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Significance of the interval between first and second transurethral resection on recurrence and progression rates in patients with high-risk non-muscle-invasive bladder cancer treated with maintenance intravesical Bacillus Calmette-Guérin

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Objectives

To evaluate the effect of the interval between the initial and second transurethral resection (TUR) on the outcome of patients with high-risk non-muscle-invasive bladder cancer (NMIBC) treated with maintenance intravesical Bacillus Calmette-Guérin (BCG) therapy.

Patients and Methods

We reviewed the data of patients from 10 centres treated for high-risk NMIBC between 2005 and 2012. Patients without a diagnosis of muscle-invasive cancer on second TUR performed ≤90 days after a complete first TUR, and received at least 1 year of maintenance BCG were included in this study. The interval between first and second TUR in addition to other parameters were recorded. Multivariate logistic regression analysis was used to identify predictors of recurrence and progression.

Results

In all, 242 patients were included. The mean (SD, range) follow-up was 29.4 (22.2, 12–96) months. The 3-year recurrence- and progression-free survival rates of patients who underwent second TUR between 14 and 42 days and 43–90 days were 73.6% vs 46.2% ($P < 0.001$) and 89.1% vs 79.1% ($P = 0.006$), respectively. On multivariate analysis, the interval to second TUR was found to be a predictor of both recurrence [odds ratio (OR) 3.598, 95% confidence interval (CI) 1.885–8.137; $P = 0.001$] and progression (OR 2.144, 95% CI 1.447–5.137; $P = 0.003$).

Conclusions

The interval between first and second TUR should be ≤42 days in order to attain lower recurrence and progression rates. To our knowledge, this is the first study demonstrating the effect of the interval between first and second TUR on patient outcomes.

Keywords

non-muscle-invasive bladder cancer, second transurethral resection, Bacillus Calmette-Guérin, maintenance Bacillus Calmette-Guérin

Introduction

Bladder cancer is the second most common malignancy of urinary system and non-muscle-invasive bladder cancer (NMIBC) accounts for ≈75% of the cases [1]. In patients with high-risk NMIBC, most studies showed a reduction in the risk of progression with intravesical BCG including a maintenance schedule after a six weekly induction. Although the optimal duration of maintenance instillations is controversial, European Association of Urology (EAU) guidelines, based on a recently published European Organisation for the Research and Treatment of Cancer (EORTC) trial recommended 1–3 years of full-dose maintenance BCG, in patients with high-risk tumours if

radical cystectomy is not considered [1,2]. Also, recurrence and progression rates are significantly associated with a second transurethral resection (TUR) [3–5]. In a recently published review on clinical value of second TUR, the authors reported that this procedure improves staging and reduces recurrence, as well as progression rates of high-risk NMIBC [4]. Although there is no consensus about the strategy and timing of second TUR, EAU guidelines, as well as many other publications, recommend that it should be performed within 14–42 days after initial TUR [1,4–6]. However, this interval appears empirical, as the current literature lacks any evidence to support this interval or to what extent a second TUR can safely be delayed. To our knowledge, there is no clinical trial comparing the effect of 14–42 days or longer intervals between first and second TUR, on tumour recurrence and progression during follow-up.

In this retrospective multicentre trial, we aimed to identify the effect of the interval between the initial and second TUR on recurrence and progression rates in a population of high-risk NMIBC treated with maintenance BCG therapy.

Patients and Methods

The study was planned and performed by bladder cancer study group of Association of Uro-oncology in Turkey. Retrospective data of patients treated for high-risk NMIBC between 2005 and 2012, who received induction BCG and at least 1 year of maintenance BCG, were collected from 10 participating centres.

Patients were included if; (i) a high-grade Ta or any T1 urothelial carcinoma with or without carcinoma *in situ* (CIS) was present in the first TUR specimen, (ii) a complete first TUR of bladder carcinoma and second TUR was performed, (iii) patients received six weekly instillations of BCG therapy and at least 1 year of maintenance BCG therapy, and (iv) at least 12 months of follow-up after completion of maintenance BCG. Patients with a histology other than urothelial carcinoma, incomplete resection at initial TUR, a diagnosis of muscle-invasive cancer on second TUR, an interval between first and second TUR of >90 days, and those who did not complete 1 year of maintenance therapy were excluded. During second TUR aggressive resection of all visible and suspected tumours with adequate sampling of muscle layer was performed. Patients were assessed with cystoscopy, cytology and tumour resection, as indicated every 3 months for the first 2 years and then biannually for a minimum of 5 years, and annually thereafter. Progression was defined as an increase in pathological stage (Ta to T1 or T1 to T2).

Demographic characteristics of the patients such as age, gender, and parameters related to bladder tumour such as tumour grade, T stage, concomitant CIS, primary or recurrent tumour, number of tumours, main tumour size, application of early single-dose intravesical chemotherapy, recurrence, and progression were recorded.

The time lapse to second TUR and its association with recurrence-free survival (RFS) and progression-free survival (PFS) rates was the primary outcome measure of the study. As a secondary outcome measure predictors of recurrence and progression were also analysed.

To assess the effect of the interval between first and second TUR on tumour recurrence and progression rates, patients were divided into four groups. The interval in respective groups was; Group 1: 14–28 days, Group 2: 29–42 days, Group 3: 43–56 days, and Group 4: 57–90 days. Separate analysis was also performed for patients who had second TUR at ≤42 and >42 days (Group A and Group B). The interval between first and second TUR was investigated as a categorical variable in RFS and PFS analysis; however, it is investigated as a continuous variable in the multivariate analysis for recurrence and progression.

Statistical analysis was performed with SPSS version 20.0 (Chicago, IL, USA). The chi-square test was used to compare categorical variables and the Student's *t*-test and ANOVA were used for continuous variables of the groups based on time to re-TUR. Univariate and multivariate logistic regression analyses were performed to identify predictors of recurrence and progression. Kaplan–Meier curves were constructed for RFS and PFS and groups were compared with the log–rank test. A $P < 0.05$ was considered to indicate statistical significance.

Results

Of 264 retrospectively evaluated patients, 242 patients fulfilled the inclusion criteria. Of the 22 excluded patients, 13 were due to incomplete initial TUR, six had an interval between first and second TUR of >90 days, two had histology other than urothelial cancer, and one had a short follow-up (<6 months) after completion of BCG. The mean (SD) age of study population was 64.7 (10.7) years and the mean (SD, range) follow-up was 29.4 (22.2, 12–96) months, without a significant difference between the groups. Of our patients, 212 (87.6%) were male and 30 (12.4%) were female. Stage Ta and T1 tumours were present in 40 (16.5%) and 202 (83.5%) patients, respectively and concomitant CIS was present in 19 patients. High-grade tumours were present in 214 (88.4%) patients and immediate postoperative single-dose intravesical chemotherapeutic instillation was given to 162 (66.9%) patients. Pathological evaluation of the surgical specimens of the second TUR revealed NMIBC in 104 (42.9%) patients and 53 (50.9%) of them were stage T1 disease.

The mean (SD, range) time to second TUR was 42.5 (18.1, 14–90) days. The number of patients who underwent a second TUR within 14–28 days (Group 1), 29–42 days (Group 2), 43–56 days (Group 3) and 57–90 days (Group 4)

were 50, 90, 49 and 53, respectively. There were no differences between the groups in age, sex, T stage, concomitant CIS, tumour grade, largest tumour diameter, tumour multiplicity, tumour status (primary, recurrent) or instillation of immediate postoperative intravesical chemotherapy (all $P > 0.05$; Table 1). However, patients in Group B had a higher incidence of tumour in the second TUR compared with patients in Group A [49/140 (35%) patients vs 55/102 (53.9%) patients, $P = 0.004$].

During the follow-up, 35 (14.5%) patients underwent radical cystectomy or radiation therapy (with or without chemotherapy). In Groups A and B, 14 (10%) and 21 (20.6%) patients received such treatment and the difference was statistically significant ($P = 0.026$). When the four groups were compared, two (4%), 12 (13.3%), five (10.2%) and 16 (30.2%) patients in Groups 1, 2, 3 and 4 respectively, underwent radical cystectomy or radiation therapy. Patients in Group 4 received a significantly higher rate of such treatment compared with the other three groups ($P = 0.001$). The differences between the other three groups was not statistically significant.

Survival Analysis

The 3-year RFS rates of the patients were 64.6%, 70.4%, 53.2% and 42.6% in Groups 1, 2, 3 and 4, respectively ($P < 0.001$; Fig. 1a). Although there was no significant difference between Groups 1 and 2 ($P = 0.445$), and 3 and 4 ($P = 0.642$), statistically significant differences were found between Groups 1 and 3 ($P = 0.009$), 1 and 4 ($P = 0.001$), 2 and 3 ($P = 0.039$), and 2 and 4 ($P = 0.008$). When we performed a separate analysis by dividing patients into two groups based on the interval between first and second TUR (Group A; ≤42 days and Group B; >42 days), recurrence was observed in 34 of the 140 (24.3%) Group A patients, and 40 of the 102 (39.2%) Group B patients ($P = 0.016$). The 3-year RFS rates of patients in Group A and B were 73.6% and 46.2%, respectively ($P < 0.001$; Fig. 1b).

The 3-year PFS rates of the patients were 87.9%, 78.7%, 68.6% and 60.1% in Groups 1, 2, 3 and 4, respectively ($P = 0.05$; Fig. 2a). There was no significant difference between Groups 1 and 2 ($P = 0.733$), and 3 and 4 ($P = 0.833$); however, there were statistically significant differences between Groups 1 and 3 ($P = 0.035$), 1 and 4 ($P = 0028$), 2 and 3 ($P = 0.044$), and 2 and 4 ($P = 0.039$). In a separate analysis of patients with an interval of ≤42 days (Group A) and >42 days (Group B), there was progression in 12 of the 140 (8.6%) Group A patients, and 18 of the 102 (17.6%) Group B patients ($P = 0.034$). The 3-year PFS rates of patients in Group A and B were 89.1% and 79.1%, respectively ($P = 0.006$; Fig. 2b).

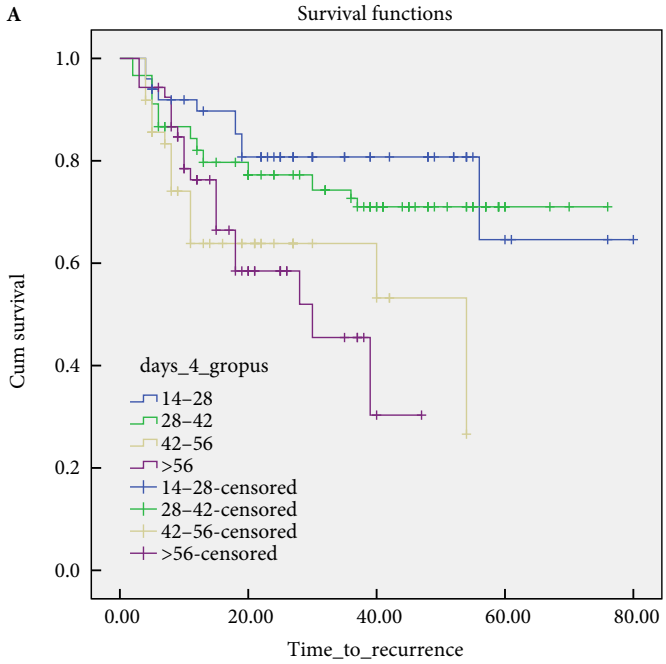
On univariate analysis tumour grade [odds ratio (OR) 3.107, 95% CI 1.724–7918, $P < 0.001$), concomitant CIS (OR 1.933, 95% CI 1.302–5.267, $P = 0.001$) and interval to second TUR (OR 4.878, 95% CI 2.254–9.966, $P < 0.001$) were associated with higher risk of recurrence. Tumour grade (OR 2.221, 95% CI 1.488–6.178, $P = 0.002$) and interval to second TUR (OR 3.078, 95% CI 1.881–7.043, $P < 0.001$) were identified as predictors of progression on univariate analysis.

On multivariate analysis tumour grade (OR 2.533, 95% CI 1.121–5822, $P = 0.003$), concomitant CIS (OR 1.534, 95% CI 1.078–2.544, $P = 0.008$) and interval to second TUR (OR 3.227, 95% CI 1.655–8.437, $P = 0.001$) were detected as predictors of recurrence (Table 2). We also identified tumour grade (OR 1.664, 95% CI 1.108–3.118, $P = 0.006$) and interval

Table 1 Baseline patient characteristics of four patient groups according to the interval between first and second TUR.

Variable	Groups according to the interval between first and second TUR							
	Group 1 14–28 days	Group 2 29–42 days	Group 3 43–56 days	Group 4 57–90 days	*P*	Group A 14–42 days	Group B 43–90 days	*P*
Number of patients	50	90	49	53		140	102	
Mean (SD) age, years	64.8 (9.5)	61.1 (12.3)	66 (9.8)	64.6 (9.9)	0.798	62.4 (10.5)	65.2 (9.8)	0.657
Sex, *n* (%)								
Male	44 (88)	79 (87.8)	46 (93.9)	43 (81.1)	0.280	123 (87.8)	89 (87.2)	0.888
Female	6 (12)	11 (12.2)	3 (6.1)	10 (18.9)		17 (12.2)	13 (12.8)	
Stage, *n* (%)								
Ta	5 (10)	15 (16.7)	8(16.3)	12 (22.6)	0.394	20 (14.3)	20 (19.6)	0.271
T1	45 (90)	75 (83.3)	41 (83.7)	41 (77.4)		120 (85.7)	82 (80.4)	
Concomitant CIS, *n* (%)	4 (8)	6 (6.6)	4 (8.1)	5 (9.4)	0.544	10 (7.1)	9 (8.8)	0.631
High grade tumour, *n* (%)	46 (92.6)	76 (84.4)	46 (93.9)	46 (86.8)	0.311	122 (87.1)	92 (90.2)	0.463
Mean (SD) tumour size, cm	2.89 (1.5)	2.49 (1.2)	2.83 (1.2)	2.79 (1.3)	0.264	2.63 (1.4)	2.81 (1.2)	0.488
Patients with multiple tumours, *n* (%)	13 (26)	26 (28.9)	14 (28.6)	20 (37.7)	0.576	39 (27.8)	34 (33.3)	0.359
Patients with primary tumours, *n* (%)	42 (84)	78 (86.7)	40 (81.6)	47 (88.7)	0.749	120 (85.7)	87 (85.3)	0.926
Immediate postoperative intravesical chemotherapy, *n* (%)	30 (60)	56 (62.2)	33 (67.3)	33 (62.2)	0.498	86 (61.4)	66 (64.7)	0.602

Fig. 1 Kaplan–Meier curves of the RFS rates for the groups. (**A**) according to the four interval from first to second TUR groups (Group 1, 14–28 days; Group 2, 29–42 days; Group 3, 43–56 days; Group 4, 57–90 days). (**B**) according to the two interval from first to second TUR groups (Group A, ≤42 days; Group B, >42 days).



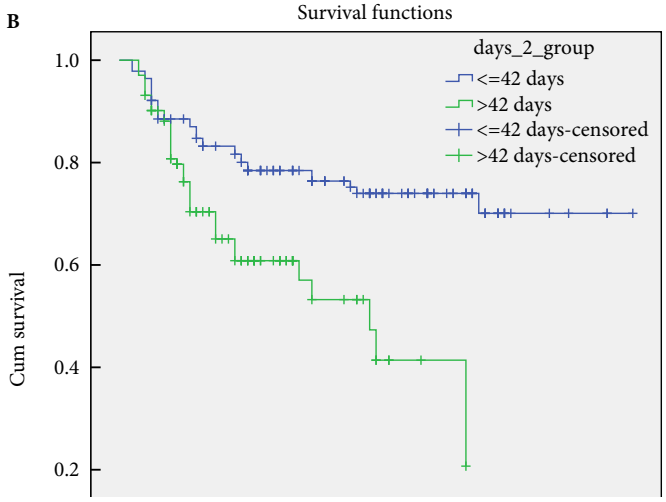
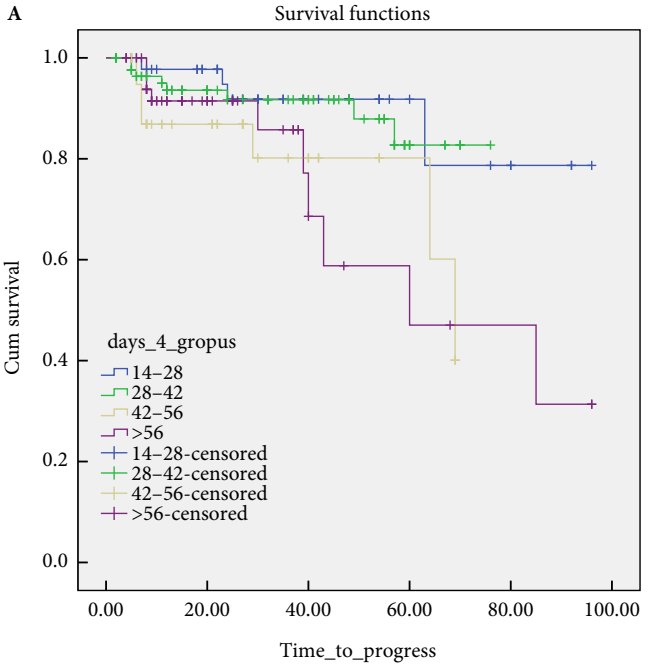
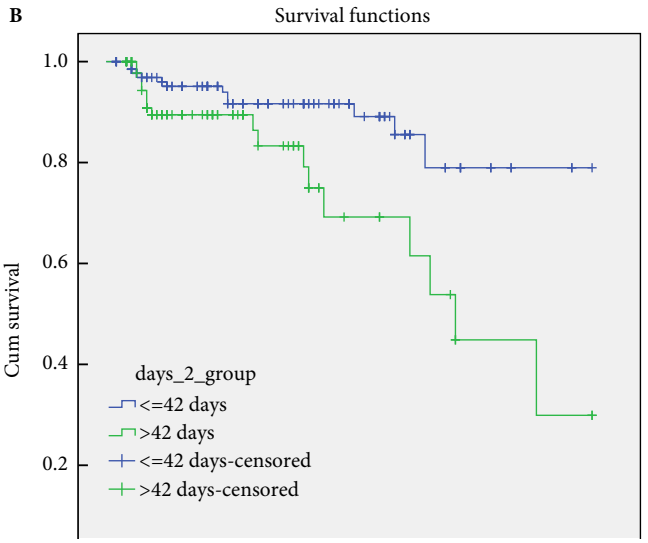


Fig. 2 Kaplan–Meier curves of the PFS rates for the groups. (**A**) according to the four interval from first to second TUR groups (Group 1, 14–28 days; Group 2, 29–42 days; Group 3, 43–56 days; Group 4, 57–90 days). (**B**) according to the two interval from first to second TUR groups (Group A, ≤42 days; Group B, >42 days).





to second TUR (OR 1.877, 95% CI 1.297–4.197, $P = 0.003$) as predictors of progression on multivariate analysis (Table 3).

Discussion

After an apparently complete initial TUR, a second TUR is recommended in patients with high-risk NMIBC to improve staging accuracy and resection of residual tumours [1,3–5,7]. In patients who had no muscle-invasive disease on second TUR, maintenance BCG is the mainstay of further treatment [1,8–10]. Although many studies showed that a second TUR improves patient outcomes, appropriate timing for performing such an effective and important procedure is not well established. Review of the literature concerning the timing of a second TUR reveals a large variation ranging from an immediate second TUR to 3 months after the initial TUR [11,12]. Even in the recent EAU guidelines, it is stated that, there is no consensus about the strategy and timing of second TUR and it is mostly recommended within

Table 2 Multivariate analysis according to recurrence.

Variables	OR	95% CI	P
Age	1.066	0.455–1.856	0.844
Sex	1.147	0.792–2.889	0.814
Stage (Ta vs T1)	1.399	0.680–3.102	0.428
Grade (low vs high)	2.533	1.121–5.822	0.003
Concomitant CIS	1.534	1.078–2.544	0.008
Size	1.225	0.556–2.487	0.788
Immediate postoperative intravesical chemotherapy	1.266	0.603–2.655	0.781
Tumour status (primary vs recurrent)	1.205	0.497–2.667	0.821
Tumour focality (solitary vs multiple)	1.115	0.398–2.012	0.838
Interval to second TUR	3.227	1.655–8.437	0.001

Table 3 Multivariate analysis according to progression.

Variables	OR	95% CI	P
Age	1.007	0.326–1.174	0.997
Sex	1.047	0.555–1.872	0.866
Stage (Ta vs T1)	1.148	0.677–1.842	0.808
Grade (high vs low)	1.664	1.108–3.118	0.006
Concomitant CIS	1.209	0.804–2.114	0.572
Size	1.015	0.417–1.887	0.894
Immediate postoperative intravesical chemotherapy	1.107	0.571–1.874	0.667
Tumour status (primary vs recurrent)	1.117	0.566–1.997	0.821
Tumour focality (solitary vs multiple)	1.085	0.381–1.884	0.965
Interval to second TUR	1.877	1.297–4.197	0.003

14–42 days after initial TUR [1]. In our present study, a second TUR was performed within 14–42 days after the initial TUR in 140 (57.8%) of the 242 patients and it was performed from 43–90 days in the remaining 102 (42.2%) patients. Residual tumour was detected in 104 of 242 (42.9%) patients at the second TUR. This finding is concordant with the results of previous studies, as residual cancer can be found in 20–78% of cases on a second TUR [3,4,13]. The risk of residual tumour is reported to be higher in patients with multiple and/or high-grade tumours [6]. The quality of the first TUR and the stage of the original tumour (Ta or T1) may also affect the risk of residual tumour [6,14]. Thus, a second TUR should first strongly be encouraged at least for elimination of residual tumours in high-risk NMIBC cases.

Although second TUR is recommended within 14–42 days after initial TUR [1,3,4], the effect of the time lapse between the first and second TUR on tumour recurrence and progression rates have not been investigated previously. To our knowledge, this is the first study that evaluates the effect of the interval between first and second TUR on tumour recurrence and progression rates in a population of high-risk NMIBC treated with maintenance BCG therapy. In our present study, there was recurrence in 30.6% of the patients during follow-up. Patients who underwent a second TUR within 14–42 days had a significantly lower recurrence rate of 24.3% compared with 39.2% in those who underwent second TUR within 43–90 days ($P = 0.016$). The 3-year RFS rates were also significantly better in patients who had a second TUR within 14–42 days compared with patients who had a second TUR at >42 days (73.6% vs 46.2%, $P < 0.001$). When we evaluated the recurrence rates after dividing patients into four groups according to the interval between the first and second TUR, there was no significant difference in 3-year RFS rates between those patients who had a second TUR within 14–28 and 29–42 days ($P = 0.445$). On the other hand, patients who had a second TUR either within 14–28 or 29–42 days had significantly better 3-year RFS rates compared with patients who had a second TUR within 43–56 days ($P = 0.009$, $P = 0.039$, respectively). Although many studies reported significant influence of second TUR on recurrence rates of bladder cancer [3,5,11], these results revealed that performing second TUR within 14–42 days after the initial TUR results in significantly decreased recurrence rates compared with performing second TUR after 42 days.

On multivariate analysis, the interval to second TUR was also found to be a significant predictor of recurrence in association with tumour grade and concomitant CIS.

Improved progression rates of high-risk NMIBC with second TUR were also reported [3–5]. In our present study, progression was defined as an increase in pathological stage (Ta to T1 or T1 to T2) and was seen in 12.4% of the patients. Progression was seen more frequently in patients who underwent a second TUR within 43–90 days than in those who had a second TUR within 14–42 days (8.6% vs 17.6%, $P = 0.034$). The 3-year PFS rates were also significantly better in patients who underwent a second TUR within 14–42 days compared with those who had a second TUR at >42 days (89.1% vs 79.1%, $P = 0.006$).When we evaluated the progression rates after dividing patients into four groups according to the interval between the first and second TUR, there was no significant difference in 3-year PFS rates in those who had a second TUR within 14–28 and 29–42 days ($P = 0.733$). On the other hand, patients who had a second TUR either within 14–28 or 29–42 days had significantly better 3-year PFS rates compared with patients who had a second TUR within 43–56 days ($P = 0.035$, $P = 0.044$, respectively). These results revealed that performing second TUR within 14–42 days after the initial TUR, results in significantly decreased progression rates compared with performing second TUR after an interval of 42 days.

On multivariate analysis, the interval to second TUR was also found to be a significant predictor of progression. Therefore, although retrospective, our present data suggests that to decrease both recurrence and progression rates in high-risk NMIBC, a second TUR should be performed within 14–42 days of the initial TUR.

Regarding the different recurrence and progression rates of the groups, a possible selection bias for performing the second TUR in a later period for those patients under higher

risk of recurrence and progression may be suspected. This could not be verified based on the retrospective nature of the study. However, none of the investigators made any contribution about tendency to perform TUR later in patients with higher risk of recurrence and progression, during the planning of the study. The timing of the second TUR was decided based on the surgeons' and patients' preferences and schedules. A prospective randomised study would be the best to overcome such selection bias.

The present study is limited by its retrospective nature. Patients were included from 10 different centres and therefore the quality of TUR is probably variable. However, this aspect better represents real life. Also, our present data includes a relatively homogeneous patient population that consisted of patients with high-risk NMIBC who were all treated with maintenance BCG. Therefore, cautious use of these findings is recommended in patients who receive only induction BCG after second TUR. Additionally due to the retrospective nature of the study, data about the delay to initiation of the BCG could not be gathered, which may have an effect on recurrence and progression rates. In addition, central pathological review could not be performed. This might also be a limitation of the study, as interobserver differences are common in reporting tumour grade and stage.

In conclusion, second TUR should be performed in patients with high-risk NMIBC before initiating maintenance BCG therapy and the interval between first and second TUR should be ≤42 days in order to attain lower recurrence and progression rates. To our knowledge, this is the first study demonstrating the effect of the interval between first and second TUR on patient outcomes. A prospective randomised study is needed to validate these findings.

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Conflict of Interest

None of the contributing authors have any conflicts of interest, including specific financial interests or relationships and affiliations relevant to the subject materials discussed in the manuscript.

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Abbreviations: CIS carcinoma *in situ*; EAU European Association of Urology; NMIBC non-muscle-invasive bladder cancer; OR odds ratio; PFS progression-free survival; RFS recurrence-free survival; TUR transurethral resection.