Efficacy and tolerability of bacillus Calmette-Guérin strain Russia for the treatment of non-muscle-invasive bladder cancer: Analysis of a prospective registry

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Cite as: Flury-Stutter S, Heuzeroth F, Arbelaez E, et al. Efficacy and tolerability of bacillus Calmette-Guérin strain Russia for the treatment of non-muscle-invasive bladder cancer: Analysis of a prospective registry. *Can Urol Assoc J* 2024 March 1; Epub ahead of print. http://dx.doi.org/10.5489/cuaj.8552

Published online March 1, 2024

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ABSTRACT

Introduction: Little is known about the efficacy and tolerability of intravesical bacillus Calmette-Guérin (BCG) strain Russia for treatment of non-muscle-invasive bladder cancer (NMIBC) in a middle-European population.

Methods: A prospective collection of outcomes of 101 BCG-naive patients with urothelial bladder carcinoma was carried out between January 2013 and October 2023 at the University Hospital Basel, Basel, Switzerland. Patients underwent BCG (ONCO-BCG-SIIL, Serum Institute of India, Pune, India) induction and a maximum of three maintenance cycles within one year. Adverse events were classified according to the World Health Organization rating scale.

Results: One-, three-, and five-year recurrence-free survival (RFS) was 75.9%, 65.6%, and 61.6%, respectively. Tumor recurrence was seen in 31.7% of patients. One-, three-, and five-year progression-free survival (PFS) was 100%, 93.4%, and 93.4%, respectively. Cystectomy rate was 8.9%, with progression to muscle-invasive disease seen in two patients. Adverse events occurred in 72.3% of patients, with adverse events >class II seen in 8.9%. No BCG-

KEY MESSAGES

- BCG Russia performs comparably to historical results of other BCG strains in terms of efficacy for adjuvant treatment of papillary NMIBC and for treatment of CIS of the urinary bladder.
- Intravesical instillation therapy with BCG Russia is well-tolerated and safe.
- In times of BCG shortage, BCG Russia appears to be a valid BCG alternative for intravesical instillation therapy.

related deaths occurred. Early cessation due to side effects resulting in non-adequate BCG therapy was seen in 3% of patients during induction and in 1% during maintenance therapy. **Conclusions:** BCG Russia was well-tolerated and resulted in comparable RFS and PFS to historical results of prospective clinical trials with other BCG strains. The use of BCG Russia for adjuvant treatment of papillary NMIBC and therapy of carcinoma in situ of the urinary bladder could help alleviate the BCG shortage.

INTRODUCTION

Intravesical immunotherapy using Bacillus Calmette-Guérin (BCG) is considered the optimal adjuvant therapy for intermediate- and high-risk papillary urothelial non-muscle-invasive bladder cancer (NMIBC) after transurethral resection and for treating urothelial carcinoma in situ (CIS).[1] However, there is a worldwide BCG shortage due to production and supply chain constraints.[2] In addition, the global demand for BCG is increasing due to the rising numbers of elderly people in industrial countries at risk for bladder cancer.[3] Furthermore, mass production of mycobacteria is challenging as they have long doubling times.[4] Consequently, and despite increasing production, the growing global demand for BCG can still not be met.[2,5] In France, BCG shortage has been shown to have significant medical and economic consequences, notably showing higher bladder cancer recurrence and progression rates and, consequently, increased cystectomy rates and costs for the care of patients with intermediate- and high-risk NMIBC.[6]

To overcome the problem of BCG shortage, Health Canada approved BCG Russia under the condition to perform a phase III non-inferiority study, comparing BCG Russia against BCG Tice in patients with pathologically confirmed and completely resected urothelial bladder carcinoma stage Ta or T1 with or without associated CIS.[7] According to Health Canada, BCG Russia is currently, outside of the ongoing study, only indicated for pTa and pT1 urothelial bladder cancer without CIS.[8] In November 2022, France had granted permission for the import of BCG Russia to overcome supply shortages of the BCG strain RIVM, which is used in France since the halt of production of BCG Connaught in 2019.[9]

In January 2020, the producer of BCG Russia performed a prospective study in India reporting the efficacy and tolerability of intravesical administered BCG Russia in 104 patients.[10] No further and independent information about BCG Russia is currently available; particularly in middle European patients. In Basel, Switzerland, we are using BCG Russia under a special governmental agreement since 2015. Here, we report on the results from our prospective registry of patients undergoing BCG therapy regarding the efficacy and tolerability of BCG Russia.

METHODS

Patients

From January 2015 to October 2023, 101 BCG naïve patients receiving BCG Russia (ONCO-BCG-SIIL, Serum Institute of India, Pune, India) were enrolled in our prospective registry at

the Department of Urology, University Hospital Basel, Basel, Switzerland (Figure 1). The database was locked for analysis in October 2023. All patients were >18 years of age and gave written informed consent. Inclusion criteria were a biopsy-proven (CIS) or a transurethral completely resected papillary (pTa/pT1) primary (n = 85) or recurrent (n = 16) urothelial carcinoma of the bladder and the possibility of at least one re-assessment by cystoscopy 3 months after the last instillation of BCG induction therapy. Patients who stopped BCG therapy due to adverse events were also included in the study. All patients with no confirmed presence of cancer-free detrusor muscle and all patients with T1 tumors underwent re- transurethral resection of the bladder. Indication for BCG therapy was made according to the European Association of Urology (EAU) guidelines. Patients in the intermediate and high-risk group were included in the study, as well as patients in the very high-risk group, if they refused or were unfit for cystectomy. The EAU NMIBC 2021 scoring model was used for risk group assignment.[11] The study was approved by the local ethics committee (EKBB 361/09).

BCG Russia

BCG strain Russia (ONCO-BCG-SIIL) is available in 40-mg ampoules, with each ampoule containing 1-19.2 x 10^8 colony-forming units. To perform 1 bladder instillation, 3 ampoules (for a total of 120 mg) of the product were reconstituted in 50 ml of 0.9% sodium chloride solution. After careful disinfection, the instillation into the bladder was performed using a self-lubricating transurethral catheter without applying intraurethral antiseptics. After administration, the catheter was removed, and the patients were instructed to refrain from urinating for at least 120 min.

Procedures

All patients underwent an induction therapy regimen that included 6 once-weekly treatments with BCG, in compliance with the guidelines set forth by the EAU. Subsequent to the completion of induction therapy, a first control cystoscopy and cytology of the bladder was performed after 3 months. If the control did not reveal any signs of recurrence and the patients did not exhibit any contraindications for further BCG treatments, the first cycle of maintenance therapy was initiated. A maintenance therapy cycle comprised 3 once-weekly instillations of BCG and was applied at 3, 6, and 12 months after the first instillation of the induction therapy.

The follow-up protocol included 3-monthly cystoscopies/cytologies for a period of 2 years, which was subsequently followed by a 6-monthly follow-up for up to 5 years and annually thereafter. Additionally, a contrast-enhanced computed tomography scan of the abdomen was performed yearly to monitor the upper urinary tract.

The loco-regional and systemic adverse events of intravesical BCG therapy were assessed by questionnaire according to a 4-class rating scale based on WHO recommendation,[12] as well as by clinical physical examination and, if necessary, laboratory chemistry tests before each further instillation.

Outcomes

The primary endpoint of the study was RFS, defined as the period from the first BCG administration of the induction cycle until histological proven recurrence. Secondary endpoints included progression-free survival (PFS), cystectomy-free survival (CFS) and the assessment of tolerability. Progression was defined as occurrence of muscle invasion or metastatic disease. We also analyzed NMIBC progression defined as tumor recurrence with an upstaging (pTa to pT1) or upgrading (low-grade to high-grade) or new occurrence of CIS. Tolerability was defined as the fraction of patients able to tolerate adequate induction and maintenance therapy, without those stopping due to recurrence. Adequate BCG exposition was defined, according to the EAU, as ≥5 instillations of the induction course and ≥2 instillations of the maintenance therapy.[13]

Statistical analysis

Categorical data were summarized using frequency and percentage and continuous data using median and range. For all time-to-event endpoints, the median was estimated using the Kaplan-Meier method, and the Kaplan-Meier estimator was evaluated at a fixed time, together with a 95% confidence interval (CI) used to evaluate these endpoints at 1, 3, and 5 years. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA) and R 4.2.1 (The R Foundation; www.r-project.org).

RESULTS

Between January 2013 and October 2023, a total of 101 participants were enrolled in this study. The patient characteristics are displayed in Table 1. The median follow-up was 3.3 years (CI 2.5-4 years). The mean follow-up was 3.5 years.

31.7% (n = 32) of participants, including 17 (16.8 %) patients with pure or concurrent CIS, had a recurrence of urothelial bladder carcinoma after or during BCG therapy. One-, 3-, and 5- year RFS was 75.9%, 65.6%, and 61.6%, with a 95% confidence interval of 0.66–0.83, 0.54–0.75, and 0.5–0.72, respectively (Figure 2, Table 2). Median RFS was not reached. One-, 3-, and 5-year RFS for patients with pure or concurrent CIS was 64.8%, 53.8%, and 48.9%, with a confidence interval of 0.47-78, 0.35-0.69 and 0.3-0.65, respectively. Median RFS for patients with pure or concurrent CIS was 7 months. Only 21.9% (n = 7) of patients with relapse recurred after 12 months after the first instillation of BCG induction therapy; therefore, the majority of patients had earlier recurrence.

In 25% (n = 8) of our patients, histological examination of the first bladder recurrence showed NMIBC progression and no progression to muscle-invasive disease was observed. 2 patients showed upgrading from a low- to a high-grade tumor, 3 patients presented with pathological upstaging from a pTa to a pT1 tumor, and 3 patients developed new occurrence of a bladder CIS. One-, 3-, and 5-year NMIBC PFS was 94.7%, 89.8%, and 89.8%, with a 95% CI of 0.88–0.98, 0.80–0.95, and 0.80–0.95, respectively (Table 2). One-, 3-, and 5-year NMIBC PFS for patients with pure or concurrent CIS was 94.5%, 90%, and 90 %, with a 95% CI of 0.8–0.99, 0.71–0.97, and 0.71–0.97, respectively. In 43.8% (n = 14) of patients with relapse, the first recurrence of the urothelial carcinoma of the urinary bladder was treated with BCG re-induction, in 15.6% (n = 5) of patients intravesical chemotherapy with epirubicin or gemcitabine was administered, in 15.6% (n = 5) of patients, a cystectomy was

performed, in 21.9 % (n = 7) of patients best supportive care (inclusive fulguration in local anesthesia) was initiated. One patient died of bronchopneumonia before initiation of a new therapy.

During the entire observation period, 5 (5%) patients developed urothelial bladder carcinoma stage ≥T2 (n = 2) or metastases (M) (n = 3), which was diagnosed by imaging or histology. 4 out of these 5 patients (80%) presented with a pure or concurrent CIS at the initial diagnosis of the urothelial bladder cancer. One-, 3-, and 5- year PFS for development of stage ≥T2/M urothelial bladder carcinoma was 100%, 93.4%, and 93.4%, with a 95% CI of 1, 0.83–0.98, and 0.83–0.98, respectively (Table 2). One-, 3- and 5-year PFS for development of stage ≥T2/M urothelial bladder carcinoma for patients with concurrent or pure CIS was 100%, 85.7%, and 85.7%, with a 95% CI of 1, 0.62-0.95, and 0.62-0.95, respectively.

Cystectomy was finally performed in 8.9% (n = 9) of the patients after BCG therapy was finished. 77.8% of patients (7 patients) undergoing cystectomy presented with pure or concurrent CIS at the initial diagnosis of the urothelial bladder cancer. The indication for cystectomy was given due to BCG-unresponsive tumor recurrence in 7 patients and late relapsing tumor recurrence in 2 patients. Three patients received neoadjuvant chemotherapy before cystectomy. Finally, histological examination of the cystectomy specimens showed muscle-invasive urothelial cancer in 2 out of the 9 cystectomized patients. One-, 3-, and 5-year CFS was 99%, 90.3%, and 88.3%, with a 95% CI of 0.93–1, 0.81–0.95, and 0.78–0.94, respectively (Table 2). One-, 3-, and 5-year CFS for patients with pure or concurrent CIS (n=39) was 97.4%, 80.8% and 75.8%, with a CI of 0.83–1, 0.59–0.92 and 0.53–0.89, respectively.

At the time of data analysis, 99% (n = 100) of the patients had no further BCG therapy planned. 96% (n = 97) of the patients received adequate induction (at least 5 of 6 doses of an initial induction course), and 74.3% (n = 75) of patients received adequate maintenance therapy (at least 2 doses of maintenance therapy). The reasons for inadequate induction and maintenance therapy are displayed in the Consort Flow Diagram (Figure 1). The main reason for inadequate induction therapy was adverse events (3% of the patients). The main reason for inadequate maintenance therapy was tumor recurrence in 13 patients (12.9%). The main reasons for <3 maintenance cycles were tumor recurrence in 36.8% (n = 21), adverse events in 22.8% (n = 13) and the patient's choice to end BCG therapy in 12.3% (n = 7).

A total of 1,103 instillations were administered during the study period. Adverse events occurred in 175 out of 1,1103 (15.9%) instillations and in 72.3% (n = 73) of patients. Class >II with adverse events were seen in 8.9% (n = 9) of patients and in 0.8% of all administered instillations, respectively. 27.7% (n = 28) of patients had no adverse events during the entire period of BCG instillation therapy. Early cessation due to side effects resulting in non-adequate BCG therapy was seen in 3% (n = 3) during induction and in 1% (n= 1) of patients during maintenance therapy. Class I irritative micturition complaints and hematuria were the most common adverse events (Table 3). Local adverse events were seen in 64.4% (n = 65) and systemic adverse events in 37.6% (n = 38) of patients, respectively. No BCG-related death occurred during the entire follow-up period.

DISCUSSION

Here, we present, to the best of our knowledge, the first analysis of clinical outcomes in patients who have undergone intravesical therapy with BCG Russia for treatment of NMIBC in the Western world. According to our results, the efficacy of BCG Russia, as measured by recurrence and progression rates, is comparable to that of historical results of other BCG strains. A large meta-analysis by Malmström et al. published 2009 included 9 trials with a total of 2,820 patients to compare the efficacy of BCG Pasteur, RIVM, TICE, Connaught and mitomycin C. In this study 74 % of patients belonged to the intermediate and 21.8 % to the high-risk group. 11.6 % of patients had CIS. The authors reported a recurrence rate in the BCG group of 42% and a rate of progression to muscle-invasive disease (stage ≥T2) in 10.9%. The cystectomy rate was 8.6%. With a recurrence rate of 31.7%, a progression rate (progression to ≥T2 and/or metastasis) of 5% and a cystectomy rate of 8.9%, our results are quite similar to those mentioned in the meta-analysis of Malmström et al.[14]

The sole prospective study on BCG therapy using the BCG Russia strain was conducted by the manufacturer in September 2019. This study, which involved 104 patients in India, compared the effectiveness and tolerability of two different doses (80 vs. 120 mg) for intravesical BCG therapy. The induction therapy with BCG Russia followed a 3-year maintenance schedule. Median follow-up time was 3 years. All included patients had a stage T1 urothelial carcinoma of the urinary bladder. The study team published a recurrence rate of only 15.69% in the 80-mg dose group and 13.21% in the 120-mg dose group. These are amongst the lowest recurrence rates published in the literature and could not be confirmed in our study in a middle European population. Whether this low recurrence rate was due to the three-year maintenance therapy, compared to the conducted one-year BCG maintenance treatment in our study, remains to be evaluated. [10] In summary, the efficacy of BCG Russia is comparable to most historical data on the efficacy of other BCG strains. However, in our cohort, it did not meet the very low recurrence rates as defined in the Indian population. The large multicenter European Organization for Research and Treatment of Cancer Genito-Urinary Group Phase III Trial in 2013 reported side effects from BCG Tice during the 1-year treatment schedule in 62.3% and systemic side effects in 30.4% of the participants. The results are quite similar in our study, where a total of 64.4% of the patients had local and 37.6% had systemic side effects during BCG therapy. In 7% of the patients, local or systemic side effects led to early termination of BCG therapy in this study,[15] while in our study, only 4% of the patients had inadequate therapy with BCG Russia due to adverse events. The manufacturer of BCG Russia reported that 66% patients in the 120-mg group experienced at least one adverse event.[10] In our cohort, 72.3% of patients suffered from at least one adverse event. Ultimately, we observed no BCG-associated fatalities and adverse events exceeding class II in only 8.9% of the patients throughout the entire observation period.

The main limitation of our study is the lack of a control group. However, the selected historical prospective studies to compare our results, included patients with similar patient and tumor baseline data and same duration and dosage of BCG therapy. The limited number of patients at risk after 5 years in our study stems from the absence of follow-up appointments, largely because many patients, who were often elderly and dealing with

multiple health conditions, ceased attending. Importantly, further follow-up would have had no consequential clinical impact on these patients.

CONCLUSIONS

According to our study results, BCG Russia performs equally in terms of efficacy compared with historical results of other BCG strains. Intravesical BCG therapy for urothelial NMIBC with BCG Russia is a well-tolerated therapy with very rare occurrence of local and systemic class 3–4 adverse events. The use of BCG Russia could also be a solution for other countries in order to mitigate the BCG shortage in the context of NMIBC therapy.

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FIGURES AND TABLES

Figure 1. Flow diagram of the study population.

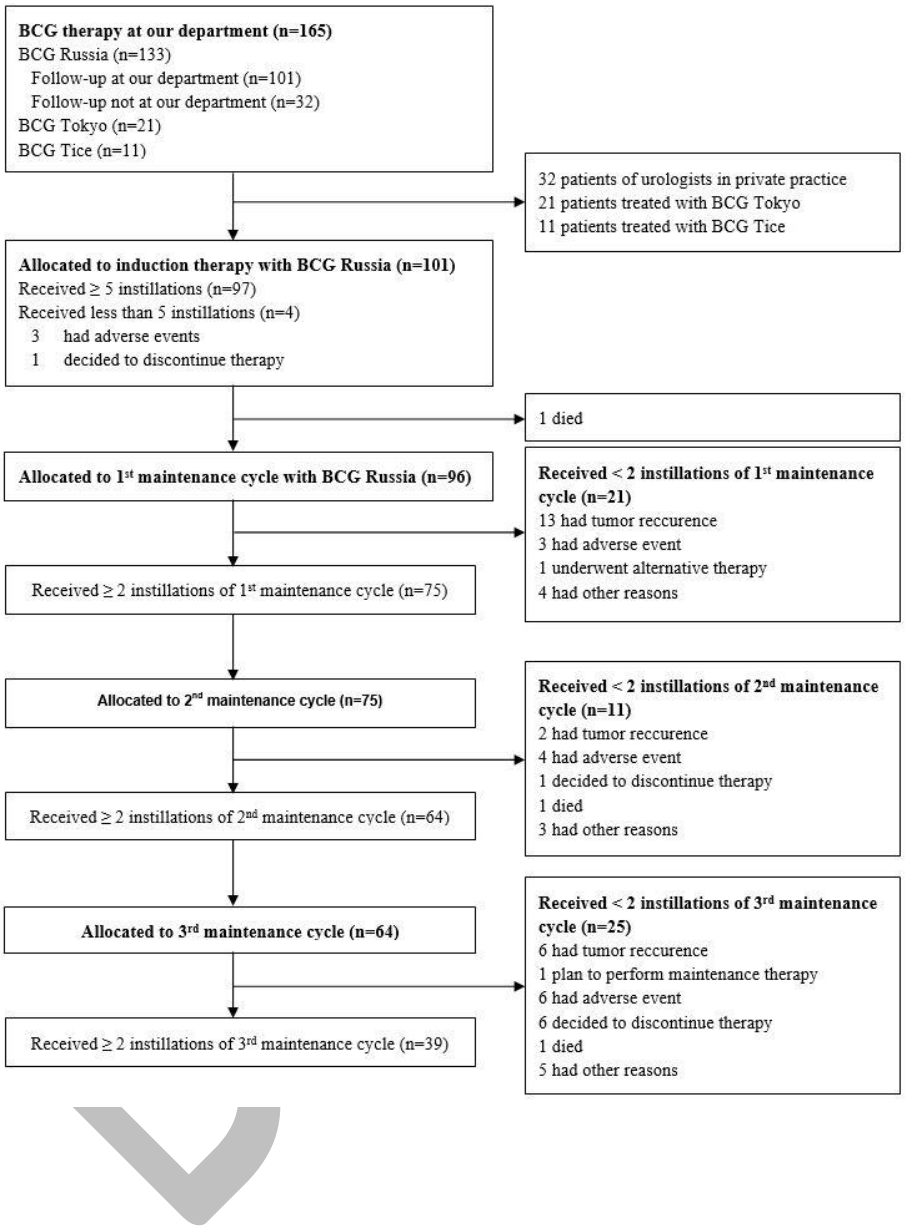

Figure 2. Kaplan-Meier plot for recurrence-free survival (RFS) after intravesical therapy with BCG Russia with a 95% confidence band.

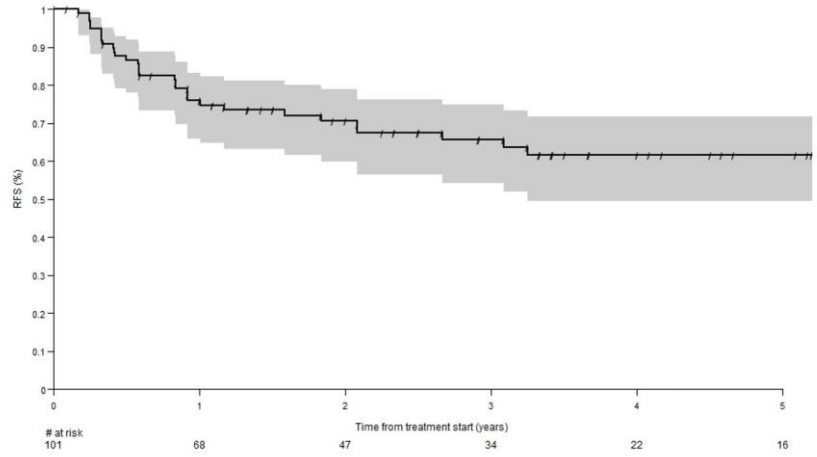

Table 1. Baseline patient and pathologic tumor characteristics before induction therapy with BCG Russia	
	N=101
Patient characteristics	
Age, years, median ± SD (range)	72±11 (37–92)
Sex, male, n (%)	86 (85.1)
Median followup time, y	3.3
Mean followup time, y	3.5
Tumor characteristics	**n (%)**
Primary tumor	
Yes	85 (84.2)
No	16 (15.8)
Number of papillary tumors	
Single	42 (41.6)
Multiple	41 (40.6)
Size of papillary tumors	
<3 cm	62 (61.4)
>3 cm	22 (21.8)
Pathologic T (pT) category	
pTa	54 (53.5)
pT1	30 (29.7)
CIS	
Pure	17 (16.8)

Concurrent	22 (21.8)
Tumor grade	
Low	14 (13.9)
High	87 (86.1)
Risk group*	
Intermediate	29 (28.7)
High	61 (60.4)
Very high	11 (10.9)

*Risk group assignment according to European Association of Urology non-muscle-invasive bladder cancer 2021 scoring model. BCG: bacillus Calmette-Guérin; CIS: carcinoma in situ; SD: standard deviation.

Table 2. Survival data after intravesical therapy with BCG Russia

	1 year	**3 years**	**5 years**
RFS (%) (CI)	75.9 (66–83)	65.6 (54–75)	61.6 (50–72)
PFS NMIBC (%) (CI)	94.7 (88–98)	89.8 (80–95)	89.8 (80–95)
PFS ≥T2 (%) (CI)	100 (100–100)	98.6 (90–100)	96.7 (87–100)
MFS (%) (CI)	100 (100–100)	96.6 (87–99)	96.6 (87–99)
CFS (%) (CI)	99 (93–100)	90.3 (81–95)	88.3 (78–94)

Summary of survival data after therapy with intravesical BCG Russia instillation therapy. BCG: bacillus Calmette-Guérin; CFS: cystectomy-free survival; CI: confidence interval; MFS: metastasis-free survival; PFS ≥T2: progression-free survival ≥T2 defined as tumor recurrence with a progress to stage ≥T2; PFS NMIBC: progression-free survival non-muscle-invasive bladder cancer defined as tumor recurrence with an upstaging (pTa to pT1) or upgrading (low-grade to high-grade) or new occurrence of CIS; RFS: recurrence-free survival.

Table 3. Percentage of patients with treatment-associated adverse events during BCG induction and maintenance therapy according to the recommended WHO rating scale				
	Class			
	I	**II**	**III**	**IV**
Systemic				
Fever	11.9	5.9		
Flu-like syndrome	11.9	2		
Headache	5.9	1		
Fatigability	5.9	1		
Myalgia	2	1		
Common bacterial sepsis				1
BCGitis			2	
Renal pain	2			
Circulatory collapse				2
Obstructive pyelonephritis			1	
Allergic exanthem			1	
Local				
Burning when urinating	42.6	2		
Nocturnal frequent micturition	28.7	1		
Diurnal frequent micturition	28.7			
Cystitis	18.8	3		
Hematuria	17.8			
Bladder contract	10.9	2		
Weak stream	3	1		
Prostatitis			2	
Stress incontinence	1	1		
Involuntary micturition	2			
Bladder instability	1			
Perineal pain	1			

BCG: bacillus Calmette-Guérin; WHO: World Health Organization.