Systematic Review and Meta-Analysis

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Dose, duration and strain of bacillus Calmette–Guerin in the treatment of nonmuscle invasive bladder cancer

Meta-analysis of randomized clinical trials

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Abstract

Background: Intravesical bacillus Calmette–Guerin (BCG) instillation is widely used as an adjuvant therapy after transurethral resection of bladder tumor (TURBT) in patients with intermediate- and high-risk nonmuscle invasive bladder cancer (NMIBC). However, the effective dose, duration, and strain of BCG have not yet been clearly determined. We aimed to elucidate the relationship between dose, duration, and strain of BCG and clinical outcomes in NMIBC patients treated with TURBT.

Methods: We conducted a literature search in Embase, Scopus, and PubMed databases for all relevant articles published up to October 2016 in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis guidelines. The relative risks of clinical outcomes, including recurrence, progression, cancer-specific mortality, and all-cause mortality according to dose (standard vs low), duration (induction vs maintenance), and strain of BCG were presented as the pooled risk ratio (RR) and 95% confidence interval (CI).

Results: Nineteen studies meeting the inclusion criteria were finally selected in this meta-analysis. The risk of recurrence was significantly highly observed in case of low-dose BCG (RR, 1.17; 95% CI 1.06–1.30) and induction BCG (RR, 1.33; 95% CI 1.17–1.50) only group without heterogeneity among the included studies. Although there were no significant differences between dose or duration and other clinical outcomes. On direct comparison in each study comparing BCG strains, the Tice stain showed a relatively high probability of recurrence compared with the Connaught (RR, 1.29; 95% CI 1.01–1.64) and RIVM (RR, 2.04, 95% CI 1.28–3.25) strains. Funnel plot testing revealed no significant publication bias.

Conclusion: The use of standard dose and maintenance BCG instillation may be effective to reduce recurrence rate after TURBT for NMIBC. Further large scale, well-designed, and prospective studies, with stratification of the patients into risk group at randomization, will be required to determine the optimal guideline of BCG use to improve clinical outcomes in NMIBC.

Abbreviations: BCG = bacillus Calmette–Guerin, CI = confidence interval, CIS = carcinoma in situ, CSS = cancer-specific survival, HR = hazard ratio, NMIBC = nonmuscle invasive bladder cancer, OS = overall survival, PFS = progression-free survival, RFS = recurrence-free survival, RR = risk ratio, TURBT = transurethral resection of bladder tumor.

Keywords: BCG vaccine, carcinoma, disease progression, recurrence, transitional cell, urinary bladder neoplasms

Editor: Muhammed Mubarak.

HSK and JHK contributed equally to this work as correspondence.

Authorship: Conception and design: HSK, JHK, CWJ, CK, and HHK. Data acquisition: YQ, HSK, and JHK. Data analysis and interpretation: JHK and HSK. Manuscript drafting: YQ, HSK, and JHK. Critical revision of the manuscript for scientific and factual content: JHK and HSK. Statistical analysis: YQ, HSK, and JHK. Supervision: HSK, JHK, CWJ, CK, and HHK.

Funding/support: This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (No. 2016R1A2B4011623) and Samyang Biopharm.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

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Medicine (2017) 96:42(e8300)

Received: 21 July 2017 / Received in final form: 17 August 2017 / Accepted: 27 August 2017

http://dx.doi.org/10.1097/MD.0000000000008300

1. Introduction

Nonmuscle invasive bladder cancer (NMIBC), which accounts for approximately 75% of initially diagnosed bladder cancers and consists of either tumor confined to the mucosa (Ta, carcinoma in situ [CIS]) or tumor invading the submucosa (T1), is primarily treated with transurethral resection of bladder tumor (TURBT). NMIBC has considerably varied clinical behaviors depending on the risk of disease recurrence and progression after TURBT.[1,2] Depending on the European Organization of Research and Treatment of Cancer risk tables,[3,4] low-risk tumors (<3 cm, solitary, Ta, low grade [LG]) have an average of recurrence rate of 20% (15%–31%), but show a low progression rate to muscle invasive disease of less than 1%. In contrast, intermediate- (multiple and/or ≥3 cm, Ta, LG) and high-risk tumors (T1 and/or high grade (HG) and/or CIS) have high recurrence rates ranging from 24% to 78% and high potential risk to progress into muscle invasive disease (1%–45%).

A crucial issue in the management of NMIBC is the reduction of disease recurrence and prevention of progression into muscle invasive disease. Progression leads to the need of adjuvant therapy in almost all NMIBC patients treated with TURBT. Intravesical bacillus Calmette–Guerin (BCG) instillation has been widely used as the mainstay of adjuvant therapy after TURBT in NMIBC patients.[5] The efficacy and safety of adjuvant BCG immunotherapy for the treatment of NMIBC have been proven by several randomized controlled trials (RCTs) and meta-analyses.[6–10] Current international guidelines recommend using intravesical BCG instillation in intermediate- and high-risk NMIBC patients to decrease the risk of disease recurrence and progression.[1,2,11]

However, the effective dose, duration, and strain of BCG for intravesical instillation have not yet been clearly determined. Although a number of RCTs have assessed the differences of clinical outcomes according to dose (standard vs low),[12–19] duration (induction vs maintenance),[20–27] and strain of BCG[28–30] in NMIBC, conflicting results have prevented any consensus concerning the effective BCG strategy.

In the present study, we sought to evaluate whether the clinical outcomes show significant difference according to dose, duration, and strain of used BCG in NMIBC through a systematic review and meta-analysis of relevant published RCTs.

2. Materials and methods

2.1. Ethics statement

Ethical approval or informed consent was not necessary for this meta-analysis because our analysis has not affected participants directly, and required data were extracted from previous published studies.

2.2. Search strategy

We conducted the current study according to Cochrane Collaboration and Preferred Reporting Items for Systematic Review and Meta-analysis guidelines.[31] A comprehensive literature search was made using the Embase, Scopus, and PubMed databases. All articles in English published up to October 31, 2016 identified using the following search terms were used as key words separately or in combination were identified: "bladder cancer," "BCG," and "randomized." Citation lists of all retrieved studies were then used to identify other potentially relevant publications. Two reviewers (YQ and CWJ) independently selected the relevant articles, and any conflicts between reviewers reached a consensus after discussion.

2.3. Inclusion and exclusion criteria

Depending on the Preferred Reporting Items for Systematic Review and Meta-analysis guidelines, we adopted the population, intervention, comparator, outcome, and study design approach to define study eligibility.[31] The population was patients with NMIBC. The intervention was intravesical BCG immunotherapy. The comparator was dose, duration, and strain of BCG. The outcome was recurrence-free survival (RFS), progression-free survival (PFS), cancer-specific survival (CSS), and overall survival (OS). The study design was a meta-analysis of RCTs. Studies were considered eligible for further evaluation if they met the following inclusion criteria: original article; human research; English language; histologically conformed NMIBC; primarily treated with TURBT; availability of Kaplan–Meier/uni- or multivariable Cox proportional hazard models-derived results describing the differences of outcomes depending on dose, duration, and strain of BCG; and RCTs. The exclusion criteria were: letters, commentaries, case reports, reviews, and conference abstracts owing to limited data; articles in other languages than English; studies using other analyses instead of survival analysis; and overlapping articles or those with duplicated data. If the same study subjects or analyses of repeat data were found in more than 1 publication, only the most recent or the largest study was preferentially included in the analysis to avoid duplication of the same survival data. Each study was screened by 2 independent reviewers (CK and HHK) according to study eligibility. Any disagreements were resolved by consensus through discussion.

The primary endpoint of the meta-analysis was RFS. Recurrence was defined as any tumor relapse, either local or systemic, irrespective of bladder muscle invasion after TURBT. Secondary endpoints included PFS, CSS, and OS. Progression was defined as either increase of pathologic tumor stage and/or grade or the emergence of bladder muscle invasive disease with or without distant metastasis. CSS and OS were defined as the interval from the time of TURBT to death from bladder cancer and/or any cause, respectively.

2.4. Data extraction

Three investigators (YQ, HSK, and JHK) independently reviewed each eligible article and retrieved data from all publications meeting the inclusion criteria. Retrieved data were subsequently crosschecked to ensure their accuracy and any disparities among investigators reached a consensus after discussion. Information was extracted according to the reporting recommendations for tumor marker prognostic studies guidelines for reporting prognostic marker[32] including: publication data (name of first author, publication year, geographic location, and recruitment period), characteristics of the study population (sample size including randomized number and eligible population, median age with range, gender, definition of progression, and median follow-up (FU) duration with range), tumor characteristics (tumor stage and grade) in each study, treatment characteristics in each study (dose, duration, and strain of BCG regimen used in each randomized group), and statistical data (survival curves, exact data of total, and exposed number in case and control groups) as well as hazard ratios (HRs) and their confidence intervals (CIs). Discrepancies were discussed to reach consensus.

2.5. Statistical analyses

The meta-analysis used the DerSimonian and Laird random effects model,[33] applying the inverse of variance as a weighing factor, which provided the pooled risk ratios (RRs) with 95% CIs suggesting the difference of survival outcomes depending on each BCG regimen. For each trial, survival data were extracted and estimated according to previously described methods.[34] If RRs and the corresponding 95% CIs were not directly reported, previously reported indirect methods were used to extract the log HR and variance.[35] To evaluate the interstudy heterogeneity for the pooled RRs, we adopted both the Chi-square-based Q statistic and Higgins I-squared statistic test,[36] which demonstrates the percentage of total variation among studies caused by heterogeneity rather than by chance. We judged that $P < .05$ for the Q test or an I^2 statistic >50% implied the presence of significant heterogeneity across selected studies. Publication bias was assessed using the funnel plot. A symmetrical inspection of inverted funnel was regarded as no significant publication bias. In contrast, in case of the presence of bias, the inverted funnel plot should appear skewed and asymmetrical. All the *P*-values and 95% CIs were 2-sided, and $P < .05$ was considered statistically significant. The meta-analysis was conducted using Version 5.0 RevMan statistical software (Cochrane Collaboration, Copenhagen, Denmark).

3. Results

3.1. Study selection

The initial database search identified 892 articles. Among these, 733 articles were excluded: 441 were duplicate publications and 292 articles were excluded after reviewing the corresponding titles and abstracts. A total of 189 articles remained for full text evaluation. Further review excluded 131 articles because they were irrelevant to the current analysis, 19, because the study design was not an RCT; 11, because data were overlapped with another study; and 9, owing to other causes. Finally, 19 articles were included for the meta-analysis.[12–30]Figure 1 shows a flow diagram of the selection process for relevant studies.

3.2. Study characteristics

The study and treatment characteristics of the 19 eligible studies are summarized in Tables 1 and 2. All the studies were prospective RCTs. These eligible studies were published from 1987 to 2016. Among studies, 9 were performed in Europe,[13,14,16,19,21,23,26,28,30] 7 in Asia,[15,17,18,24,25,27,29] and 3 in America.[12,20,22] The median FU duration ranged from 2.7 to 120 months, while 6 studies did not suggest clear median FU duration. The pathologic tumor stage in all trials consisted of nonmuscle invasive urothelial carcinoma, including T1 and/or HG (grade 3) and/or CIS. The number of the studies comparing dose, duration, and strain of BCG were eight,[12–19] eight,[20–27] and three,[28–30] respectively. In case of studies comparing BCG dose, the definition of low and standard dose showed some variations among studies. Either 80, 81, or 120 mg was used as a standard dose in the most studies, and the low dose was defined as a half or one/two-third of the standard dose in the most studies.[12–18] One study did not clearly provide an exact BCG dose, but compared the efficacy between one-third and full-dose BCG at 1 and 3 years.[19] Therefore, we pooled the 2 studies having different duration as each separate study comparing BCG dose when performing the meta-analysis. The final number of studies comparing BCG dose was considered as 9 (Table 2). On the studies comparing duration of BCG, the regimen of induction BCG therapy was identical as once weekly for 6 weeks in most studies. Only 1 trial used BCG once weekly for 8 weeks for the purpose of induction.[24] Although the regimen of maintenance BCG was variably adopted among studies. The studies comparing the BCG strain (Oncotice, RIVM, ToKyo 172, and Connaught) were conducted under the conditions of induction BCG therapy only.

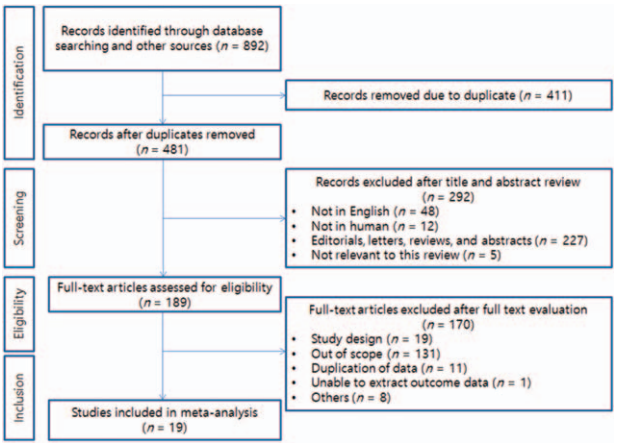

Figure 1. Flow chart of the literature search approach.

3.3. Meta-analysis

3.3.1. Dose. The pooled analysis of RFS was based on 9 studies. Compared with standard dose BCG, low-dose BCG was significantly related to worse RFS (RR, 1.17; 95% CI, 1.06–1.30). There was no obvious heterogeneity ($P = .39$; $I^2 = 5\%$; Fig. 2A). Significant differences were not found in PFS, CSS, and OS between low and standard BCG dose, and there was no interstudy heterogeneity in all analyses (Fig. 2B–D).

3.3.2. Duration. A total of 8 studies were included in the meta-analysis of RFS. Compared to maintenance BCG, induction BCG significantly showed a worse RFS (RR, 1.33; 95% CI, 1.17–1.50). The result for the test for heterogeneity was not significant ($P = .46$; $I^2 = 0\%$; Fig. 3A). In contrast, in the meta-analyses of the correlation between BCG duration and secondary endpoints (PFS, CSS, and OS), there were no significant differences according to BCG regimen (induction vs maintenance), and significant interheterogeneity was not observed in the analyses (Fig. 3B–D).

3.3.3. Strain. Owing to the small number of studies included,[28–30] meta-analysis was not performed with regard to the strains of BCG. Instead, when conducting direct comparison according to BCG strain in each study, the OncoTice strain (vs Connaught [RR, 1.29; 95% CI 1.01–1.64] or vs RIVM [RR 2.04; 95% CI 1.28–3.25]) was more likely to show a worse recurrence in some studies[28,30] (supplemental Table S1, http://links.lww.com/MD/B903). However, there were no meaningful correlations between BCG strain and other survival outcomes (RFS, CSS, and OS) (supplemental Table S1, http://links.lww.com/MD/B903).

3.4. Publication bias

No significant publication bias was found in the meta-analyses of all survival outcomes according to various BCG regimens. Funnel

Table 1

Randomized trials comparing doses, durations, and strains of bacillus Calmette–Guerin.

Study	Year	County	Recruitment period	Median age, range, y	Sex (M/F)	No randomized	No eligible	Median FU, range, mo	Definition of progression
Dose									
Morales[12]	1992	Canada	1979–1988	NA	NA	97	NA	21, 6–68	NA
Yalçinkaya[13]	1998	Turkey	1990–1994	55.3, 32–70	63/17	80	50	33.5	Increase of stage or grade
Martínez-Piñeiro (a)[14]	2002	Spain	1991–1992	NA	451/49	500	499	69	Muscle invasion, extravesical extension or metastasis
Irie[15]	2003	Japan	1996–2001	NA	68/12	80	71	NA, 2.7–64	NA
Martínez-Piñeiro (b)[16]	2005	Spain	1995–1999	NA	143/12	155	NA	61, 3–102	Muscle invasion or metastasis
Vijjan[17]	2006	India	2000–2005	NA	91/15	106	NA	NA, 4–60	NA
Argawal[18]	2007	India	2002–2005	NA, 45–84	92/36	152	128	36, 18–52	NA
Oddens[19]	2013	Europe	1997–2005	68, 29–85	1099/247	1355	1279	85.2	Muscle invasion, metastasis or death due to bladder cancer
Duration									
Badalament[20]	1987	USA	1981–1984	NA	81/12	93	NA	22, 3–44	Change in treatment strategy, muscle invasion or metastasis
Gruenwald[21]	1997	Israel	1992–1994	NA, 40–80	66/9	75	70	29.2, 6.1–43	NA
Lamm[22]	2000	USA	1985–1988	NA	332/14	284	NA	NA	Change in treatment strategy or muscle invasion
Palou[23]	2001	Europe	1989–1995	64, 31–79	122/4	131	126	77.8, 7–120	Muscle invasion or metastasis
Koga[24]	2010	Japan	2002–2005	NA	68/16	53	51	NA	Muscle invasion or metastasis
Hinotsu[25]	2011	Japan	2004–2006	NA	73/10	83	78	NA	Muscle invasion, metastasis, tumors in the upper urinary tract or the urethra, or upgrading
Martínez-Piñeiro (c)[26]	2015	Spain	1999–2007	68, 30–86	367/30	397	386	77	Muscle invasion or metastasis
Nakai[27]	2016	Japan	2004–2008	NA, 20–79	76/12	95	88	51, 9–86	Muscle invasion, metastasis or tumors in the upper urinary tract
Strain									
Witjes[28]	1996	Netherlands	1987–1990	NA	NA	289	251	36, 2–81	Increase of stage
Sengiku[29]	2013	Japan	2004–2012	NA	107/22	178	129	28.5	NA
Rentsch[30]	2014	Europe	1998–2010	NA, 46–96	111/20	142	131	NA	Increase of stage or grade

FU = follow-up, NA = not available.

plots for publication bias of the correlation between various BCG regimens (dose and duration) and survival outcomes (RFS, PFS, CSS, and OS) demonstrated a certain degree of asymmetry (supplemental Fig. S1A–D, http://links.lww.com/MD/B903, and Fig. S2A–D, http://links.lww.com/MD/B903).

4. Discussion

BCG is an attenuated mycobacterium developed as a vaccine for tuberculosis. It has shown an antitumor effect in several different cancers including bladder cancer. Intravesical BCG is widely used and has been one of the most successful immunotherapies for the management of NMIBC by inducing massive local immune response within the bladder.[5] The preventive effect of BCG on tumor recurrence and progression in NMIBC has already been proven by several investigators.[6,7,9] Therefore, based on risk predicting models, such as the European Organization of Research and Treatment of Cancer risk tables and Spanish Urological Club for Oncological Treatment scoring system,[3,4,37–39] for recurrence and progression after TURBT for NMIBC, the international guidelines have recommended the use of intavesical BCG as an adjuvant therapy in intermediate-to-high risk NMIBC cases to remove the residual tumor and prevent recurrence and progression.[1,2,11]

However, the optimal treatment dose, duration, and strain of BCG have not yet been definitely established. Although there have been a number of prospective trials assessing the optimal duration and dose of BCG in NMIBC, the conflicting results have been reported among studies.

As for BCG dose, 1 prospective RCT comparing standard (81 mg) versus low (54 mg) dose demonstrated that recurrence rates significantly differed (0.71/month in standard vs 1.49/month in low; $P < .05$) but there were no significant differences in side effects between 2 groups, which supported the superior efficacy of standard dose relative to low dose.[13] Another trial comparing standard (81 mg) with 3-fold reduced (27 mg) dose reported that the standard dose was significantly more effective against recurrences ($P = .0151$) and progression ($P = .048$) than the reduced dose in patients with multifocal tumors, and thus recommended continuing to use the standard dose for high-risk tumors.[14] Other trials comparing 2 dose[15,16] or 3 dose BCG group[17,18] described that low-dose BCG showed a similar efficacy on recurrence or progression, and its toxicity was significantly lower compared with standard dose. A recent meta-analysis pooling 8 RCTs comparing BCG dose demonstrated that compared with standard BCG dose, low-dose BCG was not inferior to reduce the risk of tumor recurrence (HR, 1.15; 95% CI, 1.00–1.31; $P = .05$) and showed no significant difference in progression (HR, 1.08; 95% CI, 0.83–1.42; $P = .57$). Additionally, the use of low-dose BCG was significantly associated with lower incidence of severe (RR, 0.52; 95% CI, 0.36–0.74; $P = .0003$) and systemic side effects (HR, 0.57; 95% CI, 0.34–0.97; $P = .01$).[40]

RCTs regarding BCG duration have mainly focused on the evaluation of the efficacy of maintenance therapy compared to induction therapy only. One trial conducted by the Southwest Oncology Group demonstrated the significant impact of maintenance therapy relative to control (induction only). Patients

Table 2

Treatment characteristics of the eligible studies.

Study	Inclusion criteria	Group	Dose, mg	Regimen	Strain
Dose					
Morales[12]	Ta, T1, or CIS	A	60	Once weekly for 6 wk	Pasteur
		B	120	Once weekly for 6 wk	Pasteur
Yalcinkaya[13]	Ta/T1	A	54	Once weekly for 6 wk	Connaught
		B	81	Once weekly for 6 wk	Connaught
Martínez-Piñeiro (a)[14]	TaG2–3, T1G1–3, CIS, or recurrent TaG1	A	27	Once weekly for 6 wk + once every 2 wk, 6 times	Connaught
		B	81	Once weekly for 6 wk + once every 2 wk, 6 times	Connaught
Irie[15]	Ta/T1	A	40	Once weekly for 6 wk	Tokyo 172
		B	80	Once weekly for 6 wk	Tokyo 172
Martínez-Piñeiro (b)[16]	T1HG or CIS	A	27	Once weekly for 6 wk + once every 2 wk, 6 times	Connaught
		B	81	Once weekly for 6 wk + once every 2 wk, 6 times	Connaught
Vijjan[17]	>G1, >Ta, >1 cm, multiple or recurrent	A	40 or 80	Once weekly for 6 wk	Danish 1331
		B	120	Once weekly for 6 wk	Danish 1331
Argawal[18]	Ta/T1 except CIS	A	40 or 80	Once weekly for 6 wk + once monthly for 1 year	Danish 1331
		B	120	Once weekly for 6 wk + once monthly for 1 year	Danish 1331
Oddens (A)[19]	Single T1G3 or multiple Ta/T1G1–3	A	1/3D	Once weekly for 6 wk + every week for 3 wk on 3, 6, and 12 mo	OncoTice
		B	FD (5×10^8 CFU)	Once weekly for 6 wk + every week for 3 wk on 3, 6, and 12 mo	OncoTice
Oddens (B)[19]	Single T1G3 or multiple Ta/T1G1–3	A	1/3D	Once weekly for 6 wk + every week for 3 wk on 3, 6, 12, 18, 24, 30, and 36 mo	OncoTice
		B	FD (5×10^8 CFU)	Once weekly for 6 wk + every week for 3 wk on 3, 6, 12, 18, 24, 30, and 36 mo	OncoTice
Duration					
Badalament[20]	Ta, T1 or CIS	A	120	Once weekly for 6 wk	Pasteur
		B	120	Once weekly for 6 wk + once monthly for 2 y	Pasteur
Gruenwald[21]	≥3 tumors, ≥3 prior recurrences or recurrence within 12 mo, CIS, T1, or G3	A	120	Once weekly for 6 wk	Pasteur
		B	120	Once weekly for 12 wk	Pasteur
Lamm[22]	Recurrent Ta/T1 (2 tumors within 1 y or 3 recurrences in recent 6 mo) and/or CIS	A	81	Once weekly for 6 wk	Connaught
		B	81	Once weekly for 6 wk + every week for 3 wk on 3, 6, 12, 18, 24, 30, and 36 mo	Connaught
Palou[23]	Primary or recurrent Ta/T1G3 or isolated CIS or CIS with G2	A	81	Once weekly for 6 wk	Connaught
		B	81	Once weekly for 6 wk + 6 weekly instillations every 6 mo for 2 y	Connaught
Koga[24]	Ta, T1, or CIS	A	80	Once weekly for 8 wk	Tokyo 172
		B	80	Once weekly for 8 wk + single instillation at 3, 6, and 12 mo	Tokyo 172
Hinotsu[25]	Recurrent Ta/T1: ≥3 tumors, ≥3 prior recurrences or recurrence within 12 mo	A	81	Once weekly for 6 wk	Connaught
		B	81	Once weekly for 6 wk + every week for 3 wk at 3, 6, 12, and 18 mo	Connaught
Martínez-Piñeiro (c)[26]	TaG3, T1G3, or CIS	A	$6.6–19.2 \times 10^8$ CFU	Once weekly for 6 wk	Connaught
		B	$6.6–19.2 \times 10^8$ CFU	Once weekly for 6 wk + every 3 mo for 3 y	Connaught
Nakai[27]	Multiple or recurrent Ta/T1 or CIS	A	81	Once weekly for 6 wk	Connaught
		B	81	Once weekly for 6 wk + every week for 3 wk at 3, 6, 12, and 18 mo	Connaught
Strain					
Witjes[28]	Ta/T1 or CIS	A	5×10^8 CFU	Once weekly for 6 wk	OncoTice
		B	5×10^8 CFU	Once weekly for 6 wk	RIVM
Sengiku[29]	Ta/T1, CIS, multiple, and a recurrence-free period of 3 mo or less	A	80	Once weekly for 6–8 wk	Tokyo 172
		B	81	Once weekly for 6–8 wk	Connaught
Rentsch[30]	HG, LG with ≥2 recurrences within 2 y or CIS	A	$2–8 \times 10^8$ CFU	Once weekly for 6 wk	OncoTice
		B	$6.6–19.2 \times 10^8$ CFU	Once weekly for 6 wk	Connaught

CIS = carcinoma in situ, FD = full dose, HG = high grade, LG = low grade.

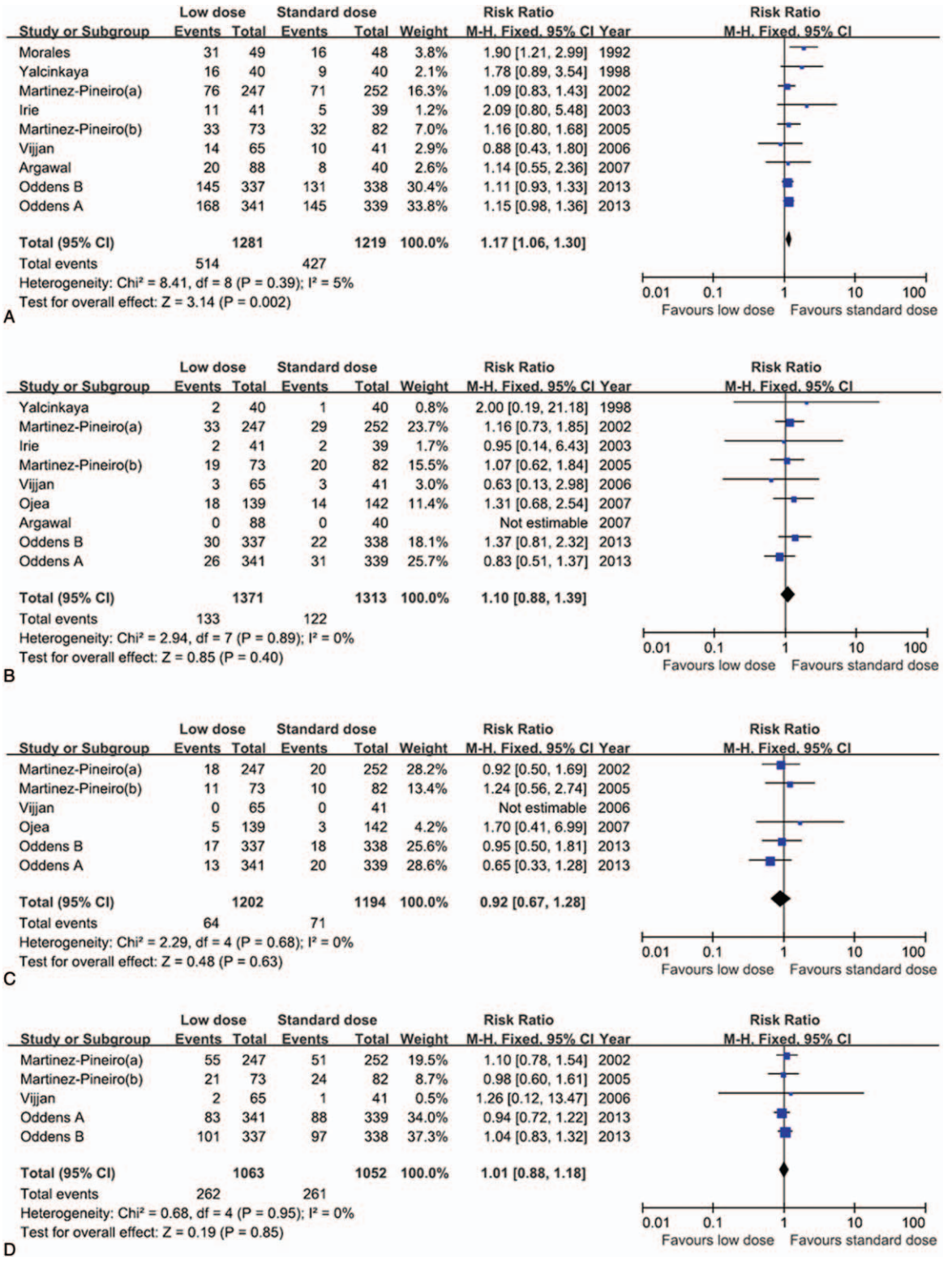

Figure 2. Forest plots of the prognosis of bacillus Calmette–Guerin (BCG) dose. The horizontal lines correspond to the study-specific hazard ratio and 95% confidence interval, respectively. The area of the squares reflects the study-specific weight. The diamond represents the results for pooled hazard ratio and 95% confidence interval. (A) recurrence-free survival, (B) progression-free survival, (C) cancer-specific survival, and (D) overall survival.

randomized in the maintenance arm received a 6-week induction course followed by 3 weekly instillations at 3 and 6 months and every 6 months thereafter for 3 years (Southwest Oncology Group regimen) and showed no toxicities above grade 3. Estimated median RFS was 76.8 months in the maintenance arm and 35.7 months in the control arm ($P = .0001$) and 5-year OS was 78% in the control arm and 83% in the maintenance arm.[22] This preventive impact of BCG maintenance therapy on the

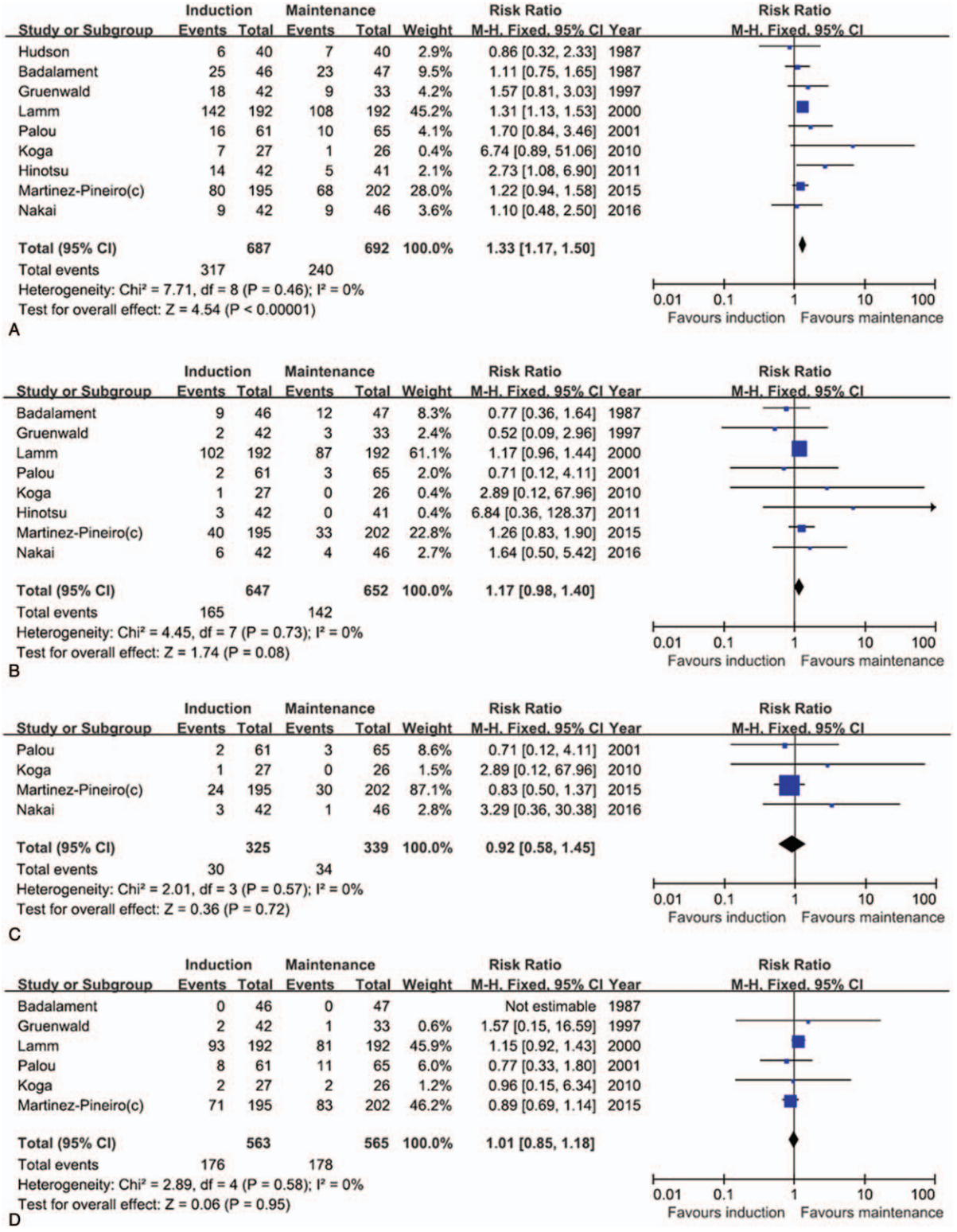

Figure 3. Forest plots of the prognosis of bacillus Calmette–Guerin (BCG) duration. The horizontal lines correspond to the study-specific hazard ratio and 95% confidence interval, respectively. The area of the squares reflects the study-specific weight. The diamond represents the results for pooled hazard ratio and 95% confidence interval. (A) recurrence-free survival, (B) progression-free survival, (C) cancer-specific survival, and (D) overall survival.

recurrence following TURBT was also identified in 2 other RCTs.[24,25] In contrast, recent RCTs have described the insignificant effect of maintenance therapy in terms of the prevention of recurrence or progression.[26,27] The Spanish Urological Club for Oncological Treatment 98013 study compared the recurrence and progression rates between BCG induction once-weekly for 6 weeks (no maintenance arm) and BCG induction followed by 1 BCG instillation every 3 months for

3 year (maintenance arm). Maintenance therapy had no significant advantages on the 5-year recurrence (33.5% in maintenance arm vs 38.5% in no maintenance arm) and progression rates (16.5% in maintenance arm vs 19.5% in no maintenance arm).[26]

Two RCTs provided conflicting results concerning the comparison of BCG strains. One RCT reported that there were no significant differences in RFS and adverse events between BCG Connaught and Tokyo strains.[29] Another recent RCT demonstrated that, compared with BCG Tice, the BCG Connaught strain was significantly associated with greater 5-year RFS (74% in Connaught vs 48% in Tice; $P = .0108$).[30]

We tried to investigate the effective BCG strategies though a systematic review and meta-analysis for the previously reported RCTs. To the best of our knowledge, this study is the first meta-analysis evaluating the differences of the clinical outcomes according to the dose, duration, and strain of BCG. Standard dose and maintenance BCG therapy showed significant benefits in terms of reduction of recurrence risk following TURBT. These findings are partially consistent with the results of the previous trials,[13,14,22,24,25] On the other hand, other clinical outcomes (PFS, CSS, and OS) were not significantly different depending on the dose and duration of BCG. Although previous meta-analysis on the BCG dose, which included many of the same studies observed in our analysis, concluded low-dose BCG was not inferior to standard dose BCG for reducing the risk of recurrence, the pooled HR for recurrence was marginal in light of 95% CI (1.00–1.31) and *P*-value (.05).[40] Therefore, we interpreted the result of previous meta-analysis supported the superiority of standard dose BCG rather than noninferiority of low-dose BCG in terms of the prevention of recurrence, which consequently corresponds well with the results of the present study. The BCG strains could not be meta-analyzed because there have been too few studies; no meaningful conclusion on the effective BCG strain could be drawn from this study.

Several limitations should be considered for the interpretation of the present findings. First, in spite of the interstudy differences on the definition for the dose or duration of used BCG regimens in the included trials, we simply compared the clinical outcomes between binary variables (low vs standard dose, nonmaintenance vs maintenance) without head-to-head comparisons among diverse BCG regimens. Thus, we cannot draw a definite conclusion concerning the optimal BCG dose and duration. Some trials[12,17,18] defined 120 mg as a standard dose and half or one/two-third of 120 mg as a low dose, while other trials[13–16] used 80 or 81 mg as a standard dose and half or one/two-third of 80 or 81 mg as a low dose. For BCG duration, various definitions were also applied in terms of the maintenance duration. These nonunified definitions of BCG dose or duration in each trial may diversely affect the prognosis of NMIBC patients treated with TURBT. Second, unknown or uncontrolled variables that could not be clearly identified in the included trials might have affected the results of this analysis. Interinstitutional variation of TURBT techniques (ie, muscle layer resection, restaging TURBT), primary tumor size, and preoperative positive urine cytology, which were suggested as the important prognostic factors of NMIBC in previous studies,[41–45] could not be adjusted through a multivariable analysis along with BCG. Third, the results of this systematic review and meta-analysis were based on unadjusted estimates, because some studies did not provide detailed information (Table 1). Finally, we cannot exclude the possibility of language bias by only including the articles published in English,[46] despite no definite evidence of publication bias.

5. Conclusions

The current meta-analysis results indicate that in patients with NMIBC, the maintenance intravesical BCG strategies using standard dose may be effective to reduce recurrence risk after TURBT. However, the optimal dose, duration, and strain of BCG could not be definitely determined. Large scale, well-designed, and prospective studies, with stratification of the patients into risk group at randomization, will be required to establish the optimal guideline of BCG use to improve clinical outcomes in NMIBC.

Acknowledgments

The authors thank the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (No. 2016R1A2B4011623) and Samyang Biopharm for the support.

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