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Low-dose versus standard-dose bacille Calmette–Guérin for non-muscle-invasive bladder cancer: Systematic review and meta-analysis of randomized controlled trials

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Purpose: Intravesical BCG (bacille Calmette–Guérin) instillation in patients with non-muscle-invasive bladder cancer decreases the risk for tumor recurrence and progression. After one BCG product was discontinued, a chronic global BCG shortage occurred. We focused on identifying a reduced dose of BCG that could maintain efficacy and reduce adverse effects.

Materials and Methods: We conducted a comprehensive literature search of PubMed, Embase, the Cochrane Library, CINAHL, Web of Science, and Scopus to identify randomized controlled trials through April 2021. The odds ratios (ORs) and 95% confidence intervals (CIs) for the low and standard doses in nine studies were compared. A low dose was defined as a low volume of BCG compared with the standard BCG dose (Armand Frappier, 120 mg; Connaught, 81 mg; Danish 1331, 120 mg; modified Danish 1331, 120 mg; Tokyo 172, 80 mg).

Results: The low-dose group experienced aggravated recurrence (OR, 1.45; 95% CI, 1.09–1.94; p=0.01) but similar progression (OR, 1.11; 95% CI, 0.76–1.62; p=0.59), similar cancer-specific survival (OR, 1.02; 95% CI, 0.60–1.75; p=0.93), similar overall survival (OR, 1.09; 95% CI, 0.76–1.56; p=0.65), favorable adverse effects (OR, 0.41; 95% CI, 0.28–0.62; p<0.0001), and favorable withdrawal (OR, 0.42; 95% CI, 0.25–0.71; p=0.001).

Conclusions: Low-dose BCG had more unfavorable outcomes than did standard-dose BCG in terms of recurrence. Tumor progression, cancer-specific survival, and overall survival were similar between the doses. Low-dose BCG improved adverse effects and withdrawal. In the setting of BCG shortage, low-dose BCG may have strong potential as an alternative.

Keywords: Administration, intravesical; Adverse effects; Recurrence; Urinary bladder neoplasms

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INTRODUCTION

Non-muscle-invasive bladder cancer (NMIBC), or superficial bladder cancer, constitutes approximately 70% of all bladder cancers [1,2]. Although NMIBC initially appears to be non-life-threatening, 50% to 70% of NMIBC will recur and 10% to 20% of NMIBC will progress to muscle invasion [1,2]. Several trials have explored reducing the recurrence and progression of NMIBC, and intravesical bacille Calmette–Guérin (BCG) has displayed greater efficacy than other chemotherapeutic agents [3]. BCG instillation after transurethral resection was introduced in the mid-1970s and has been established as standard therapy for high-risk tumors (T1 and/or high-grade and/or carcinoma *in situ*) [4]. Nevertheless, high-risk tumors often exhibit progression and unfavorable outcomes. Although the mechanism remains poorly understood, the immune response is clearly an important component of BCG action [5]. A better understanding of the mechanism of action may improve efficacy of and tolerance to treatment. To date, however, the optimal BCG strategy remains controversial.

BCG adverse effects are one of the main causes of therapy withdrawal. The most common adverse effect is local symptoms. Approximately 63% of patients develop local symptoms, such as cystitis, frequency, and hematuria [6]. The systemic adverse effects of malaise, rash, fever, and sepsis are observed in approximately 31% of patients [6]. Several trials have investigated methods to reduce these adverse effects, such as the addition of antibiotics, anticholinergics, isoniazid, or intravesical lidocaine [7]. Dose reduction of BCG could be a way to reduce the adverse effects.

Unfortunately, Sanofi Pasteur (Lyon, France) halted production of the BCG Connaught strain because of inability to maintain long-term sustainability and a stable supply [8]. Quality testing, validation, and packaging of BCG are time-consuming because of the slow growth of microorganisms; thus, a BCG shortage has begun [8]. There have been no meta-analyses conducted on various study results such as oncologic outcomes and adverse effects of low-dose BCG since the start of the BCG shortage. Considering the BCG shortage, we studied whether a lower dose could maintain efficacy while reducing adverse effects.

EVIDENCE ACQUISITION

1. Ethics statement

This meta-analysis did not require ethical approval because the data were synthesized from previously published studies.

2. Protocol and registration

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This review was registered in the PROSPERO International Prospective Registry of Systematic Reviews (CRD42021247497).

3. Search strategy

A comprehensive literature search was conducted by using several databases (PubMed, Embase, the Cochrane Library, CINAHL, Web of Science, and Scopus). The date was restricted to articles published on or before April 6, 2021; the search was conducted on April 16, 2021. The search specifics were as follows: ("urinary bladder neoplasm"[MeSH] OR "bladder cancer" OR "bladder tumor*" OR "Bladder Neoplasm*") AND ("BCG Vaccine"[MeSH] OR "Bacillus Calmette Guerin Vaccine" OR BCG OR "low dose"). The search criteria were used to identify all potentially relevant articles. A low dose was defined as a low volume of BCG compared to the BCG standard dose (Armand Frappier, 120 mg; Connaught, 81 mg; Danish 1331, 120 mg; modified Danish 1331, 120 mg; Tokyo 172, 80 mg).

After combining the results, two authors (S.Y.C. and M.S.H.) independently selected the relevant studies. The Kappa value (κ) was assessed for interrater validity. Any conflicts between the two reviewers were resolved through discussion.

4. Eligibility criteria

The inclusion criteria were as follows: 1) the patients had NMIBC; 2) the intervention was intravesical BCG therapy; 3) the comparison was based on the BCG dose; 4) the outcomes were recurrence, progression, cancer-specific survival, overall survival, adverse effects, and withdrawal; and 5) the studies were randomized controlled trials (RCTs). The exclusion criteria were review articles, animal studies, articles not in English, duplicated studies, maintenance treatments, additional treatments, and nonstandard doses of BCG.

5. Data extraction and collection

Two authors (S.Y.C. and M.S.H.) independently reviewed each eligible article and extracted the data. The data included: 1) publication data (name of first author and publication year); 2) population data (sample size of each group and definition of progression or adverse effects); 3) tumor data (tumor stage and grade); 4) treatment data (BCG dose, duration, and strain); and 5) outcome data (recurrence, progression, cancer-specific survival, overall survival, adverse effects, and withdrawal).

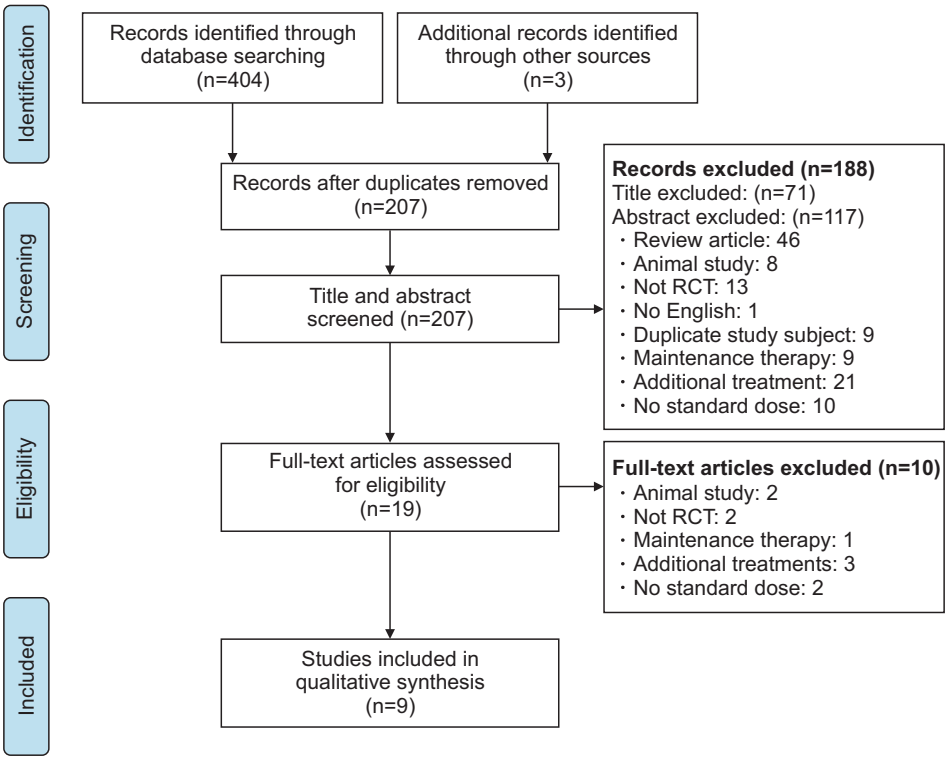

Fig. 1. Flow diagram. RCT, randomized controlled trial.

6. Assessment of risk of bias

The risk of bias was assessed by two authors independently using the Cochrane Collaboration's risk of bias tool [9]. Random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases were assessed. Any disagreements were resolved through discussion.

7. Statistical analysis

The data analyses were conducted by using Review Manager software (version 5.4; Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). The statistical heterogeneity was assessed with I^2 statistics: I^2>50%, substantial heterogeneity; 20%<I^2≤50%, moderate heterogeneity; and I^2<20%, low heterogeneity. Odds ratios (ORs) with 95% confidence intervals (CIs) for the forest plot were measured. Meta-regression analyses with a mixed-effects model were also performed to assess the effects of the potential moderators (study year <2000 vs. ≥2000). The interrater reliability was deemed as fair (κ=0.21–0.40), moderate (κ=0.41–0.60), substantial (κ=0.61–0.80), or almost perfect (κ=0.81–1.00). Statistical significance was set at $p<0.05$, and all reported p-values were from two-sided versions of the respective tests.

EVIDENCE SYNTHESIS

1. Study selection

We identified 404 articles through the initial database search and an additional 3 articles through other sources. The number of duplicate publications was 200, leaving 207 records after we removed the duplicates. A total of 188 articles were excluded by reviewing the title and abstract, and 10 articles were excluded after reviewing the full text. Finally, nine articles were included in the meta-analysis (κ=0.88, almost perfect agreement). The selection process is illustrated in the flow diagram in Fig. 1.

2. Study characteristics

In total, 1,217 patients were included in the nine eligible studies (low dose, n=612 vs. standard dose, n=605; Table 1). The studies were published from 1992 to 2016.

The treatment characteristics are listed in Table 2. The Connaught strain was used in four studies [10-13]. The Tokyo 172 strain was used in three studies [13-15]. Two studies used the Danish 1331 strain [16,17], while one study used the Armand Frappier strain [18]. The standard dose of each strain was 81 mg of Connaught, 80 mg of Tokyo 172, 120 mg of Danish 1331, and 120 mg of Armand Frappier. Most studies provided 6 weekly instillations [10,13,14,16-18], although one study used 8 instillations [15] and two studies, 12 instillations [11,12].

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Table 1. Randomized controlled trials included in meta-analysis comparing low-dose BCG with standard-dose BCG

Study	Year	No. of patients		Age (y)		Sex (F/M)		Definition of progression	Cystoscopy follow-up
		Low-dose	Standard dose	Low-dose	Standard-dose	Low-dose	Standard dose		
Morales et al. [18]	1992	49	48	NA	NA	NA	NA	NA	4, 12, and 24 weeks and at 6- to 12-month intervals thereafter
Yalçinkaya et al. [10]	1998	25	25	56.28 (37–70)	55.27 (32–68)	4/21	3/22	Increase of stage or grade of the papillary tumor	NA
Kumar et al. [16]	2002	13	13	55.9±10.83	56.7±12.8	2/11	1/12	NA	Every 3 months
Martínez-Piñeiro et al. [11]	2002	248	252	62.9±11.6	64.1±10.3	22/226	27/225	Muscle invasion, extravesical extension, metastases	NA
Irie et al. [14]	2003	41	39	62.2±11.2	61.6±15.7	8/33	4/35	Up-grade or up-stage	Every 3 months for the first 2 years and every 6 months afterward
Martínez-Piñeiro et al. [12]	2005	73	82	68.3±8.8	65.8±11.1	7/66	5/77	Muscle-invasive, distant metastases	NA
Vijjan et al. [17]	2006	65	41	54±11.8 (80 mg) 54±12.4 (40 mg)	59±10.2	4/33 (80 mg) 6/22 (40 mg)	5/36	Muscle-invasive disease	Every 3 months
Inamoto et al. [13]	2013	18	20	71.0±10.8	72.7±10.5	4/14	3/17	Muscle-invasive disease or distant metastases	Every 3 months
Yokomizo et al. [15]	2016	81	85	NA	NA	NA	NA	Muscle-invasive bladder	Every 3 months for the first 2 years and every 6 months after 2 years

Values are presented as number only, mean (range), or mean±standard deviation.
BCG, bacille Calmette–Guérin; F/M, female/male; NA, not available.

Table 2. Inclusion criteria and treatment characteristics

Study	Inclusion criteria	BCG dose (mg)		BCG strain	BCG instillation number
		Low-dose	Standard-dose		
Morales et al. [18]	Ta, T1, CIS	60	120	Armand Frappier	6
Yalçinkaya et al. [10]	Ta, T1	54	81	Connaught	6
Kumar et al. [16]	TaG2-3, T1G1-3	40	120	Modified Danish 1331	6
Martínez-Piñeiro et al. [11]	Recurrent Ta, T1, CIS	27	81	Connaught	12
Irie et al. [14]	Ta, T1	40	80	Tokyo 172	6
Martínez-Piñeiro et al. [12]	T1G3, CIS	27	81	Connaught	12
Vijjan et al. [17]	Ta or T1 with >G1, size >1 cm, multiple, recurrent	40/80	120	Danish 1331	6
Inamoto et al. [13]	TaG2-3, T1G1-3 with ≤3 cm	40	81	Tokyo 172 (low dose) Connaught (standard dose)	6
Yokomizo et al. [15]	CIS, unresectable Ta or T1	40	80	Tokyo 172	8

BCG, bacille Calmette–Guérin.

3. Assessment for risk of bias

The results of the assessment of the risk of bias in the included studies are summarized in Fig. 2. Adequate randomization methods and allocation concealment were described in five [11,12,15-17] and two studies [11,12], respectively. Blinding of the outcome assessment was performed in one study [16].

4. Tumor recurrence

The results of recurrence were described in nine studies [10-18]. Among 612 patients in the low-dose group and 605 patients in the standard-dose group, 34.0% and 27.4%, respectively, experienced recurrence during follow-up. Compared with the standard dose, the low-dose group had a poorer recurrence rate (OR, 1.45; 95% CI, 1.09–1.94; p=0.01). There was low heterogeneity (p=0.33, I^2=13%; Fig. 3A). The results of the meta-regression analysis indicated that studies conducted before 2000 had greater overall heterogeneity (p<0.01).

5. Tumor progression

Although eight studies included progression, one study reported no progression events [13]. In the low-dose group, 11.5% of patients experienced progression compared with 11.0% in the standard-dose group. There was no significant difference between the groups (OR, 1.11; 95% CI, 0.76–1.62; p=0.59). There was no interstudy heterogeneity (p=0.99, I^2=0%; Fig. 3B).

6. Cancer-specific survival

Although four studies surveyed cancer-specific survival, two studies did not [13,17]. In the low-dose group, 7.2% of patients died of bladder cancer compared with 7.6% in the standard-dose group. There was no significant difference between the groups (OR, 1.02; 95% CI, 0.60–1.75; p=0.93). There was no interstudy heterogeneity (p=0.56, I^2=0%; Fig. 3C).

7. Overall survival

Although four studies surveyed overall survival, there was no assessment of overall survival in one study [13]. Among 403 patients in the low-dose group and 395 patients in the standard-dose group, 19.4% and 19.2% died during follow-up, respectively. There was no significant difference between the groups (OR, 1.09; 95% CI, 0.76–1.56; p=0.65) and no interstudy heterogeneity (p=0.93, I^2=0%; Fig. 3D).

8. Adverse effects

Among seven studies, three [13,17,18] reported total adverse effects, and four studies [10-12,14] reported various adverse effects. Because the addition of various adverse effects

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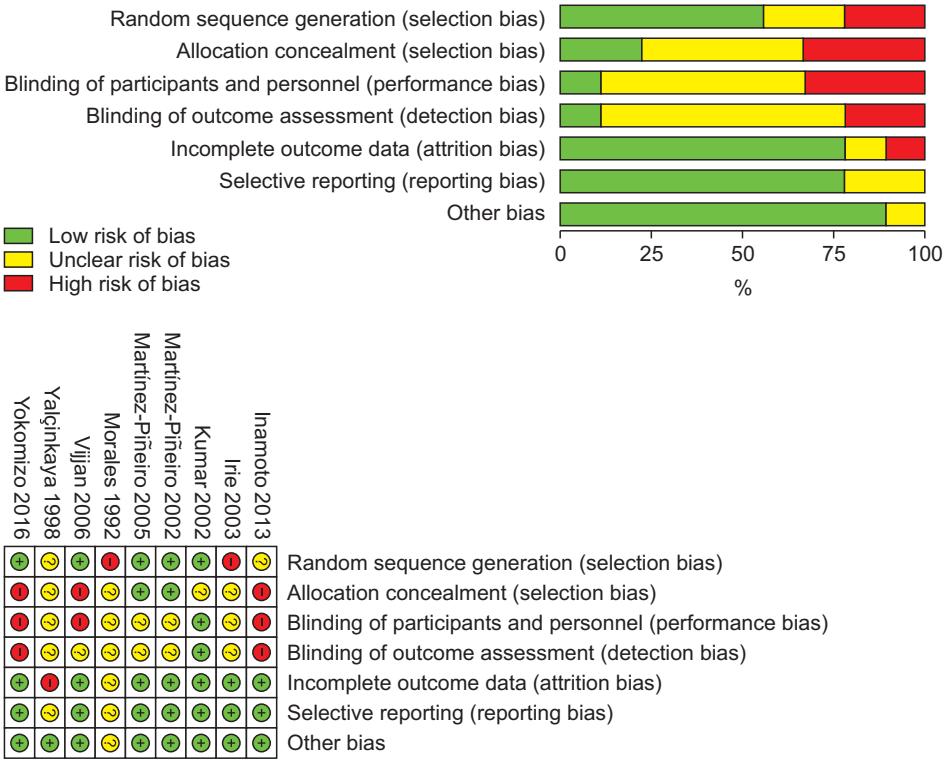

Fig. 2. Summary of the risk of bias assessment for included studies.

could lead to overestimation of the total adverse effects, we selected one major local symptom in four studies [10-12,14]. Compared with the standard dose, a low dose could significantly reduce the rate of adverse effects (OR, 0.41; 95% CI, 0.28–0.62; p<0.0001). Moderate heterogeneity was observed (p=0.14, I^2=38%; Fig. 3E).

9. Withdrawal

Six studies [11-15,17] reported the results of withdrawal from treatment. Among 525 patients in the low-dose group and 519 patients in the standard-dose group, 4.4% and 10.6% were reported to have withdrawn, respectively. Compared with the standard dose, a low dose could lead to a decrease in withdrawal (OR, 0.42; 95% CI, 0.25–0.71; p=0.001). There was no interstudy heterogeneity (p=0.50, I^2=0%; Fig. 3F).

DISCUSSION

In our meta-analysis, treatment with low-dose BCG revealed a higher possibility of recurrence than did treatment with the standard dose. However, there were no significant differences in progression, cancer-specific survival, or overall survival between the two groups. Low-dose BCG revealed favorable outcomes in terms of adverse effects and withdrawal. Over four decades ago, Morales et al. [19] published an innovative study on adjuvant BCG intravesical instillation in NMIBC, and BCG instillation has since been accepted as the standard treatment [4]. In addition, maintenance BCG therapy has been proven to be more beneficial against recurrence than standard induction therapy, and guidelines recommend maintenance therapy [4,20]. Although the requirement for BCG has increased, the shortage of BCG has continued. Therefore, additional countermeasures are required.

Morales et al. [18] conducted an RCT on the potential of BCG dose reduction to reduce adverse effects. They found that the standard dose was favorable for recurrence, but that a low dose resulted in fewer adverse effects [18]. Yalçinkaya et al. [10] reported that low-dose BCG had the same adverse effect profile and a lower success rate for recurrence. However, in other studies, a low dose exhibited no significant recurrence rate compared with the standard dose [11-17]. According to our meta-regression analysis, the heterogeneity in results on recurrence might be related to the two studies conducted before 2000 by Morales et al. [18] and Yalçinkaya et al. [10]. Except for those two studies, rates of recurrence were similar between the low-dose and standard-dose groups (Supplementary Fig. 1). In the study by Morales et al. [18], the follow-up protocol was monitored more closely, and a different follow-up protocol would be related to the heterogeneity in recurrence. In addition, there was also a significant reduction in adverse effects at low doses in other studies [11,12,14,17]. These results are from studies using induction therapy, and maintenance therapy could have different outcomes. The European Organization

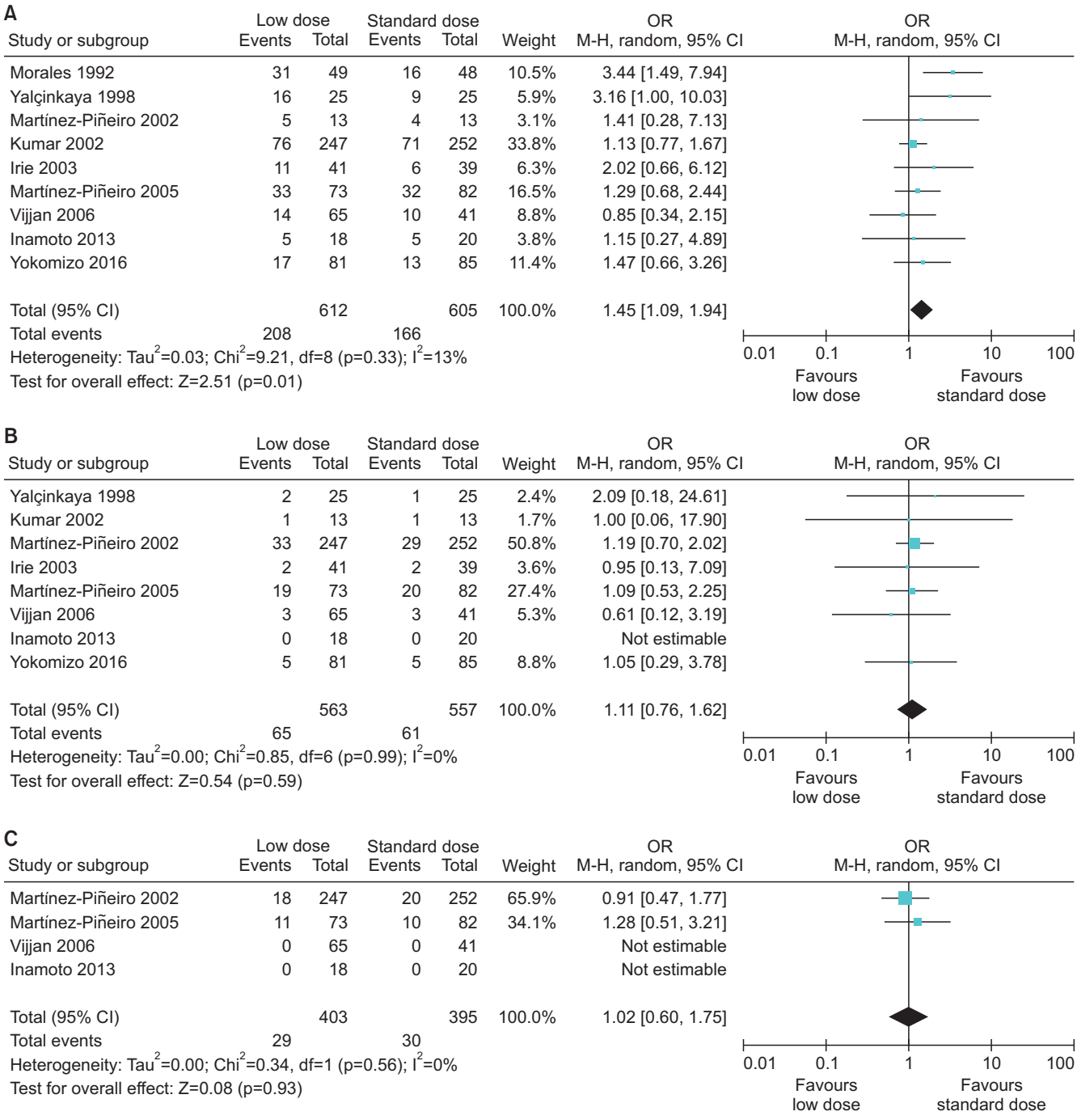

Fig. 3. Forest plots of (A) tumor recurrence, (B) tumor progression, (C) cancer-specific survival, (D) overall survival, (E) adverse effects, and (F) withdrawal.

for Research and Treatment of Cancer group performed an RCT of 1,355 patients, which revealed no significant differences in toxicity between the low and standard doses [21]. In that study, reducing the length of maintenance failed to prevent recurrence in high-risk patients [21]. As a result, maintenance therapy could suppress recurrence in high-risk patients. However, maintenance therapy requires induction therapy for 6 weeks and additional therapy for 3 weeks at 3, 6, 12, 18, 24, 30, and 36 months; therefore, 27 doses of BCG are required in total [20,21]. Miyake et al. [22] reported that approximately 77% of 2669 high-risk patients received non-maintenance therapy. Sharma et al. [23] reported reduced cost-effectiveness of maintenance therapy after induction therapy. These recent reports discuss the situation of BCG shortage and COVID-2019. The American Urological Association recommended the use of alternative chemotherapy in intermediate-risk patients or low-dose chemotherapy in high-risk patients in the setting of a BCG shortage [24].

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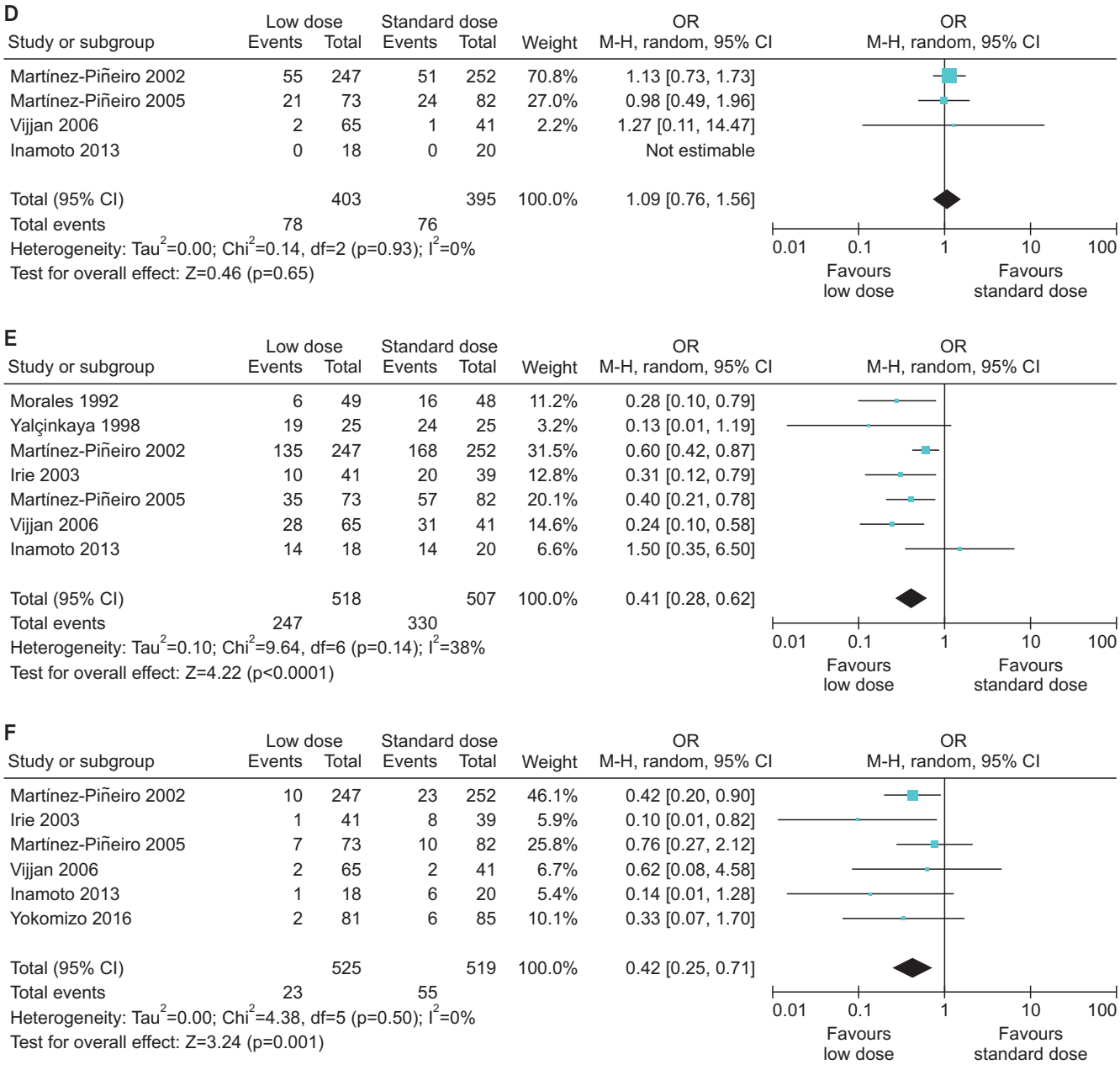

Fig. 3. Continued.

An RCT was conducted to investigate reducing the frequency of BCG instillation in high-grade NMIBC [25]. However, the reduced protocol was inferior to the standard protocol in terms of recurrence; therefore, patient recruitment was terminated [25]. Although the frequency of BCG has been determined to a certain degree, the optimal BCG dose has not been established. Each strain has a standard dose for BCG instillation [26]. To date, there has been no definitive superiority among the available strains [26].

Many studies have been conducted to investigate enhancing the efficacy of BCG instillation. First, immune checkpoint inhibitors, which are an established treatment modality for cancer, could be combined with BCG. Wang et al. [27] reported that BCG could upregulate programmed death ligand-1 (PD-L1) on the surface of bladder cancer cells. In a breast cancer mouse model, the combination of BCG and anti-PD-L1 exhibited marked oncolytic effects using immunogenic mechanisms [28]. Second, there have been attempts to keep BCG longer in the bladder. Intravesical drug delivery devices can increase the time of exposure to the drug [29]. Hydrogels, which release drugs continuously, might extend time and efficacy, preventing washout by urination [30]. Third, genetically modified BCG strains could improve the immunotherapeutic effects of BCG. Recombinant BCG

can evade the innate immune response of the host and increase the levels of antitumor cytokines [31]. Fourth, studies on increasing the invasion of BCG were conducted. Drug delivery systems such as nanocarriers or liposomes could promote endocytosis and the antitumor effects of BCG [32]. In the case of these upgraded tools, low-dose BCG can be used to reduce adverse effects. BCG has been the major treatment option for intermediate- and high-risk NMIBC for approximately the past 50 years, but the standard dose was provided empirically. Because of the BCG shortage, some patients would not be able to follow the usual protocol. Low-dose BCG could be an alternative strategy for more patients because it results in similar progression, cancer-specific survival, and overall survival and causes lower adverse effects and withdrawal compared with standard doses. High-quality RCTs will confirm the optimal dose.

This study has some limitations. First, the BCG strains varied among the studies. Over the decades, BCG subcultures have evolved genetically [33]. As a vaccine for tuberculosis, there was a concern that the different phenotypes related to the different surface proteins could influence the protective efficacy [34]. Ikeda et al. [35] reported that the Tokyo 172 and Connaught strains exhibited different binding abilities and interactions in an *in vivo* study. However, another study confirmed that the Tice, Connaught, and Armand Frappier strains have similar binding and antitumor activity [36]. Although several RCTs have been conducted to evaluate differences among the strains, the definitive superiority of any BCG strain has not been proven [37]. Second, the number of BCG instillations differed between the various studies. Different frequencies could have affected the results. However, there are still no definite instillation numbers. Our meta-regression analysis results indicated that studies based on BCG instillation numbers were not significantly different with respect to recurrence (p=0.11; Supplementary Fig. 2) and progression (p=0.72; Supplementary Fig. 3). In addition, since the same instillation number was used for both comparison groups, we believe that the impact on outcome would be minimal. Third, the statistical heterogeneity was moderate in terms of adverse effects and was caused by the use of different assessment criteria and reporting methods in each study.

CONCLUSIONS

In this meta-analysis, low-dose BCG had more unfavorable outcomes than standard BCG, but studies before 2000 were moderators in the recurrence of NMIBC. Tumor progression, cancer-specific survival, and overall survival were similar between the low and standard doses. Low-dose BCG was favorable for adverse effects and withdrawal. In the era of BCG shortage, low-dose BCG could have strong advantages with advanced technology as an alternative option. However, these results should be reinforced by large and well-designed RCTs to improve clinical outcomes.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Se Young Choi and Moon Soo Ha. Data acquisition: Jung Hoon Kim and Byung Hoon Chi. Statistical analysis: Se Young Choi and Moon Soo Ha. Data analysis and interpretation: Jin Wook Kim. Drafting of the manuscript: Se Young Choi and Moon Soo Ha. Critical revision of the manuscript: In Ho Chang, Tae-Hyoung Kim, and Soon Chul Myung. Obtaining funding: Se Young Choi. Administrative, technical, or material support: Se Young Choi. Supervision: Se Young Choi. Approval of the final manuscript: Se Young Choi.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4111/icu.20210340.

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