Low-Dose Versus Standard Dose of Bacillus Calmette-Guerin in the Treatment of Nonmuscle Invasive Bladder Cancer

A Systematic Review and Meta-Analysis

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Abstract: Whether low-dose Bacillus Calmette-Guerin (BCG) treatment can reduce the side effects while maintaining efficacy for patients with nonmuscle invasive bladder cancer (NMIBC) is controversial.

To investigate whether low-dose BCG treatment can reduce the side effects while maintaining efficacy for patients with NMIBC when compared with standard-dose BCG treatment.

A comprehensive literature search of PubMed, EMBASE, CINAHL, LILACS, and CENTRAL databases was conducted to identify relevant randomized controlled trials (RCT) or quasi-randomized controlled trials (qRCT) that have assessed the efficacy of low- and standard-dose BCG therapy for patients with NMIBC. Systematic review and meta-analysis were performed according to Preferred Reporting Items for Systematic Reviews and Meta-analysis Criteria.

Six RCTs and 2 qRCTs were eligible for meta-analysis. Low-dose BCG instillation was not inferior to reduce the risk of bladder tumor recurrence (hazard ratio [HR], 1.15; 95% confidence interval [CI], 1.00–1.31; P = 0.05), meanwhile no difference was found regarding tumor progression (HR = 1.08; 95% CI, 0.83–1.42; P = 0.57). However, low-dose BCG provided a significantly lower incidence of overall side effects (RR = 0.75; 95% CI, 0.60–0.94; P = 0.01), systemic side effects (RR = 0.57; 95% CI, 0.34–0.97; P = 0.04), severe side effects (RR = 0.52; 95% CI, 0.36–0.74; P = 0.0003), and withdrawal due to BCG toxicity (RR = 0.49; 95% CI, 0.26–0.91; P = 0.02). In contrast, local side effects were comparable between low- and standard-dose arms (RR = 0.89; 95% CI, 0.73–1.08; P = 0.24).

Low-dose BCG instillation significantly reduces the incidence of overall side effects, especially severe and systemic symptoms in patients with NMIBC, while the oncological control efficacy of low-dose BCG is not inferior to standard-dose BCG. Further studies with stratification using different risk factors at randomization are required to assess whether the efficacy of low-dose BCG is comparable to standard dose BCG for different risk of patients.

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Abbreviations: BCG = Bacillus Calmette-Guerin, CI = confidence interval, HR = hazard ratio, NMIBC = nonmuscle invasive bladder cancer, qRCT = quasi-randomized controlled trials, RR = risk ratio, TURBT = transurethral resection of the bladder tumor.

INTRODUCTION

Approximately 75% of patients with bladder cancer present with nonmuscle invasive bladder tumors (NMIBC). Although NMIBC could be completely eradicated by transurethral resection of the bladder tumor (TURBT), it is still characterized by a high risk of recurrence and to a lesser extent progression to muscle-invasive bladder cancer. Therefore, adjuvant therapy is necessary for most of NMIBC patients. Intravesical Bacillus Calmette-Guerin (BCG) immunotherapy has been confirmed as a more effective adjuvant treatment than TURBT alone or TURBT plus chemotherapy in preventing recurrence of intermediate or high-risk NMIBC. Side effects and cost are the major disadvantages of intravesical BCG treatment; consequently, urologists are reluctant to recommend BCG to their patients. It has been reported that only about 50% of patients with intermediate or high-risk NMIBC receive BCG therapy, and adverse effects related to BCG are one of the major obstacles. Therefore, many strategies have been explored to reduce the side effects of BCG, the most studied option being a decrease in dose. Two multicenter randomized clinical trials (RCT) conducted by the European Organization for Research and Treatment of Cancer, Genito-Urinary Cancer Group (EORTC-GU) and Club Urologico Espanol de Tratamiento Oncologico (CUETO) have demonstrated that the efficacy of low-dose BCG was not inferior to standard-dose BCG in preventing bladder tumor recurrence and progression. However, conflicting findings regarding the ability of low-dose BCG to reduce potential toxicity were reported in the 2 studies. It was reported by Martinez-Pineiro et al that dose reduction could significantly diminish the toxicity of BCG, while Oddens et al found no differences in toxicity between low- and standard-dose BCG.
To examine if low-dose BCG could reduce side effects while maintaining sufficient efficacy relative to standard-dose BCG, we performed a meta-analysis of RCT or quasi-randomized controlled trials (qRCT) that assessed the efficacy of low-and standard-dose BCG therapy for patients with NMIBC.

**MATERIAL AND METHODS**

**Ethical Approval or Informed Consent Is Not Required for This Meta-Analysis Since Data Were Extracted From Previous Published Studies**

**Databases Search**

A systematic literature search was performed in October 2015 using PubMed/MEDLINE, EMBASE, CINAHL, LILACS, Cochrane Central Register of Controlled Trials (CENTRAL), International Clinical Trials Register (ICTRP) Search Portal, and ClinicalTrials.gov databases. The exact search strategy for PubMed is listed in the Supplementary S1, http://links.lww.com/MD/A559, and search strategies for other databases were similar. No limits were applied regarding language. Conference proceedings and reference lists of articles were also searched to obtain relevant literature.

**Article Selection and Quality Assessment**

Eligible RCT and qRCT studies had to meet the following criteria: Trials comparing different dose of BCG instillation for patients undergoing TURBT; patients included should have histologically confirmed NMIBC; and included studies must have been published in a peer-reviewed journal and adequate information provided or obtainable from the researchers. The qRCT studies were defined as RCTs in which allocations to treatment was obtained by predictable methods, for example, alternation, use of alternate medical records, or date of birth. We excluded trials that BCG was administered simultaneously with other adjuvant agents, such as interferon-alpha, for the patients. Trials with only conference abstracts available were not included because of a lack of detailed information. Eligibility assessment of published abstracts was performed independently by 2 reviewers (SXZ and ZSZ); disagreements between reviewers were further discussed with CLX. Full article text regarding the included abstracts was retrieved for further review (Figure 1). Pairs of reviewers (SXZ and ZSZ) worked independently to assess the quality of each included study; disagreements were discussed with CLX. The level of evidence of each study was assessed according to the criteria provided by the Oxford Centre for Evidence-based Medicine. The Cochrane Collaboration’s tool for assessing risk of bias was used to assess the methodological quality of all eligible studies.

**Study Outcomes and Definitions**

The primary outcome was treatment efficacy of BCG for NMIBC, which was measured by: time to events (tumor recurrence, progression, and metastasis); frequency of events (tumor recurrence, progression, and metastasis). Tumor recurrence was defined as the first time recurrence after TURBT.
TABLE 1. Eligible Studies Compare Low- and Standard-Dose BCG Instillation for NMIBC

| Study                  | Institution (Country)                  | Study Period | Study Type | Arms | Inclusion Criteria | LE† |
|------------------------|----------------------------------------|--------------|------------|------|--------------------|-----|
| Morales et al14        | Queen’s University                     | 1979–1988    | qRCT       | 2    | NMIBC              | 2b  |
| Martinez-Pineiro et al6| CUETO (Spain)                          | 1991–1992    | RCT        | 2    | NMIBC              | 1b  |
| Irie et al13           | Kitasato University school of Medicine | 1996–2001    | qRCT       | 2    | NMIBC              | 2b  |
| Martinez-Pineiro et al7| CUETO (Spain)                          | 1995–1999    | RCT        | 2    | T1G3 and CIS NMIBC | 1b  |
| Vijjan et al22         | Sanjay Gandhi Institute of Medical Sciences (India) | 2000–2005 | RCT | 3 | High risk NMIBC | 2b  |
| Agrawal et al21        | Medical College Agra (India)           | 2002–2005    | RCT        | 3    | NMIBC without CIS | 2b  |
| Inamoto et al23        | Osaka Medical College (Japan)          | 2008–2009    | RCT        | 2    | NMIBC              | 2b  |
| Oddens et al3          | EORTC-GU (Europe)                      | 1997–2005    | RCT        | 2    | Intermediate or high risk NMIBC | 1b  |

BCG = Bacillus Calmette-Guerin, CIS = carcinoma in situ, CUETO = Club Urologicco Espanol de Tratamiento Oncologico, EORTC-GU = European Organization for Research and Treatment of Cancer Genito-Urinary cancer group, LE = level of evidence, NMIBC = nonmuscle invasive bladder cancer, qRCT = quasi randomized controlled trial, RCT = randomized controlled trial.

† Using criteria provided by the Oxford Centre for Evidence-based Medicine.

progression was defined as upgrade of tumor grade and stage or evidence of metastasis. The secondary outcome was toxicity of BCG, which was measured by frequency of side effects. Side effects were classified by National Cancer Institute Common Toxicity Criteria (NCI-CTC), severe side effects were defined with grade 3 to 5.10

Data Extraction and Synthesis

Data from the included literature were extracted by 2 independent reviewers (SXZ and XWY); disagreements were resolved by discussion. Extracted data included: the characteristics of trial participants; time to bladder tumor recurrence, progression, and metastasis; the rate of recurrence, progression, and metastasis; and disease-specific survival and related side effects. Standard dose BCG was defined as the recommended dose of different BCG strains, while low-dose BCG could vary from 1/6 to 2/3 of the standard dose. We contacted 7 authors for further information regarding dose of BCG, randomization method, details of patients lost to follow-up, and criteria for side effects stratification,3,7,11–16 and 4 responded with accurate dosage of BCG,3 randomization method,14 criteria for side effects stratification,7 and details of conference abstract.11,16

Statistical Analysis

Time to event outcomes such as time to bladder tumor recurrence, progression, and metastasis were measured using the hazard ratio (HR) with a 95% confidence interval (CI). For studies with no published HRs, but with Kaplan–Meier curve or Wilcoxon P values, the method proposed by Tierney et al17 was employed to estimate the HR and 95% CI. The relative risk ratio (RR) was used for dichotomous variables, such as incidence of side effects. Multiarm trials would be included only with those interventions were relevant to the review and meet the inclusion criteria. Study with more than one arm meet the inclusion criteria would be combined by the method proposed by Hamling et al.15 This method ensured the data were included only once when pooling data and took into consideration the correlation between estimates.

Heterogeneity among the included studies was assessed using Cochran Q and I² statistics.19 If the fixed-effect model (Mantel-Haenszel method) was used to pool estimates if no significant heterogeneity was detected (I² < 50% and P > 0.1), otherwise, the random effect model (DerSimonian-Laird method) was used. The pooled effects were examined using the Z-test and α < 0.05 was considered statistically significant. Publication bias was examined using funnel plots.50 Sensitivity analysis was conducted as prespecified in the protocol, analysis was performed based on trial quality. Subgroup analyses were performed as indicated in the protocol, different BCG strains; BCG induction and BCG maintenance treatment; and different risks of bladder cancer patients. A meta-analysis was performed using Review Manager software (RevMan v 5.3, Cochrane Collaboration, Oxford, UK).

RESULTS

Search Results and Study Characteristics

Nine eligible reports were identified for qualitative evaluation (Figure 1), but one of them was assessed as a low-quality RCT with unclear randomization method and high risk of incomplete outcome data and selective reporting.15 Authors of this article were contacted for further information but we received no reply, this study was thus discarded. The baseline characteristics of the 8 studies included were presented in Tables 1 and 2. Two studies were 3-arm trials and the 2 different doses of low-dose BCG arms were combined into a single arm by the method described before.21,22 The 8 studies included 1260 cases in the low-dose and 1199 cases in the standard dose arms. Patient demographics in the included trials are detailed in Table 3.

Assessment Risk of Bias

Eight eligible RCTs or qRCTs were eventually included to estimate the corresponding pooled estimates.3,6,7,13,14,21–23 Six studies were classified with proper randomization method,3,6,7,21–23 and 2 studies with patients sequentially allocated were categorized as qRCTs.13,14 Allocation concealment was not performed or unclear for all the included studies. Although none of the studies performed blinding of participants and personnel or masked the outcome assessors, the primary outcomes, for example, tumor recurrence and progression, were not likely to be influenced; therefore, corresponding domains...
were grades as ‘‘low risk.’’ Two studies were grades as high risk of attrition bias.13,21 The assessment of risk of bias outcome of included studies was summarized in Figure 2A, B.

Primary Outcomes

Time to First Events Outcome

Oncological outcomes reported by Morales et al14 and Agrawal et al21 were shown as binary variables with a median side effects (RR included studies was summarized in Figure 2A, B.

Secondary Outcomes

Side Effects

Regarding local side effects, there was no significant difference in overall local side effects (RR = 0.74; 95% CI, 0.73–1.08; \( P = 0.24; \) \( I^2 = 76\% \)), hemorrhia (RR = 0.57; 95% CI, 0.28–1.15; \( P = 0.12; \) \( I^2 = 87\% \)), and cystitis (RR = 0.65; 95% CI, 0.27–1.59; \( P = 0.35; \) \( I^2 = 96\% \)), while the frequency was significantly lower in the low-dose arm (RR = 0.62; 95% CI, 0.41–0.95; \( P = 0.03; \) \( I^2 = 83\% \)) (Figure 4 and Supplementary Figure 1, http://links.lww.com/MD/A560). Concerning systemic side effects, a significant difference was found in overall side effects (RR = 0.57; 95% CI, 0.34–0.97; \( P = 0.04; \) \( I^2 = 70\% \)), fever (RR = 0.47; 95% CI, 0.32–0.68; \( P < 0.0001; \) \( I^2 = 48\% \)), and malaise (RR = 0.63; 95% CI, 0.44–0.92; \( P = 0.02; \) \( I^2 = 50\% \)) (Figure 4 and Supplementary Figure 2, http://links.lww.com/MD/A560). Heterogeneity was significant for all side effect meta-analyses except for severe side effects (\( P = 0.0003; \) \( I^2 = 0\% \)), the random effect model was thus used for pooled estimates.

Subgroup and Sensitivity Analysis

Maintenance intravesical BCG instillation was performed in 3 studies,6,7,21 while patients only received BCG induction treatment in the other trials.13,14,22,23 The tumor recurrence risk and overall side effects were not significantly different between the low- and standard-dose arms when trials were divided into different subgroups (Figures 3A and 4A). Subgroup analysis of different BCG strains was also predetermined in the protocol. However, 5 different strains were used in the 8 studies; thus, this subgroup analysis was not performed. Subgroup analysis of different risks of patients was not performed since stratified analysis regarding different risks of bladder cancer was only performed by Oddens et al.3

### TABLE 2. Patient Demographics of Included Trials

| Study | No. of Patients | Mean Age, year | Gender Male/ Female | Type of Tumor | No. of Tumor | Stage | Grade |
|-------|----------------|----------------|---------------------|---------------|-------------|-------|-------|
| Morales et al14 | 49/48 | – | – | – | – | – | – |
| Martinez–Pineiro et al6 | 248/252 | 62.9/64.1 | 226/22, 225/27 | 155/93, 153/99 | 75/173, 88/164 | Ta:68/61; T1:164/168; CIS:16/23 | G1:44/42; G2:167/150 |
| Irie et al13 | 41/39 | 61.6/62.2 | 33/8, 35/4 | 38/3, 32/6 | 26/15, 25/14 | Ta:9/12; T1:32/27; CIS:3/0 | G1:23/16; G2:16/17; G3:2/6 |
| Martinez–Pineiro et al7 | 73/82 | 68.3/65.8 | 66/7, 77/5 | 51/22, 57/25 | 35/38, 38/44 | Ta:4/5; T1:61/62; CIS:29/36 | G1:–; G2:–; G3:65/67 |
| Vijjan et al22 | 65/41 | 54.0/59.0 | 55/10, 36/5 | 44/21, 23/18 | 53/12, 29/12 | Ta:16/11; T1:47/30; CIS:0 | G1:29/25; G2:31/9; G3:12/7 |
| Agrawal et al21 | 88/40 | – | – | – | – | – | – |
| Inamoto et al23 | 18/20 | 71.0/72.7 | 14/4, 17/3 | 13/5, 16/4 | 8/8, 9/7 | Ta:8/6; T1:10/12; CIS:0/1 | G1:3/4; G2:10/8; G3:5/8 |
| Oddens et al3 | 678/677 | 68.5/67.0 | 547/128, 552/119 | 403/272, 390/281 | 95/577, 84/586 | Ta:431/421; T1:244/249; CIS:– | G1:194/193; G2:309/289; G3:173/188 |

CIS = carcinoma in situ, L = low dose, S = standard dose.
4 The subtotal may possibly not equal to the gross total of patients due to unknown types of classifications.
† The criteria for pathological classification were not specified in all studies, only a few of them were described as based on 1997 TNM classification and 1973 World Health Organization grading system.
‡ The studies conducted by Agrawal et al.21 and Vijjan et al.22 were divided as 80 versus 120 mg trial and 40 versus 120 mg trial, respectively.
### TABLE 3. Treatment Characteristics and Definition of Primary Outcome of Studies

| Study                  | Group, mg  | Strain                  | Regimen       | Mean Follow-Up, months\(^1\) | Definition of Recurrence                                                                 | Definition of Progression                        |
|------------------------|------------|-------------------------|---------------|-------------------------------|----------------------------------------------------------------------------------------|-----------------------------------------------|
| Morales et al\(^{14}\) | 60 vs 120  | Institut Armand Frappier| 1/wk\#6       | 21                            | Persistent or recurrent tumor were found at any time during follow-up                   | NA                                            |
| Martinez-Pineiro et al\(^{6}\) | 27 vs 81  | Connaught               | 1/wk\#6 + 1/2wk\#6 | 69                            | First positive biopsy or reappearance of cytology after treatment                       | Pathological confirmation of muscle invasion or extravesical extension |
| Irie et al\(^{13}\)   | 40 vs 80   | Tokyo 172               | 1/wk\#6       | 20, 27.5                      | NA                                                                                     | Progression in tumor grade or stage            |
| Martinez-Pineiro et al\(^{7}\) | 27 vs 81  | Connaught               | 1/wk\#6 + 1/2wk\#6 | 61                            | First relapse occurred, persisted, or reappearance of cytology after completion of treatment | NA                                            |
| Vijjan et al\(^{22}\) | 40 vs 80 vs 120 | Danish 1331     | 1/wk\#6       | 24, 34, 36                    | NA                                                                                     | NA                                            |
| Agrawal et al\(^{21}\) | 40 vs 80 vs 120 | Danish 1331     | 1/wk\#6 + 1/mo*1yr | 36                            | NA                                                                                     | NA                                            |
| Inamoto et al\(^{23}\) | 40 vs 80   | Tokyo 172, Connaught    | 1/wk\#6       | 16.4, 16.5                    | First bladder recurrence of any stage or grade                                           | NA                                            |
| Oddens et al\(^{3}\)  | 40 vs 120  | OncoTICE                | 1/wk\#6 + 1yr or 3yr maintenance | 85.2                           | First recurrence including progression, metastasis, death due to bladder cancer         | Muscle-invasive progression, distant metastasis, death due to bladder cancer |

\(\text{DSS} = \text{disease-specific survival, mo = month, NA = not available, wk = week, yr = year.}\)

\(^1\) The mean follow-up duration was described respectively for different groups in several studies.

\(^2\) The studies conducted by Agrawal et al\(^{21}\) and Vijjan et al\(^{22}\) were divided as 80 versus 120mg trial and 40 versus 120mg trial, respectively.
The primary outcomes of the meta-analysis were unchanged after qRCT trials were omitted in the sensitivity analysis (HR = 1.14, 95%CI, 0.54–1.31, \( P = 0.06 \), figure not shown), when the studies only with level of evidence Ia were included, the tumor recurrence HR was 1.14 (95%CI, 1.00–1.32, \( P = 0.06 \)) (Figure 2A). No significant evidence of publication bias for primary outcome was detected based on funnel plots (Supplementary Figure 3, http://links.lww.com/MD/A560).

**DISCUSSION**

Intravesical instillation of BCG has been confirmed as the most effective strategy for the prophylaxis of NMIBC recurrence after complete TURBT. However, BCG side effects present a serious therapeutic conundrum for urologists.2 Numerous investigations have been conducted regarding reduction of adverse effects while maintaining or improving tumor control, for example, antibiotic prophylaxis, concurrent use of interferon, and dose reduction.3,24,25 Dose reduction is one of the most investigated methods for reducing the side effects of BCG instillation. Most studies have suggested that dose reduction could significantly reduce the incidence of side effects without compromising treatment efficacy.6,7,21,22 However, the largest RCT conducted by EORTC-GU found no significant difference between low- and standard-dose BCG instillation.3,5 Thus, the present analysis was conducted to systematically identify and critically evaluate high-quality trials, comparing low- and standard-dose BCG instillation. The important finding of our meta-analysis was that the oncological efficacy of low-dose BCG was not inferior to standard-dose; however, low-dose BCG could significantly reduce side effects, especially systemic side effects and severe side effects.

**The Role of Low-Dose BCG in Tumor Control**

The pooled estimate of the primary outcome was consistent with the majority of results from previous studies. Two convincing studies conducted by CUETO6 and EORTC-GU3 found low-dose BCG was not inferior to the standard dose, with an HR of 1.09 (95%CI, 0.79–1.51; \( P = 0.045 \)) and 1.15 (95%CI, 0.98–1.35; \( P = 0.5864 \)), respectively. The study conducted by EORTC-GU was designed as a noninferiority study that needed \( \alpha < 0.0025 \) to ascertain significance. Therefore, the pooled results of RCT or qRCT studies with larger sample sizes might be crucial in confirming these nonsignificant differences. Furthermore, there was also no significant difference for tumor progression regarding different BCG doses, which agreed with previous clinical trials.

Although the length and frequency of BCG instillation are still controversial, it was recommended by the European Association of Urology that at least 1 year of BCG instillation was required to maintain its efficacy.2 One of the most widely used schedules is based on the Southwest Oncology Group regimen, which is initiated with 6-weekly BCG instillations followed by 3-weekly instillations at 3 and 6 months, and subsequently every 6 months for 3 years.2,26 However, BCG was administered weekly for 6 weeks without maintenance among half of the included studies. Intravesical BCG
FIGURE 4. Forest plots for side effects: (A) overall side effects and subgroup analysis by different Bacillus Calmette-Guerin (BCG) instillation schedules, (B) local side effects, (C) systemic side effects, (D) severe side effects, and (E) withdraw rate.
### TABLE 4. Results of RCT Studies Comparing Low- and Standard-Dose BCG With Only Abstracts Available or Incomplete Data

| Study                          | No. of Arms | No. of Patients | Design | Year | Country | Regimen | Follow-Up, month | Main Conclusion |
|-------------------------------|-------------|----------------|--------|------|---------|---------|----------------|-----------------|
| Ennifar and colleagues2       | 2           | 275             | RCT    | 2014 | Turkey  | 1/3     | 207            | Reducing the dose of BCG decreased its toxicity while efficacy was increased by combining low-dose BCG with IFN-Y. |
| Yokomizo et al                 | 1           | 136             | RCT    | 2014 | Japan   | 1/3     | –              | No significant difference in recurrence-free survival (HR = 1.14; 95% CI, 1.01–1.32). |
| Morabito et al1               | 2           | 110             | RCT    | 2009 | India   | 1/3     | 36             | Recurrence rate was 13.2% and 25.5% in low-dose and standard-dose, respectively, while toxicity rate was <10% in low-dose. |
| Basoli et al6                 | 2           | 210             | RCT    | 1999 | Italy   | 1/3     | 60             | Low-dose had similar disease-free survival to standard dose. |
| Yokukaya et al11              | 2           | 80              | RCT    | 1998 | Turkey  | 1/3     | 33.5           | Recurrence rate was 10% and 21.2% in low-dose and standard-dose, respectively (P = 0.05). |

### Side Effects of Low-Dose BCG

The main purpose of adopting low-dose BCG instillation is to decrease BCG toxicity. Most investigations have demonstrated the efficacy of low-dose BCG in reducing side effects.6,7,13,14,21–23 In contrast, the largest RCT trial conducted by the EORTC-GU group found no significant differences in side effects between low- and standard-dose arms.20 However, our meta-analysis suggested that low-dose BCG had significant efficacy in decreasing the incidence of overall side effects.
(RR = 0.75; 95%CI, 0.60–0.94; \( P = 0.01 \)). In clinical practice, severe side effects associated with BCG instillation are of the utmost concern. The current meta-analysis demonstrated that low-dose BCG had a 48% lower risk of severe side effects than the standard dose (RR = 0.52; 95%CI, 0.36–0.74; \( P = 0.0003 \)). Patients were more compliant to accept low-dose BCG instillation and this was reflected by a lower toxicity resulted withdrawal rate in the low-dose arm (RR = 0.49; 95%CI, 0.26–0.91; \( P = 0.02 \)). The main benefit of low-dose BCG, in terms of side effects, was a decrease in systemic side effects. It was found in our meta-analysis that the incidence of systemic side effects, especially fever and malaise, was significantly reduced; while local side effects (eg, hematuria and cystitis) were comparable in the low and standard dose arms (with the exception of frequency).

The result of pooled estimate of adverse effect should be considered with caution. It should be noted that the heterogeneity of all the pooled estimates of side effects was significant except for severe side effects (\( P = 0.66; I^{2} = 0\% \)). This heterogeneity might be the result of different standards of reporting regarding the side effects of BCG treatment and schedules of BCG instillation. The pooled data regarding severe side effects with grade 3 to 4 toxicity were based on the reports using the NCI-CTC grading of severity. Therefore, no significant heterogeneity was detected in this situation. Different standards and definitions of adverse effects reporting were likely to play a critical role in heterogeneity. This reflects the importance of adopting a unified standard to classify side effects, which would make the results of different studies considerably more compatible. To date, however, no standard guidelines or criteria exist for reporting the side effects of adjuvant prophylaxis treatment in the field of urology.\(^2,30\)

**Study Limitations**

The present analysis was conducted based on 8 studies involving 8 studies. Six of the 8 studies were RCTs with low (1 study) to medium (5 studies) methodological quality, and 2 studies were qRCTs with patients sequentially allocated to each arm. Two studies did not adhere to the intention-to-treat analysis principle.\(^13,14\) The blinded method was not used in any of the 8 studies. However, the primary outcome of these studies was oncological outcome, for example, recurrence and progression, which was less likely to be influenced by the unblinded method. Several RCTs involving only conference abstracts were not included in the meta-analysis because the methodological quality was not assessable, and the data were incomplete for extraction; the results of these studies with only abstracts available are listed in Table 4.\(^11,12,15,16,31\) Last but not least, the clinical relevancy of bladder tumor recurrence changes dramatically with the risk category; however, no study was randomized with risk factor stratifications. Therefore, it was not possible to infer whether the efficacy of low-dose BCG was comparable to both intermediate and high risk patients.

**Implication for Future Studies**

There is a lack of evidence regarding comparison of the efficacy of low-dose BCG with standard BCG for different risks concerning bladder tumors. Patients need to be stratified using different risk factors at randomization in future studies of low-dose BCG. The current multicenter studies involving BCG are usually conducted in Europe; the results of these studies may not represent the immune response to BCG on other continents. In developing countries with higher tuberculosis exposure and poor sanitary conditions, the efficacy of BCG may vary and requires proving in large multicenter RCT studies. Finally, the heterogeneity of side effects suggests that unified criteria and definitions for their recording are strongly expected to be established in future clinical trials.

In conclusion, this meta-analysis of 8 RCTs or qRCTs comparing low- and standard-dose BCG suggests that low-dose BCG instillation significantly reduces the incidence of overall side effects, especially severe and systemic symptoms in patients with NMIBC, while the oncological control efficacy of low-dose BCG is not inferior to standard dose BCG. Low-dose BCG for patients with high-risk factors should be recommended with meticulous discussion, further studies with stratification using different risk factors at randomization are required to assess whether the efficacy of low-dose BCG is comparable to standard-dose BCG for the different risk of patients.

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