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Bladder Cancer

## Comparison of Bacillus Calmette-Guérin Maintenance Therapy with Monthly Instillations and the Southwest Oncology Group Protocol in the Treatment of Non-muscle-invasive Bladder Cancer

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### Abstract

**Background:** Bacillus Calmette-Guérin (BCG) therapy using the Southwest Oncology Group (SWOG) maintenance protocol is the standard in non-muscle-invasive bladder cancer (NMIBC). Maintenance with monthly instillations is also widely used, but evidence comparing the two maintenance protocols is scarce.

**Objective:** To compare monthly and SWOG instillation schedules in maintenance BCG therapy.

**Design, setting, and participants:** We retrospectively identified patients with NMIBC treated with maintenance BCG according to either the monthly or the SWOG instillation regimen in two tertiary care centers in Finland between 2009 and 2019.

**Outcome measurements and statistical analysis:** We compared discontinuation rates of the monthly and SWOG maintenance protocols due to toxicity, and recurrence and progression rates by protocols. Baseline characteristics were compared with the Wilcoxon rank sum test, chi-square test, and Fisher's exact test. The Kaplan-Meier method and Cox proportional hazards model were used to evaluate the discontinuation of BCG due to toxicity and oncological efficacy.

**Results and limitations:** We identified 723 patients, of whom 545 (75%) and 178 (25%) received maintenance according to the monthly and SWOG protocols, respectively. The median follow-up time was 66 (interquartile range: 45–99) mo. In the monthly and SWOG groups, 131 (24%) and 50 (28%) patients, respectively, discontinued BCG due to toxicity, with no difference in a univariate or multivariate analysis (hazard ratio 1.01, 95% confidence interval [CI]: 0.73–1.40,  $p = 0.940$ ). The 5-yr recurrence-free survival rates in the monthly and SWOG groups were 65% (95% CI: 61–69%) and 71% (95% CI: 64–79%,  $p = 0.370$ ), respectively. The 5-yr progression-free survival rates were 89% (95% CI: 86–92%) and 91% (95% CI: 86–96%,  $p = 0.240$ ), respectively.

**Conclusions:** Monthly maintenance is a comparable alternative to the SWOG protocol.

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**Patient summary:** In this study, we compared two schedules of intravesical bacillus Calmette-Guérin (BCG) treatment used in the treatment of non-muscle-invasive bladder cancer. We found that there were no significant differences between the two instillation schedules in terms of tolerability or efficacy.

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## 1. Introduction

Intravesical bacillus Calmette-Guérin (BCG) therapy is the standard treatment for non-muscle-invasive bladder cancer (NMIBC). According to meta-analyses, BCG should include, besides an induction phase, a maintenance period of 1–3 yr to reduce recurrences and progression of disease [1–4]. Various maintenance protocols have been introduced, but the maintenance protocol presented by the Southwest Oncology Group (SWOG) using repeated 3-wk cycles became the mainstay since the landmark paper by Lamm et al [5] showed the most decisive results with a 3-yr maintenance period compared with an induction period alone.

In Finland, a single monthly instillation schedule is widely adopted, which attributes to FinnBladder trials using monthly maintenance with good long-term results [6–8]. However, only few head-to-head comparisons are available between the two maintenance protocols. Two small studies have compared the monthly maintenance and the SWOG protocol, suggesting that monthly maintenance is a viable alternative to the SWOG protocol [9,10]. Given the small number of patients included in these studies, more evidence is needed to conclude whether the monthly maintenance is an alternative to the SWOG protocol in terms of tolerability and efficacy.

The aim of this study is to compare tolerability and oncological efficacy of monthly maintenance and the SWOG protocol in the treatment of NMIBC, characterized by the rate of discontinued BCG courses due to toxicity and the rate of recurrences and progression of disease during follow-up.

## 2. Patients and methods

### 2.1. Patient identification

After receiving an institutional review board approval, we identified patients with a diagnosis of bladder cancer (ICD10: C67) and bladder instillation between 2009 and 2019 in Turku University Hospital and Helsinki University Hospital in Finland. We performed a medical chart review and included patients who had been treated with BCG against bladder cancer.

### 2.2. Characterization of patients

Collected clinical data included age, sex, smoking history, comorbidities according to the Charlson classification, immunosuppression, history of upper tract urothelial carcinoma (UTUC), histopathological details of bladder cancer, number of previous bladder resections, and details of BCG instillations. Based on patient age and oncological details, patients were categorized according to the European Organisation for Research and Treatment of Cancer (EORTC) 2021 risk tables into low-, intermediate-, high-, and very-high-risk groups [11]. The state of

immunosuppression during BCG treatment was defined as the presence of hematological disorder, history of splenectomy, or systemic prednisolone use for any indication with a daily dose of  $\geq 10$  mg.

### 2.3. BCG maintenance schedules and follow-up

During the study period, only BCG RIVM and TICE strains were available in Finland. Both maintenance schedules—monthly and the SWOG protocol—were used in both institutions during the study period. After a 6-wk induction period, maintenance therapy followed a preplanned schedule as follows: in the monthly maintenance therapy, a single instillation was administered monthly for 1–2 yr. In the SWOG protocol, maintenance therapy consisted of 3-wk mini courses at 3 and 6 mo, whereafter mini courses were applied every 6 mo until 1–3 yr. There was no strict protocol on the planned length of BCG course in either group, as it was decided individually by the treating urologist, according to the European Association of Urology (EAU) guidelines [12]. Follow-up included voided urinary cytology and cystoscopy. Follow-up visits were scheduled according to the EAU guidelines' risk-adopted principles [12]. For imaging, there were no strict follow-up protocols.

### 2.4. Discontinuation of BCG course

The dates of all administered and cancelled BCG instillations were collected. The reason for discontinuation of BCG was categorized as follows: (1) *BCG failure*, if BCG was discontinued due to recurrences or progression; (2) *toxicity*, if BCG was discontinued due to local or general symptoms such as dysuria, urgency, hematuria, fever, fatigue, or general malaise; (3) *BCG infection*, if BCG was discontinued due to BCG infectious complication warranting antituberculosis medication; (4) *compliance*, if the patient did not want to proceed with BCG and no side effects or BCG inefficacy were reported; and (5) *other*, if BCG was discontinued due to comorbidities (eg, another malignancy), the patient died due to reasons not related to BCG or bladder cancer, or if the reason for discontinuation of BCG was unclear.

### 2.5. Oncological results

Oncological follow-up data including recurrences and progression of bladder cancer following BCG instillations were collected. Recurrence was defined as any bladder cancer recurrence including low- or high-grade recurrence, and progression was defined as worsening of T category or a diagnosis of metastases.

### 2.6. Statistical analysis

Associations between monthly maintenance versus the SWOG protocol and explanatory variables (age, gender, smoking, Charlson Comorbidity Index, immunosuppression, T category, grade, number of tumors, size of the tumor, number of resections before BCG, performed resection, history of UTUC, EORTC 2021 risk groups, disease history at initiation of BCG, number of instillations, duration of BCG, number of discontinued BCG courses, and reasons for discontinuation) were summarized with descriptive statistics, and studied one by one with the Wilcoxon rank sum test for nonparametric continuous variables,

Pearson's chi-square test for categorical variables, and Fisher's exact test for categorical variables with small sample sizes. The Kaplan-Meier method was used to estimate the discontinuation of BCG due to toxicity, recurrence, and progression. Explanatory variables (gender, smoking status, Charlson Comorbidity Index, immunosuppression, number of resections before BCG, re-resection, history of UTUC, EORTC 2021 risk group, and maintenance protocol) to all endpoints were studied using the stepwise Cox proportional hazards model. The statistical significance level was set at 0.05 in all tests (two tailed), and 95% confidence intervals (CIs) were calculated. The analyses were performed using the RStudio (version 2022.7.1.554) based on R (version 4.1.0; RStudio, PBC, Boston, MA, USA).

### 2.7. Ethical statement

This noninterventional retrospective study was conducted according to good clinical practice and the declaration of Helsinki.

## 3. Results

We identified a total of 802 consecutive patients (196 in Turku and 606 in Helsinki) who had been treated with BCG for bladder cancer. We excluded 76 patients not receiving maintenance therapy and three patients whose pathological stage was ultimately classified as pT2, and included 723 NMIBC patients in final analyses. Of these patients, 545 (75%) received monthly maintenance and 178 (25%) received maintenance according to the SWOG protocol.

Baseline characteristics and oncological details of the two groups are presented in [Table 1](#). Patients in the monthly maintenance group were older than those in the SWOG group, with a median age of 73 (interquartile range [IQR]: 67–79) yr and 71 (IQR: 65–77) yr, respectively ( $p = 0.019$ ). Additionally, there were fewer high-grade tumors in the monthly maintenance group than in the SWOG group, 93% and 96%, respectively ( $p = 0.040$ ). However, there was no difference in the EORTC 2021 risk group classification between the groups ( $p = 0.700$ ) [11]. The median follow-up time was 66 (IQR: 45–99) mo.

Details of BCG instillations and data on unplanned discontinuation of BCG in the two groups are presented in [Table 2](#). Patients in the monthly maintenance and SWOG groups received a median of 17 (IQR: 14–22) and 18 (IQR: 13–21) instillations, respectively ( $p = 0.200$ ). However, the instillations were administered during a shorter period of time in the monthly maintenance group with a median of 13 (IQR: 11–20) mo and in the SWOG group with a median of 17 (IQR: 8–25) mo ( $p = 0.036$ ). Overall, there were no differences in the rate of unplanned discontinuation of BCG between the groups, with 241/545 (44%) in the monthly maintenance group and 79/178 (44%) in the SWOG group ( $p \geq 0.9$ ).

The Kaplan-Meier plot estimating the unplanned discontinuation of BCG due to toxicity or BCG infection is illustrated in [Figure 1](#). In the SWOG group, the rate of discontinued BCG courses was slightly higher during the first half of the maintenance period and lower in the latter half with curves crossing at 18 mo. As a result, no significant difference was observed in a univariate Cox regression analysis (hazard ratio [HR] 1.01, 95% CI: 0.73–1.41,  $p = 0.940$ ).

[Figure 2](#) illustrates the Kaplan-Meier plot estimating the survival for recurrences ([Fig. 2A](#)) and progression ([Fig. 2B](#)). In the whole cohort, disease recurrence was observed in 253/723 (35%) patients, with 198/545 (36%) in the monthly maintenance group and 55/178 (31%) in the SWOG group. In a univariate Cox regression analysis, no significant difference in recurrence rate was observed (HR 0.87, 95% CI: 0.65–1.18,  $p = 0.370$ ). The 5-yr recurrence-free survival rates in the monthly and SWOG groups were 65% (95% CI: 61–69%) and 71% (95% CI: 64–79%), respectively ( $p = 0.370$ ). Disease progression was observed in 86/723 (12%) patients, 70/545 (13%) in the monthly maintenance group and 16/178 (9%) in the SWOG group. In a univariate Cox regression analysis, there was no significant difference in progression rate (HR 0.72, 95% CI: 0.42–1.24,  $p = 0.240$ ). The 5-yr progression-free survival rates in the monthly and SWOG groups were 89% (95% CI: 86–92%) and 91% (95% CI: 86–96%), respectively ( $p = 0.240$ ).

The Cox proportional hazards model assessing risk factors for discontinuation of BCG due to toxicity or BCG infection, recurrences, and progression is presented in [Table 3](#). In the multivariable model, neither maintenance schedule nor other independent risk factors affected the risk of discontinuation of BCG due to toxicity. Independent risk factors for recurrences included a history of UTUC (HR 1.77, 95% CI: 1.15–2.73) and a very high EORTC risk group (HR 1.91, 95% CI: 1.15–3.18), while risk factors for progression included a history of UTUC (HR 2.53, 95% CI: 1.24–5.19), Charlson Comorbidity Index >4 (HR 1.90, 95% CI: 1.11–3.24), and a high (HR 4.09, 95% CI: 1.23–13.60) or very high (HR 7.26, 95% CI: 2.01–26.17) EORTC risk group. On the contrary, performing re-resection appeared a significantly protective factor for both recurrence (HR 0.61, 95% CI: 0.45–0.84) and progression (HR 0.51, 95% CI: 0.29–0.91).

## 4. Discussion

Our study showed that there is no difference in the rate of discontinuation of BCG courses due to toxicity between the study groups. Less recurrences and progressions were observed in the SWOG group, but the difference was not significant in the univariate or multivariate analysis. Rather than the chosen maintenance schedule, patient characteristics and oncological factors were shown to significantly affect recurrence and progression rate, such as history of UTUC, EORTC risk group, and Charlson Comorbidity Index, which were all independent risk factors for progression. Re-resection appeared to be protective for both recurrences and progression, highlighting the importance of meticulous surgical eradication of bladder tumors before proceeding with any BCG instillation regimen. Our study confirms the conclusion of previous reports that there is no difference regardless of which maintenance schedule is used [9,10].

In the paper by Lamm et al [5], the 5-yr recurrence-free survival versus 5-yr worsening-free survival rates in the maintenance arm and no maintenance arm were 60% versus 41% ( $p \leq 0.001$ ) and 76% versus 70% ( $p = 0.040$ ), respectively. The gold standard status of the SWOG maintenance protocol attributes to this study, as early trials comparing monthly instillation schedule with induction period alone

**Table 1 – Baseline characteristics and oncological details of the patients treated with bacillus Calmette-Guérin (BCG) therapy using the monthly maintenance or the maintenance schedule by the Southwest Oncology Group (SWOG)**

		Overall, n (%)	Monthly, n (%)	SWOG, n (%)	p value <sup>a</sup>
Number of patients		723	545 (75)	178 (25)	
Age	Median (IQR)	73 (66–79)	73 (67–79)	71 (65–77)	0.019
Gender					0.200
	Male	607 (84)	452 (83)	155 (87)	
	Female	116 (16)	93 (17)	23 (13)	
Smoking					0.500
	Never	210 (33)	155 (32)	55 (35)	
	Ex-smoker	256 (40)	190 (40)	66 (42)	
	Active smoker	170 (27)	134 (28)	36 (23)	
	NA	87	66	21	
Charlson Comorbidity Index					0.500
	2	355 (49)	261 (48)	94 (53)	
	3	179 (25)	139 (26)	40 (22)	
	≥4	189 (26)	145 (27)	44 (25)	
Immunosuppression					0.900
	No	696 (96)	525 (96)	171 (96)	
	Yes	27 (4)	20 (4)	7 (4)	
<i>Oncological characteristics</i>					
T category					0.500
	Ta	237 (33)	173 (32)	64 (36)	
	T1	368 (51)	280 (51)	88 (49)	
	Carcinoma in situ	118 (16)	92 (17)	26 (15)	
Grade					0.040
	High grade	669 (94)	504 (93)	165 (96)	
	Low grade	40 (6)	35 (7)	5 (3)	
	PUNLMP	3 (0.4)	1 (0.2)	2 (1)	
	NA	11	5	6	
Number of tumors					0.130
	1	355 (50)	276 (51)	79 (45)	
	2–7	339 (47)	251 (47)	88 (50)	
	≥8	20 (3)	12 (2)	8 (5)	
	NA	9	6	3	
Size of the largest tumor (cm)					0.140
	<1	80 (11)	68 (12)	12 (7)	
	1–3	400 (56)	299 (55)	101 (60)	
	>3	231 (32)	177 (33)	54 (32)	
	NA	12	1	11	
Number or resections prior to BCG	Median (IQR)	2 (2–3)	2 (2–3)	2 (2–2)	0.600
Re-resection performed					0.200
	No	302 (43)	234 (44)	68 (38)	
	Yes	407 (57)	297 (56)	110 (62)	
	NA	14	14	0	
History of UTUC					0.900
	No	668 (92)	504 (92)	164 (92)	
	Yes	55 (8)	41 (8)	14 (8)	
EORTC risk group					0.700
	Low risk	1 (0.1)	1 (0.2)	0 (0)	
	Intermediate risk	99 (14)	79 (15)	20 (11)	
	High risk	479 (67)	359 (66)	120 (68)	
	Very high risk	141 (20)	104 (19)	37 (21)	
	NA	3	2	1	

EORTC = European Organisation for Research and Treatment of Cancer; IQR = interquartile range; NA = not available; PUNLMP = papillary urothelial neoplasm of low malignant potential; UTUC = upper tract urothelial carcinoma.

<sup>a</sup> Wilcoxon rank sum test, chi-square test, and Fisher's exact test.

were, in fact, unable to show as clear a benefit as SWOG maintenance in reducing recurrences [4,13,14]. This may have been related to the small sample size in trials using monthly instillations [15]. Despite the limitations of previous studies, the FinnBladder group has previously reported results of three long-term trials comparing 1–2 yr of monthly maintenance instillation therapy with BCG to various induction and maintenance instillation therapies with intermediate-risk NMIBC patients [6–8]. Noteworthy, in the FinnBladder-4 trial, mitomycin C was also used for the induction period in the BCG arm [6]. Compared with the

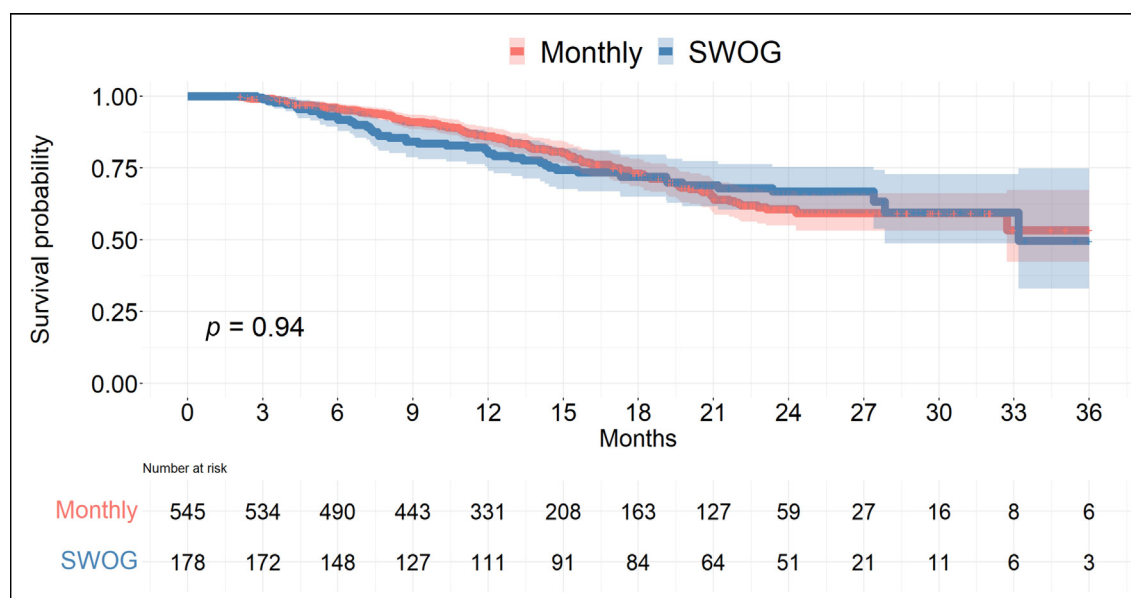
results of Lamm et al's [5] study, results of the BCG arms of the maintenance groups in the FinnBladder studies are similar to the reported recurrent rates of approximately 32–50%, 43–57%, and 45–59% at 5, 10, and 15 yr, respectively. These results suggest that monthly maintenance is effective treatment and therefore represents a valid option for maintenance therapy. Our present study directly comparing the monthly and SWOG maintenance groups showed consistent results with these randomized trials.

There are two previous studies comparing the monthly instillations and the SWOG protocol, both of which have a

**Table 2 – Details of bacillus Calmette-Guérin (BCG) treatment in 723 patients in monthly maintenance and maintenance according to the Southwest Oncology Group (SWOG) protocol**

Variable	Group			p value <sup>a</sup>
	Overall (n = 723)	Monthly (n = 545)	SWOG (n = 178)	
Disease history at initiation of BCG				0.200
	Primary tumor	523 (72)	387 (71)	136 (77)
	Recurrent disease	200 (28)	158 (29)	42 (23)
Days between TURBT and first instillation, median (IQR)	41 (32–55)	41 (32–56)	40 (33–52)	0.600
Number of instillations, median (IQR)	17 (14–21)	17 (14–22)	18 (13–21)	0.200
Duration of BCG (mo), median (IQR)	13 (10–22)	13 (10–20)	17 (8–25)	0.036
Completion of BCG				>0.900
	Finished BCG	400 (56)	301 (56)	99 (56)
	Discontinued BCG	320 (44)	241 (44)	79 (44)
	NA	3	3	0
Reasons for discontinuation				0.300
	BCG failure	70 (22)	56 (24)	14 (18)
	Toxicity	164 (51)	116 (48)	48 (61)
	BCG infection	17 (5)	15 (6)	2 (2)
	Compliance	19 (6)	16 (7)	3 (4)
	Other	49 (15)	37 (15)	12 (15)

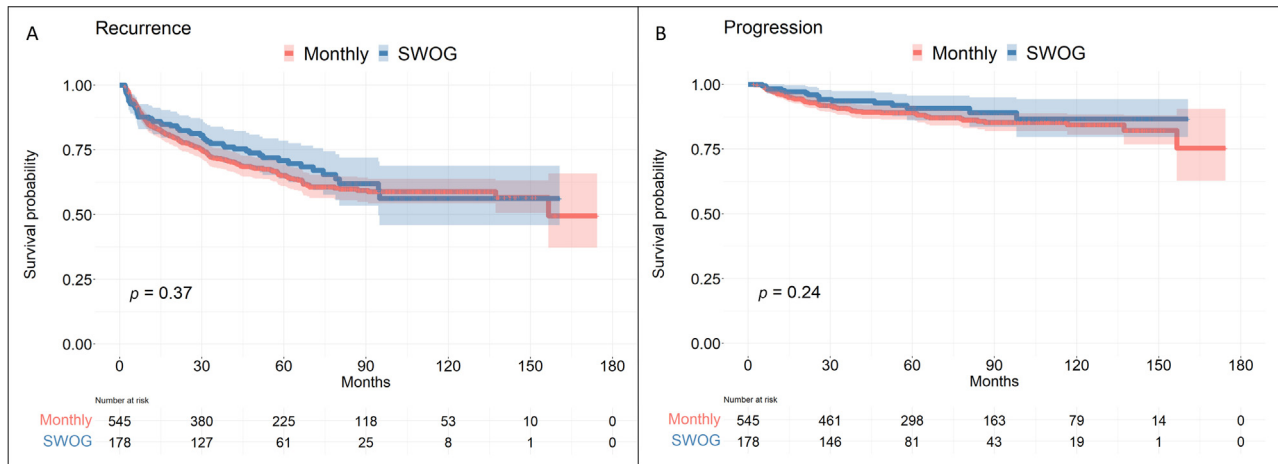
IQR = interquartile range; NA = not available (moved to another hospital district); TURBT = transurethral resection of bladder tumor.  
<sup>a</sup> Wilcoxon rank sum test, chi-square test, and Fisher's exact test.

**Fig. 1 – Kaplan-Meier curves of unplanned discontinuation of bacillus Calmette-Guérin (BCG) course due to toxicity or suspected BCG infection among 723 patients receiving BCG maintenance therapy with monthly instillations (red curve) or according to the maintenance protocol by the Southwest Oncology Group (SWOG; blue curve). Censored values (+) indicate events such as discontinuation due to BCG failure, poor compliance, other reason, or death due to reasons not related to BCG.**

small number of patients and observed events [9,10]. Gupta et al [9] reported the results of a recent prospective randomized trial randomizing 90 patients to receive either maintenance therapy according to the SWOG protocol for 3 yr or monthly instillations for 1 yr. The authors observed six recurrences among patients allocated in the SWOG arm, five recurrences in the monthly instillation arm, and one progression of disease in both arms. Two patients discontinued treatment due to toxicity in both arms, showing no difference in terms of efficacy or toxicity [9]. Lashay et al [10] reported similar results in a retrospective study of 80 patients, with 18% and 25% recurrence rates in the monthly

and SWOG arms, respectively ( $p = 0.340$ ). Our study provides a substantially higher number of patients and events with 253 recurrences and 86 progressions observed, and confirms the results of these studies.

In a prospective randomized trial (NIMBUS) by Grimm et al [16], the authors compared a reduced number of induction and maintenance instillations during 1-yr maintenance therapy with the standard 1-yr SWOG protocol, but found that the reduction of the number of instillations affected efficacy negatively. In addition, it was shown that the patients who discontinued BCG due to toxicity were at a greater risk for recurrence and progression, with the major-



**Fig. 2 – Kaplan-Meier curves of (A) recurrences and (B) progression of non-muscle-invasive bladder cancer following bacillus Calmette-Guérin (BCG) therapy among 723 patients receiving BCG maintenance therapy with monthly instillations (red curve) or according to the maintenance protocol by the Southwest Oncology Group (SWOG; blue curve). The median follow-up time was 66 (IQR: 45–99) mo. Censored values (+) indicate events such as loss to follow-up or death due to reasons not related to urothelial cancer. IQR = interquartile range.**

**Table 3 – Assessment of risk factors for discontinuation of bacillus Calmette-Guérin (BCG) therapy due to toxicity or BCG infection, disease recurrence, and progression using Cox proportional hazards model among 723 patients with non-muscle-invasive bladder cancer**

Variable	Discontinuation of BCG due to toxicity or BCG infection HR (95% CI)	Recurrence HR (95% CI)	Progression HR (95% CI)
<b>Gender</b>			
Female	Ref	Ref	Ref
Male	1.01 (0.64–1.60)	0.95 (0.65–1.37)	0.83 (0.44–1.55)
<b>Smoking status</b>			
No smoking	Ref	Ref	Ref
Ex-smoker	1.23 (0.84–1.80)	1.01 (0.73–1.38)	1.03 (0.58–1.84)
Currently smoking	0.89 (0.57–1.38)	0.72 (0.49–1.05)	1.11 (0.59–2.07)
<b>Charlson Comorbidity Index</b>			
2	Ref	Ref	Ref
3	1.02 (0.69–1.50)	1.03 (0.73–1.45)	0.59 (0.29–1.22)
>4	0.94 (0.63–1.39)	1.26 (0.91–1.75)	1.90 (1.11–3.24)
<b>Immunosuppression</b>			
No	Ref	Ref	Ref
Yes	0.74 (0.27–2.02)	1.06 (0.55–2.03)	0.29 (0.04–2.13)
<b>Number of resections before BCG</b>			
Re-resection performed	0.98 (0.75–1.29)	1.16 (0.95–1.41)	0.98 (0.66–1.46)
No	Ref	Ref	Ref
Yes	0.76 (0.52–1.13)	0.61 (0.45–0.84)	0.51 (0.29–0.91)
<b>History of UTUC</b>			
No	Ref	Ref	Ref
Yes	0.43 (0.17–1.05)	1.77 (1.15–2.73)	2.53 (1.24–5.19)
<b>EORTC 2021 risk group</b>			
Low-intermediate risk	Ref	Ref	Ref
High risk	0.94 (0.53–1.66)	1.19 (0.78–1.81)	4.09 (1.23–13.60)
Very high risk	1.20 (0.62–2.30)	1.91 (1.15–3.18)	7.26 (2.01–26.17)
<b>Maintenance protocol</b>			
Monthly	Ref	Ref	Ref
SWOG	0.93 (0.65–1.34)	0.88 (0.64–1.21)	0.76 (0.42–1.38)

CI = confidence interval; EORTC = European Organisation for Research and Treatment of Cancer; HR = hazard ratio; IQR = interquartile range; Ref = reference variable; SWOG = Southwest Oncology Group; UTUC = upper tract urothelial carcinoma.  
Median follow-up time is 66 (IQR: 45–99) mo.

ity of BCG courses being interrupted during the 1st year [17]. These results suggest that the completion of the 1st year is most important to maintain the therapeutic effect of BCG [2]. However, despite more instillations being administered during the 1st year in the monthly maintenance group, the difference did not translate into better oncological results in our study. Therefore, the nine maintenance instillations in the SWOG protocol during the 1st year

seem sufficient to maintain the potential efficacy of BCG [5]. It is also worth noting that in the SWOG protocol, BCG consumption is extended over a longer time period, and hence more BCG courses may simultaneously be initiated during the times of BCG shortage.

The main limitation of this study is the retrospective design, which precluded us from investigating the effect of maintenance on the quality of life and irritative symptoms,

which did not lead to treatment discontinuation. Owing to this, we used a definitive endpoint of unplanned discontinuation of BCG due to toxicity or BCG infection, which was clearly identifiable in the medical charts. However, multiple factors may have affected the discontinuation, especially among elderly and patients with comorbidities, which might harbor a source of bias. In addition, patients in the monthly maintenance group were older than patients in the SWOG group ( $p = 0.019$ ), which may have affected the results, since it has previously been shown that oncological efficacy of BCG therapy is worse among elderly patients [18,19]. However, age does not seem to affect the risk of discontinuation of BCG due to toxicity [20,21]. As we compared the groups using the EORTC 2021 risk tables, which applies multiple factors—including age and grade—the baseline risk of progression in the study groups were similar ( $p = 0.700$ ) [11]. Nevertheless, the difference in age between the groups represents a limitation in our study, and the analysis of efficacy needs to be interpreted with some degree of caution. Finally, we did not have the individual data on the used BCG strains, and therefore the distribution of RIVM and TICE between the study groups cannot be estimated. However, BCG TICE represents <5% proportion of BCG instillations in this cohort, and therefore, the effect of strain in this study is likely to be minimal.

## 5. Conclusions

Monthly maintenance and the SWOG protocol resulted in a similar number of discontinued BCG courses, and no significant difference in efficacy could be observed, supporting the results of previous studies. The use of the widely adopted SWOG protocol needs not to be questioned, but monthly maintenance may be considered a valid alternative to the SWOG protocol in terms of tolerability and oncological efficacy.

**Author contributions:** Pertti Nurminen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Nurminen, Nummi, Järvinen, Sairanen, Ettala, Kaipia, Boström.

**Acquisition of data:** Nummi, Kesti, Nurminen.

**Analysis and interpretation of data:** Högerman, Nurminen, Ettala, Boström.

**Drafting of the manuscript:** Nurminen.

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