Effect of Bacillus Calmette-Guérin Instillation Timing on Oncological Survivals After Transurethral Resection of Bladder Tumor

Taha Çetin, Deniz Bolat, Murat Akgül, Sertaç Yazıcı, Güven Aslan, Serkan Akan, Sümer Baltacı, Talha Müezzinoğlu, and Yıldırım Bayazıt

OBJECTIVE To investigate whether the timing of bacillus Calmette-Guerin instillation (TTBCG), which plays a key role in treating non-muscle invasive bladder cancer (NMIBC), after transurethral resection of bladder tumor (TURBT) affects oncologic outcomes.

METHODS Patient data obtained from the Urologic Cancer Database-Bladder (UroCaD-B) of Turkish Uro-oncology Association (TUOA) were evaluated. Data from 292 patients from 12 centers with primary T1HG treated with TURBT and maintenance BCG between 2003 and 2023 were retrospectively analyzed. The population was subdivided according to TTBCG, while recurrence-free survival (RFS) and progression-free survival (PFS) were estimated by log-rank tests and univariable and multivariable regression analyses.

RESULTS A total of 292 patients were followed, and 86% (n = 251) of those included in the study were male. The median duration of TTBCG was 38.5 days (19-73). The median follow-up period was 38.4 months (21.5-72.1 months). During follow-up, recurrence was detected in 55 (18.5%) patients and progression was detected in 22 (7.5%) patients. In univariate Cox regression analysis, long TTBCG (> 27.5 days) was found to have a statistically significant effect on the risk of short RFS and PFS (P = .05). BCG-related side effects were not associated with TTBCG (P = .313). Kaplan-Meier analysis showed that there was a significant difference in RFS and PFS between the TTBCG groups (P = .04, P = .011, respectively).

CONCLUSION In this retrospective non-randomized study, we showed the negative effects of BCG delay on progression and recurrence in T1HG patients. Therefore, we think that BCG should be instilled within 4 weeks after surgery. UROLOGY 197: 126–132, 2025.

Bladder cancer (BC) is the 10th most common malignancy worldwide, while it ranks sixth when only the male gender is considered.[1] Approximately 75% of patients with BC present with a disease confined to the mucosa (stage Ta, CIS) or submucosa (stage T1) and called non-muscle invasive bladder cancer (NMIBC).[2] In order to facilitate adjuvant treatment recommendations and tailor surveillance programs, NMIBC patients were stratified into risk groups based on their probability of progression to muscle-invasive disease.[3] The standard first-line treatment in the intermediate- and high-risk group is Transurethral Resection of Bladder Tumor (TURBT) followed by adjuvant intravesical bacillus Calmette-Guérin (BCG) therapy.[2]

Intravesical BCG significantly reduces the risk of progression after TURBT in patients with NMIBC who receive maintenance treatment.[4] Despite this, approximately one-third of patients with NMIBC will not respond to BCG therapy and 50% of those with an initial response will experience recurrence or progression of their disease.[5] Furthermore, BCG was shown to have many side effects that greatly affect treatment adherence. Previous reports show that over 70% of patients had some form of adverse effect with 8% of patients discontinuing BCG due to toxicity.[6]

From the Izmir University of Economics Medical Point Hospital Urology Dept., Izmir, Turkey; the Health Science University Izmir City Hospital Urology Dept, Izmir, Turkey; the Health Science University Umraniye Research and Training Hospital Urology Dept., Istanbul, Turkey; the Hacettepe University Faculty of Medicine Urology Dept. Ankara, Turkey; the Dokuz Eylul University Faculty of Medicine Urology Dept., Izmir, Turkey; the Health Science University Fatih Sultan Mehmet Research and Training Hospital Urology Dept., Istanbul, Turkey; the Ankara University Faculty of Medicine Urology Dept., Ankara, Turkey; the Celal Bayar University Faculty of Medicine Urology Dept., Manisa, Turkey; and the Cukurova University Faculty of Medicine Urology Dept., Adana, Turkey

Address correspondence to: Taha Cetin, M.D., F.E.B.U., Izmir University of Economics Medical Point Hospital Urology Dept., Izmir, Turkey.

E-mail: tahacetin88@gmail.com

Submitted: October 6, 2024, accepted (with revisions): December 2, 2024

 https://doi.org/10.1016/j.urology.2024.12.003
0090-4295

Many factors were examined to reduce side effects and intolerance while maintaining the effectiveness of BCG therapy. However, these studies mostly focused on the BCG strains, dose and schedule.[7-9] The optimal time interval from TURBT to the first dose of BCG induction therapy has not been clearly identified. Although the European Association of Urology (EAU)[2] and the National Comprehensive Cancer Network (NCCN)[10] guidelines recommend a period of 2-4 weeks from TURBT to BCG induction therapy, this time interval is based on the estimated re-epithelization time of the bladder mucosa, and it is not based on evidence.

In this research, we aimed to identify the optimal period between TURBT and the first dose of BCG induction (TTBCG). When determining this period, we also aimed to avoid side effects while maintaining the effectiveness of BCG therapy.

MATERIAL AND METHODS

We retrospectively analyzed data for 292 patients and included with primary T1HG NMIBC, with or without concomitant carcinoma in-situ (CIS) or lympho-vascular invasion (LVI) or variant histology, who received "adequate" BCG immunotherapy between 2003 and 2023 at 12 tertiary care centers. Adequate BCG treatment was defined as those who received a minimum of 5 instillations of the 6 induction courses and 2 of the 3 maintenance courses.[11] Pathological evaluation was performed in the pathology department of each institution using for staging, the Tumor, Node, Metastasis (TNM) Classification (2017, eighth edition) and the 2004 WHO classification for grading. The follow-up protocol was standardized according to EAU NMIBC guidelines. Concomitant CIS was defined as the coexistence of CIS pathology detected in the specimen together with T1HG. Perioperative chemotherapy (one-time instillation of epirubicin or mitomycin-c administered in the first 24-hour after TURBT), second TURBT, and BCG timing were left to the discretion of providers.

A total database of 7872 bladder cancer patients was analyzed. The exclusion criteria for this study were residual tumor after the first TURBT, BCG resistant variant histology (such as micropapillary, plasmacytoid and sarcomatoid) patients who did not receive adequate BCG treatment, and those with concomitant upper urinary tract carcinoma. The study data were obtained from the Research Electronic Data Capture (REDCap) electronic data tools hosted by TUOA.[12,13] REDCap is a secure, web-based software platform designed to support data capture for research studies.

Recurrence was defined as the detection of tumors of any stage or grade that were histopathologically confirmed as NMIBC during follow-up cystoscopies or imaging. Progression was defined as the development of muscle-invasive disease or invasion into the prostatic stroma. The prognostic evaluation was based on recurrence-free survival (RFS) and progression-free survival (PFS).

All procedures performed in studies involving human participants were in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. Approval for the research protocol was obtained from an Institutional Review Board: TUOUR-22-04.

Statistical Analysis

As descriptive statistics, median interquartile range: [Q1-Q3], ([IQR=Q1 and Q3]) are given for numerical variables, and number and percentage values are given for categorical variables. The conformity of the data to normal distribution was analyzed using Shapiro-Wilk test. In this study, the effects of age, gender, smoking, some clinical characteristics, laboratory and treatment methods on the occurrence of recurrence or progression in the cases were first examined using the univariate logistic regression (LR) method and the variables found to be significant were analyzed with stepwise multivariate LR (Enter method). The Kaplan-Meier (Kaplan-Meier product limit) method was used to estimate the median RFS and PFS outcomes for the cases. Univariable Cox regression and subsequently multivariate Cox regression (Enter method) models were used to determine associations between risk factors and RFS and PFS. The cut-off values for recurrence and progression based on the time between TURBT and BCG was determined by the ROC curve method. SPSS Windows version 25 (SPSS Inc., Chicago, IL, USA) package program was used for statistical analysis.

RESULTS

This multicenter study followed 292 patients. Of those included in the study, 86% (n = 251) were male. The median age (IQR) was 65 years[60-70] and the median BMI (IQR) was 26.5 (24.5-29.3). The median duration (IQR) of TTBCG was 38.5 days,[19-73] with a minimum of 3 days and a maximum of 364 days. While the primary endpoints of the study were RFS and PFS, the secondary endpoint was BCG-related side effects. The median follow-up period was 38.4 months (21.5-72.1 months). Descriptive statistics for the complete cohort are shared in Table 1. Some patients were found to have no muscle tissue in their first TURBT pathologies, but a second TURBT was performed for all these patients to minimize the risk of possible downgrade.

The prognostic value of clinical and socio-demographic characteristics on the risk of RFS was analyzed (Table 2). In univariate Cox regression analysis; long TTBCG (> 27.5 days), not receiving maintenance BCG, tumor multifocality, tumor size larger than 3 cm, presence of variant histology, prostatic urethra involvement, muscle tissue in the specimen and lympho-vascular invasion were found to have statistically significant effect on the risk of short RFS ($P < .05$). Multivariate stepwise

Table 1. Descriptive statistics for the complete cohort.

Patient Characteristics	
	(n = 292)
Age M [IQR]	65 [60-70]
BMI M [IQR]	26,5 [3,5-29]
TTBCG M [IQR]	38,5 [19-73]
Follow-up M [IQR]	38,4 [1,8-72]
Gender n (%)	
Male	251 (86)
Female	41 (14)
Maintenance n (%)	
Received	175 (59,9)
Not received	117 (40,1)
Smoking n (%)	
Current	153 (52,4)
Ex Smoker	38 (13)
Never	101 (34,6)
Multifocality n (%)	
Unifocal	153 (52,4)
Multifocal	139 (47,6)
Tumor size n (%)	
< 1 cm	61 (24,6)
1-3cm	138 (55,6)
> 3 cm	49 (19,8)
TUR-MT n (%)	
Incomplete	13 (4,5)
Complete	279 (95,5)
Prostatic urethra involvement N (%)	
Yes	15 (5,1)
No	277 (94,9)
Variant Histology n (%)	
Yes	39 (13,4)
No	253 (86,6)
Concomittant CIS n (%)	
Yes	56 (19,2)
No	236 (80,8)
Muscle presence in Specimen n (%)	
Yes	115 (40,2)
No	171 (59,8)
Lymphovascular Invasion n (%)	
Yes	13 (4,5)
No	279 (95,5)
Perioperative Chemotherapy n (%)	
Var	22 (7,5)
Yok	270 (92,5)
Re Tur-MT history	
Yes	246 (84,2)
No	46 (15,8)
BCG side effect n(%)	
Yes	81 (31,8)
No	174 (68,2)
Recurrence n(%)	
Yes	54 (18,5)
No	238 (81,5)
Progression n(%)	
Yes	22 (7,5)
No	270 (92,5)

(Enter method) Cox regression analysis showed that patients who did not receive maintenance BCG treatment had 2.437 (95% CI: 1.137-5.226) times shorter RFS (P = .022). Patients with tumor size greater than 3 cm had 2.387 (95% CI: 1.033-5.512) times shorter RFS (P = .042). Patients with variant histology had 3.12 (95% CI: 1.351-7.207) times shorter RFS compared to patients without variant histology, and patients with prostatic urethra involvement had 3.169 (95% CI: 1.035-9.705) times shorter RFS compared to patients without variant histology. In the presence of lympho-vascular invasion, the risk of RFS was 3.034 (95% CI: 1.120-8.213) times shorter than in the absence of invasion (P < .05).

The prognostic value of clinical and socio-demographic characteristics on the risk of short PFS was analyzed (Table 3). In univariate Cox regression analysis, long TTBCG (> 32.5 days), multifocality of the tumor, tumor size greater than 3 cm, presence of variant histology, and concomitant CIS had a statistically significant effect on the risk of short PFS (P < .05). Multivariate stepwise (Enter method) Cox regression analysis showed that patients with multifocal tumors had 4.507 (%95 CI: 1,299-15,635 times shorter PFS risk (P = .018). Tumor size larger than 3 cm was associated with 6.004 (95% CI: 1.003-35.956) times shorter PFS (P = .049). In addition, the risk of PFS was 3.736 (95% CI: 1.032-13.518) times shorter in cases with variant histology and 2.993 (95% CI: 1.035-8.659) times shorter in cases had concomitant CIS (P = .045 and P = .043, respectively).

Univariate LR analysis showed that age, prolonged TTBCG, not receiving maintenance therapy, large tumor size, prostatic urethra involvement, and lympho-vascular invasion were statistically significant risk factors for recurrence (P < .05). Patients over 65 years of age had 1.91-fold (95% CI: 1.021-3.572) increased risk of recurrence compared to patients of younger ages (P = .043), a 1 day increase in the time from TURBT to BCG increased the risk of recurrence 1.006-fold (95% CI: 11.000-1.012) (P = .034), patients who did not receive maintenance had 1.95-fold (95% CI: 1.021-3.730) increased risk of recurrence compared to patients who received maintenance (P = .044), and patients with tumor size greater than 3 cm had 2.709-fold (%95 CI: 1104-6647) (P = .004) increased risk of recurrence compared to patients with tumor size of 1 cm or less. The risk of recurrence increased 4.282-fold (%95 CI: 1481-12,381) (P = .007) in cases with prostatic urethra involvement, while lympho-vascular invasion increased the risk of recurrence 4.125-fold (95% CI: 1.327-12.819) (P = .014) (Table 4).

Before analyzing RFS and PFS with TTBCG, the value with the highest specificity was determined by ROC analysis. This value was 27.5 days for recurrence (AUC: 0.526 Sensitivity: 70.4%, Specificity: 40.8%, P = .544) and 32.5 days for progression (AUC: 0.563 Sensitivity: 72.3%, Specificity: 45.6%, P = .323).

A total of 292 TURBT patients were divided into 2 groups according to the median value (27.5) of TTBCG and Kaplan-Meier curve analysis was performed. When the Kaplan-Meier curves were compared according to the log rank test, the median RFS for short TTBCG (< 27.5)

Table 2. Univariate and multivariate Cox regression analysis for RFS after BCG therapy.

	Univariable		Multivariable	
Variable	HR (95% CI)	p	HR (95% CI)	*P*
Age > 65 (ref:≤65 years old)	1,105 (0,611-1,999)	.741		
TTBCG (cont. variable)	1,005 (1,002-1,009)	**.003**		
TTBCG (Ref. < 27.5 days)	2,382 (1,307-4,343)	**.005**	1,769 (0,847-3,695)	.129
Male (ref: Female)	0,977 (0,441-2,163)	.995		
BMI > 26.5 (ref:≤26.5 kg/cm2)	1,836 (0,972-3,469)	.061		
Not received Maintenance BCG (ref:received)	3,119 (1,633-5,958)	**.001**	2,437 (1,137-5,226)	**.022**
Smoking current/past (ref:never)	1,105 (0,629-1,942)	.728		
Tumor Multifocality (ref:focal)	1,726 (1,003-2,972)	**.040**	1,724 (0,892-3,331)	.105
Tumor size (ref: < 1cm)	1	**< .001**		**< .001**
1-3 cm	0,666 (0,302-1,471)	.315	0,487 (0,209-1,138)	.097
> 3 cm	2,683 (1,226-5,870)	**.014**	2,387 (1,033-5,512)	**.042**
Tur BT: Complete (ref:Incomplete)	1,284 (0,312-5,286)	.729		
Presence of Variant Histology (Ref. no)	1,985 (1,019-3,869)	**.044**	3,120 (1,351-7,207)	**.008**
Prostatic urethra involvement yes (ref:no)	4,285 (1,916-9,585)	**< .001**	3,169 (1,035-9,705)	**.043**
CIS present (Ref. no)	1,789 (0,983-3,256)	.057		
Muscle presence in Specimen (Ref. No)	2,706 (1,498-4,888)	**.001**	1,677 (0,796-3,535)	.174
Lymphovascular Invasion (Ref. No)	3,990 (1,689-9,423)	**.002**	3,034 (1,120-8,213)	**.029**
Perioperative Chemotherapy (Ref. No)	0,573 (0,178-1,848)	.352		
Second TUR-BT yes (ref:No)	0,846 (0,396-1,809)	.667		
Side Effect present (Ref. No)	1,194 (0,668-2,132)	.550		

HR, hazard ratio, CI, confidence interval

Table 3. Univariate and multivariate Cox regression analysis for PFS after BCG therapy.

	Univariable COX Reg.		Multivariable COX Reg.	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Age > 65 (ref:≤65 years old)	1,427 (0,532-3,829)	.480		
TTBCG (cont. variable)	1,004 (0,997-1,011)	.284		
TTBCG (Ref. < 32.5 days)	3,472 (1,266-9,524)	**.016**	3,837 (0,928-15,874)	.063
Male (ref: Female)	1,522 (0,514-4,505)	.448		
BMI > 26.5 (ref:≤26.5 kg/cm2)	0,604 (0,237-1,537)	.290		
Not received Maintenance BCG (ref:received)	1,838 (0,736-4,586)	.192		
Smoking current/past (ref:never)	1,610 (0,620-4,177)	.328		
Tumor Multifocality (ref:focal)	2,437 (1,007-5,900)	**.048**	4,507 (1,299-15,635)	**.018**
Tumor size (ref: < 1cm)	1	**.037**		**.050**
1-3 cm	2,003 (0,432-9,290)	.375	1,641 (0,286-9,404)	.578
> 3 cm	4,964 (1,010-24,724)	**.048**	6,004 (1,003-35,956)	**.049**
Tur BT: Complete (ref:Incomplete)	21,675 (0,003-1690,154)	.499		
Presence of Variant Histology (Ref. no)	3,502 (1,420-8,638)	**.007**	3,736 (1,032-13,518)	**.045**
Prostatic urethra involvement yes (Ref:no)	2,460 (0,567-10,676)	.229		
CIS present (Ref. no)	2,717 (1,120-6,590)	**.027**	2,993 (1,035-8,659)	**.043**
Muscle presence in Specimen (Ref. Yes)	2,637 (1,007-6,901)	**.048**	1,981 (0,232-16,912)	.532
Lymphovascular Invasion (Ref. No)	2,783 (0,639-12,126)	.173		
Perioperative Chemotherapy (Ref. No)	0,426 (0,056-3,211)	.407		
Second TUR-BT yes (ref:No)	3,060 (0,408-22,954)	.277		
Side Effect present (Ref. No)	1,044 (0,425-2,565)	.925		

HR, hazard ratio; CI, confidence interval

was estimated as 185.52 months (95% CI, 155.70-215.34 months), while the median RFS for long TTBCG (> 27.5) was estimated as 121.47 months (95% CI, 67.62-175.31 months) (log rank P = .004). Prolonged TTBCG was associated with worse RFS (Fig. 1).

In addition, the median value for progression for TTBCG was determined and found to be 32.5 days. Kaplan-Meier curve analysis was performed by dividing patients into 2 groups according to the median value (32.5). When the Kaplan-Meier curves were compared according to the log rank test, the median PFS for low TTBCG (< 32.5) was estimated as 227.55 months (95% CI, 207.12-247.99 months) and the median PFS for high TTBCG (> 32.5) was estimated as 141.40 months (95% CI, 112.22-150.4 months) (log rank P = .011) (Fig. 1).

DISCUSSION

BCG therapy is used as a cornerstone treatment for intermediate-high risk NMIBC patients. Until today,

Table 4. Univariate logistic regression for recurrence.

	Univariable LR		Multivariable LR	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*
Age > 65 (ref:≤65 years old)	1,910 (1,021-3,572)	**.043**	0,508 (0,240-1,078)	.078
TTBCG (cont. variable)	1,006 (1,000-1,012)	**.034**	1,004 (0,997-1,010)	.244
TTBCG (Ref. < 32.5 days)	1,632 (0,863-3,095)	.132		
Male (ref: Female)	0,894 (0,373-2,140)	.801		
BMI > 26.5 (ref:≤26.5 kg/cm2)	1,687 (0,832-3,425)	.147		
Not received Maintenance BCG (ref:received)	1,950 (1,020-3,730)	**.044**	1,644 (0,767-3,522)	.201
Smoking current/past (ref:never)	0,967 (0,521-1,799)	.919		
Tumor Multifocality (ref:focal)	1,479 (0,817-2,680)	.196		
Tumor size (ref: < 1cm)	1	**.002**	1	.051
1-3 cm	0,669 (0,284-1,573)	.357	0,451 (0,182-1,119)	.086
> 3 cm	2,709 (1,104-6,647)	**.030**	1,474 (0,543-4,000)	.446
Tur BT: Complete (ref:Incomplete)	1,260 (0,271-5,856)	.768		
Presence of Variant Histology (Ref. no)	1,919 (0,888-4,147)	.098		
Prostatic urethra involvement yes (Ref:no)	4,282 (1,481-12,381)	**.007**	2,744 (0,651-11,574)	.169
CIS present (Ref. no)	1,848 (0,933-3,662)	.078		
Muscle presence in Specimen (Ref. No)	1,622 (0,878-2,996)	.122		
Lymphovascular Invasion (Ref. No)	4,125 (1,327-12,819)	**.014**	2,510 (0,669-9,416)	.173
Perioperative Chemotherapy (Ref. No)	0,678 (0,193-2,379)	.544		
Second TUR-BT yes (ref:No)	1,092 (0,478-2,498)	.834		
Side Effect (Ref. No)	1,018 (0,532-1,948)	.956		

OR, odds ratio; LR, logistic regression.

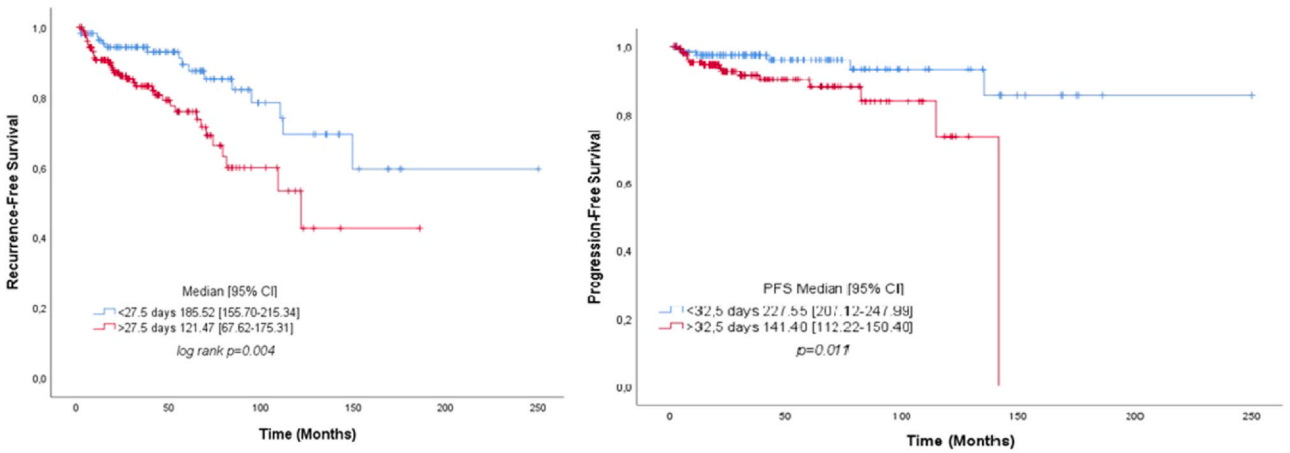

Figure 1. Curves for recurrence-free survival and progression free survival for BCG instillation timing.

several studies aimed to investigate different strains, dose amounts, administration schedules and treatment combinations to improve BCG efficacy and tolerance.[14-16] However, the timing of the first instillation is still unclear. Guidelines recommend starting BCG treatment 2-3 weeks after surgery.[2,17] The time between surgery and BCG administration is known to have poor oncologic outcomes.[18] However, the duration of pathological evaluation, the need for second TURBT, the insurance status of the patient, difficulties in BCG transportation, and the impossibility of starting BCG immunotherapy within 2 weeks are factors for many patients.

The first study in the literature about the efficacy and side effects of the time between TURBT and the first dose of BCG induction is the study by Hensley et al. In this study, 518 patients receiving "adequate" BCG treatment were evaluated and it was emphasized that early or late BCG administration had no effect on recurrence and progression and tolerability was not different between the groups.[19] In another study, Cai et al. evaluated 403 patients and found that giving the first dose of BCG after 4 weeks tended to have worse outcomes and giving it before 2 weeks showed more adverse effects.[20] The urothelial carcinoma working group study by the European Association of Urology-Young Academic Urologists (EAU-YAU) examined 429 patients from 13 centers and showed that the risk of recurrence and progression was dependent on TTBCG. The risk of progression increased gradually until about 18 weeks for TTBCG. In the recurrence analysis, the increase in risk was similar to that seen in the progression analysis; however, no specific change point was found. However,

in the analysis of patients, the basis for the mean value of TTBCG was 101 days and when recurrence was analyzed according to this value, the risk of recurrence statistically increased after 101 days.[21]

To determine the TTBCG in this multicenter study, we first assessed by quartiles. Quarter periods Q1: 3-19 days, Q2: 20-39 days, Q3: 40-73 days and Q4: 74-364 days. When patients were evaluated according to these quartiles, no significant difference was observed between groups in logistic regression, Cox regression and Kaplan Meier survival estimation analysis ($P = .297$). Then, empiric periods for TTBCG were determined. TTBCG was categorized as < 2 weeks, 2-4 weeks, 4-6 weeks, 6-8 weeks and > 8 weeks and statistically significant differences were not found for PFS and RFS estimates according to log rank test ($P = .148$). ROC analysis was performed to find a significant change point and the basis of the mean value was determined as 27.5 days for recurrence and 32.5 days for progression. As a result of our study, TTBCG longer than 27.5 days was shown to be a risk for recurrence and longer than 32.5 days was shown to be a risk for progression.

BCG side effects may be more frequent and serious than other intravesical chemotherapy treatments.[22] These side effects may be cystitis-related symptoms such as hematuria, dysuria or life-threatening sepsis. Fortunately, the incidence of sepsis was reported to be less than 1%.[23,24] Waiting for the completion of epithelialization of the bladder wall is thought to reduce side effects. It is recommended to wait at least 2 weeks after surgery to avoid serious adverse effects.[25] However, it is thought that this 2-week period is a traditional time frame and does not have strong literature support. Contradictory results in terms of side effects continue to be reported in the literature. Although there are data indicating that administration before 2 weeks increases side effects, results indicating that early administration is not different from late administration were also reported.[19,20] In our study, the relationship between BCG intolerance and TTBCG could not be demonstrated (both median value and quartile periods).

Our study has some limitations. First of all, the fact that it was a multicenter study, although there was a guideline-based follow-up and treatment protocol, patient characteristics and personal preferences of the centers and physicians may have had an impact on the method and duration of BCG application. In addition, the fact that the pathological evaluation was not performed in a single center and the heterogeneity in the distribution of data due to the nature of the retrospective study can be shown as limitations. We believe that stronger data will be obtained through well-designed prospective studies.

In conclusion, it was shown that the time between TURBT and the first dose of BCG induction has an effect on recurrence and progression in high-risk NMIBC. There was no difference in early or late application in terms of side effects. Therefore, we recommend that the first dose of BCG be administered within the first 4 weeks after surgery in high-risk NMIBC patients.

Ethical Declarations

Approval of the research protocol by an Institutional Reviewer Board: TUO-UR-22-04 Turkish uro-oncology association project approve number.

Disclosures

The authors declare that they have no relevant financial interests.

CRediT Authorship Contribution Statement

Sertac Yazıcı: Data curation. Murat Akgül: Investigation, Data curation. Serkan Akan: Investigation. Güven Aslan: Supervision. Talha Müezzinoğlu: Data curation. Sumer Baltacı: Supervision. Yıldırım Bayazıt: Supervision. Deniz Bolat: Writing—review and editing, Methodology, Conceptualization. Taha Cetin: Writing—original draft, Conceptualization.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

Acknowledgments

The authors thank Prof. Sinan Sozen, Prof. Ozan Bozkurt, Prof. Volkan Izol, and Turkish Urooncology Association members for sharing data with us.

Informed Consent

Informed consent was obtained from all patients before the procedure.

Registry and the Registration No. of the Study/trial

N/A.

Animal Studies

N/A.

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