.001. The chi-square value was 10.878, **(c)** Progression-free survival Kaplan-Meier curve according to the presence of the second TURBT. The log-rank method p-value was 0.084. The chi-square value was 2.994

TURBT: transurethral resection of a bladder tumor

progression-free survival and disease-free survival, independent of the second TURBT. When the effect of the second TURBT was evaluated independently, it was observed that it contributed positively to the disease-free survival approximately in the first 3 years even when it was not statistically significant. Although it was not significant, progression-free survival after the first 3 years favored the group in which the second TURBT was performed. Our study, which shows that if there is no muscle tissue present in the first TURBT, not performing the second TURBT significantly increased the likelihood of progression, supports the literature at this stage. An important point to be discussed in our results is that although it shows that when there is muscle in the first TURBT, the second TURBT does not have a significant effect on progression or recurrence rate, the second TURBT application increases median DFS (32 vs 16 months, p<0.001). Our study also showed that tumor size, presence of muscle tissue, and multiple tumors in primary TURBT are independent factors affecting disease relapse in primary Ta/HG tumor.

The mainstay of advanced therapy is adjuvant intravesical BCG in the NMIBC population, which has high-risk features in the second TURBT (18,19). In both the European Association of Urology and National Comprehensive Cancer Network guidelines, it's stated that priority intravesical BCG instillations are preferred or intravesical chemotherapy is recommended after TURBT in pTa grade 3/HG urothelial carcinoma (10,11). Studies on the importance of the second TURBT in Ta/HG patients revealed few reports of an insufficient number of BCG treatments as well and a limited number of patients (6,7,16). Lazica et al. (7) did not report on intravesical BCG treatment and recurrence/progression rates during the follow-up period. Dangi et al. (6), only 23.4% of their patients received at least 1 year of intravesical BCG treatment (5). Herr (16) stated that they did not use intravesical BCG therapy in their institutions and noted it as a limitation of their study. Only Tinay et al.'s (14) study was similar to ours in terms of providing maintenance BCG treatment in the Ta/HG NMIBC patient group and evaluating recurrence and progression rates, albeit with a smaller sample group.

Our study is important because it investigated the progression and recurrence rates in the Ta/HG patient group in relation to the presence of detrusor muscle, which is an unclear subject in the literature. It also is one of the rare studies conducted with a population of patients receiving BCG maintenance treatment for a minimum period of 1 year. Moreover, it is a multicenter study with the largest sample size to date. Lastly, the relatively homogeneous patient population is represented in our data.

Study Limitations

However, our study also has some limitations. These include retrospective design and the pathology reports not being interpreted by the same pathologists. The lack of a randomly allocated head-to-head study was another limitation.

Additionally, varying surgeons and surgeon experiences, the lack of genetic markers can be considered limitations.

Conclusion

Our study showed that in patients with a complete primary Ta/HG tumor treated with BCG, a second TURBT reduces the risk of progression if the detrusor muscle tissue is absent at the time of the first TURBT. If the muscle tissue is present at the first TURBT, second TURBT only increases median DFS, but does not affect progression or recurrence rates. It also showed that tumor size, presence of muscle tissue, and multiple tumors are independent factors affecting disease relapse. Further randomized trials are needed to confirm these findings.

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Ethics

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Clinical Research Ethics Committee (decision number: 2021/01-28, date: 25.01.2021)

Informed Consent: Retrospective study.

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Authorship Contributions

Concept: U.M., E.K., Design: U.M., M.Ç.Ç., B.Ö., Supervision: B.Ö., E.K., R.G.A., A.Y., Data Collection or Processing: U.M., M.Ç.Ç., E.K., M.K., S.Ç., M.Ç., O.N.Y., M.Y.Y., E.Ka., Analysis-Interpretation: U.M., M.Ç.Ç., Literature Review: U.M., Writing: U.M., M.Ç.Ç., B.Ö., Critical Review: M.Ç.Ç., B.Ö., E.K., R.G.A., A.Y.

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