의학박사 학위논문

Dose, Duration and Strain of Bacillus Calmette-Guerin in the Treatment of Non-Muscle Invasive Bladder Cancer: Systematic Review and Meta-Analysis of Randomized Clinical Trials

비근침윤성 방광암 환자에서 Bacillus Calmette-Guerin 치료의 투여량, 투여시간, 균종에 대한 연구: 무작위 임상시험 결과에 대한 체계적 문헌고찰과 메타분석

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Abstract

Dose, Duration and Strain of Bacillus Calmette-Guerin in the Treatment of Non-Muscle Invasive Bladder Cancer: Systematic Review and Meta-Analysis of Randomized Clinical Trials

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Introduction: 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 non-muscle 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 (PRISMA) guidelines. The relative risks of clinical outcomes, including recurrence,

progression, cancer-specific mortality, and all-cause mortality according to dose (standard versus low), duration (induction versus 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. While there were no significant differences between dose or duration and other clinical outcomes. Chi-square-based Q statistic and Higgins I-squared statistic test revealed that there was no significant inter-study heterogeneity in all analyses. On direct comparison in each study comparing BCG strains, the Tice strain 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.

Conclusions: 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.

Keywords: Bacillus Calmette-Guerin, bladder cancer, recurrence

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Introduction

Bladder cancer is the second frequent urinary tract malignancy and ranks as the 7th in men and 17th in women of all malignancies worldwide [1, 2]. 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 [3, 4]. Depending on the European Organization of Research and Treatment of Cancer (EORTC) risk tables [5, 6], low–risk tumors (<3 cm, solitary, Ta, low grade) have an average of recurrence rate of 20% (15% to 31%), but show a low progression rate to muscle invasive disease of less than 1%. In contrast, intermediate– (multiple and/or ≥3 cm, Ta, low grade) and high– risk tumors (T1 and/or high grade and/or CIS) have high recurrence rates ranging from 24% to 78% and high potential risk to progress into muscle invasive disease (1% to 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.

As an attenuated strain of Mycobacterium bovis, BCG was a live original vaccine against tuberculosis developed by Calmette and Guerin [7]. Instead of directly acts on neoplastic cells, intravesical BCG induces the inflammatory reaction and stimulates cytokine production. It acts as triggering local immune reaction to destroy

the neoplastic cells that keep in the bladder after TURBT [8, 9].

Intravesical BCG instillation has been widely used as the mainstay of adjuvant therapy after TURBT in NMIBC patients [10]. 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 [11-15]. Current international guidelines recommend using intravesical BCG instillation in intermediate-and high-risk NMIBC patients to decrease the risk of disease recurrence and progression [3, 4, 16].

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 versus low) [17-24], duration (induction versus maintenance) [25-32], and strain of BCG [33-35] 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.

Materials and Methods

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.

Search strategy

We conducted the current study according to Cochrane Collaboration and Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines [36]. 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.

Inclusion and exclusion criteria

Depending on the PRISMA guidelines, we adopted the Population, Intervention, Comparator, Outcome, and Study design (PICOS) approach to define study eligibility [36]. 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: (1) original article; (2) human research; (3) English language; (4) histologically conformed NMIBC; (5) primarily treated with TURBT; (6) 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 (7) RCTs. The exclusion criteria were: (1) letters, commentaries, case reports, reviews, and conference abstracts owing to limited data; (2) articles in languages other than English; (3) studies using other analyses instead of survival analysis; and (4) overlapping articles or those with duplicated data. If the same study subjects or analyses of repeat data were found in more than one 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 two 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.

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 (REMARK) guidelines for reporting prognostic marker [37] including: (i) publication data (name of first author, publication year, geographic location, and recruitment period), (ii) 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 duration with range, (iii) tumor characteristics (tumor stage and grade) in each study, (iv) treatment characteristics in each study (dose, duration, and strain of BCG regimen used in each randomized group), and (v) 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.

Statistical analyses

The meta-analysis used the DerSimonian and Laird random effects model [38], 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 [39]. If RRs and the corresponding 95% CIs were not directly reported, previously reported indirect methods were used to extract the log HR and variance [40]. To evaluate the inter-study heterogeneity for the pooled RRs, we adopted both the Chi-square-based Q statistic and Higgins I-squared statistic test [41], which demonstrates the percentage of total variation among studies caused by heterogeneity rather than by chance. We judged that $p<0.05$ 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 two-sided, and $p<0.05$ was considered statistically significant. The meta-analysis was conducted using Version 5.0 RevMan statistical software (Cochrane Collaboration, Copenhagen, Denmark).

Results

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 a RCT, 11 because data were overlapped with another study, and 9 owing to other causes. Finally, 19 articles were included for the meta-analysis [17-35]. Figure 1 shows a flow diagram of the selection process for relevant studies.

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 and 2016. Among studies, 9 were performed in Europe [17, 20, 22, 23, 26, 29, 31, 33, 35], 7 in Asia [18, 19, 21, 25, 27, 28, 34], and 3 in America [24, 30, 32]. The median follow-up duration ranged from 2.7 months to 120 months, while six studies did not suggest clear median follow-up duration. The pathologic tumor stage in all trials consisted of non-muscle invasive urothelial carcinoma, including T1 and/or high grade (grade 3) and/or CIS. The number of the studies comparing dose, duration, and strain of BCG were eight [17-24], eight [25-32], and three [33-35], 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 [18-24]. One study did not clearly provide an exact BCG dose, but compared the efficacy between one-third and full-dose BCG at one and 3 years [17]. Therefore, we pooled the two 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 nine (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 one trial used BCG once weekly for 8 weeks for the purpose of induction [28]. While, 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.

Meta-analysis

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 ($p=0.39$; $I^2=5\%$; Fig. 2A). Significant differences were not found in PFS, CSS, and OS between low and standard BCG dose, and there was no inter-study heterogeneity in all analyses (Fig. 2B, 2C, and 2D).

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=0.46; 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 versus maintenance), and significant inter- heterogeneity was not observed in the analyses (Fig. 3B, 3C, and 3D).

Strain

Owing to the small number of studies included [33-35], 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 (versus RIVM [RR, 1.29; 95% CI 1.01-1.64] or versus Connaught [RR 2.04; 95% CI 1.28-3.25]) was more likely to show a worse recurrence in some studies [33, 35] (Table 3). However, there were no meaningful correlations between BCG strain and other survival outcomes (RFS, CSS, and OS) (Table 3).

Publication bias

No significant publication bias was found in the meta-analyses of all survival outcomes according to various BCG regimens. Funnel 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 (Fig. 4A–D and Fig. 5A–D).

Discussion

BCG is an attenuated mycobacterium developed as a vaccine for tuberculosis. It has shown an anti-tumor 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 [10]. The preventive effect of BCG on tumor recurrence and progression in NMIBC has already been proven by several investigators [12, 14, 15]. Therefore, based on risk predicting models, such as the EORTC risk tables and Spanish Urological Club for Oncological Treatment (CUETO) scoring system [5, 6, 42-44], 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 [3, 4, 16].

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, one prospective RCT [23] comparing standard (81 mg) vs. low (54 mg) dose demonstrated that recurrence rates significantly differed (0.71/month in standard vs. 1.49/month in low; $p<0.05$) but there were no significant differences in side effects between two groups, which supported the superior efficacy of standard dose relative to low dose. Another trial [22] comparing standard (81 mg) with three fold reduced (27 mg) dose reported

that the standard dose was significantly more effective against recurrences ($p<0.05$) and progression ($p<0.05$) than the reduced dose in patients with multifocal tumors, and thus recommended continuing to use the standard dose for high-risk tumors. Other trials comparing two dose [20, 21] or triple dose BCG group [18, 19] 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 [45] 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 (hazard ratio [HR], 1.15; 95% CI, 1.00-1.31; $p=0.05$) and showed no significant difference in progression (HR, 1.08; 95% CI, 0.83-1.42; $p=0.57$). Additionally, the use of low-dose BCG was significantly associated with lower incidence of severe (RR, 0.52; 95% CI, 0.36-0.74; $p<0.01$) and systemic side effects (HR, 0.57; 95% CI, 0.34-0.97; $p=0.01$).

RCTs regarding BCG duration have mainly focused on the evaluation of the efficacy of maintenance therapy compared to induction therapy only. One trial [30] conducted by the Southwest Oncology Group (SWOG) demonstrated the significant impact of maintenance therapy relative to control (induction only). Patients randomized in the maintenance arm received a 6-week induction course followed by three weekly instillations at 3 and 6 months and every 6 months thereafter for 3 years (SWOG 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 ($p<0.01$) and 5-year OS was 78% in the control arm and 83% in the maintenance arm. This preventive impact of BCG maintenance therapy on the recurrence following TURBT was also identified in

two other RCTs [27, 28]. In contrast, recent RCTs have described the insignificant effect of maintenance therapy in terms of the prevention of recurrence or progression [25, 26]. The CUETO 98013 study [26] compared the recurrence and progression rates between BCG induction once-weekly for 6 weeks (no maintenance arm) and BCG induction followed by one 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 versus 38.5% in no maintenance arm) and progression rates (16.5% in maintenance arm versus 19.5% in no maintenance arm).

Two RCTs [33, 34] provided conflicting results concerning the comparison of BCG strains. One RCT [34] reported that there were no significant differences in RFS and adverse events between BCG Connaught and Tokyo strains. Another recent RCT [33] demonstrated that, compared with BCG Tice, the BCG Connaught strain was significantly associated with greater 5-year RFS (74% in Connaught versus 48% in Tice; $p<0.05$).

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 [22, 23, 27, 28, 30]. 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 [45] 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 (0.05).

Therefore, we interpreted the result of previous meta-analysis supported the superiority of standard dose BCG rather than non-inferiority 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 inter-study 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 versus standard dose, non-maintenance versus 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 [18, 19, 24] defined 120 mg as a standard dose and half or one/two third of 120 mg as a low dose, while other trials [20-23] used 80 or 81 mg as a standard dose and half or one/two third of 80 or 81 mg as a low dose. As for BCG duration, various definitions were also applied in terms of the maintenance duration. These non-unified 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. Inter-institutional variation of TURBT techniques (i.e. 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 [46-50], 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 [51], despite no definite evidence of publication bias.

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.

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Table 1. Randomized trials comparing doses, duration, and strains of Bacillus Calmette–Guerin

Study	Year	Country	Recruitment period	Median age, range (years)	Sex (M/F)	No. randomized	No. eligible	Median FU, range (months)	Definition of progression
Dose									
Morales [24]	1992	Canada	1979–1988	NA	NA	97	NA	21, 6–68	NA
Yalcinkaya [23]	1998	Turkey	1990–1994	55.3, 32–70	63/17	80	50	33.5	Increase of stage or grade
Martinez-Pineiro (a) [22]	2002	Spain	1991–1992	NA	451/49	500	499	69	Muscle invasion, extravesical extension or metastasis
Irie [21]	2003	Japan	1996–2001	NA	68/12	80	71	NA, 2.7–64	NA
Martinez-Pineiro (b) [20]	2005	Spain	1995–1999	NA	143/12	155	NA	61, 3–102	Muscle invasion or metastasis
Vijjan [19]	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 [17]	2013	Europe	1997–2005	68, 29–85	1099/247	1355	1279	85.2	Muscle invasion, metastasis or death due to bladder cancer
Duration									
Badalament [32]	1987	USA	1981–1984	NA	81/12	93	NA	22, 3–44	Change in treatment strategy, muscle invasion or metastasis
Gruenwald [31]	1997	Israel	1992–1994	NA, 40–80	66/9	75	70	29.2, 6.1–43	NA
Lamm [30]	2000	USA	1985–1988	NA	332/14	284	NA	NA	Change in treatment strategy or muscle invasion
Palou [29]	2001	Europe	1989–1995	64, 31–79	122/4	131	126	77.8, 7–120	Muscle invasion or metastasis
Koga [28]	2010	Japan	2002–2005	NA	68/16	53	51	NA	Muscle invasion or metastasis
Hinotsu [27]	2011	Japan	2004–2006	NA	73/10	83	78	NA	Muscle invasion, metastasis, tumors in the upper urinary tract or the urethra, or

Study	Year	Country	Recruitment period	Median age, range (years)	Sex (M/F)	No. randomized	No. eligible	Median FU, range (months)	Definition of progression
									upgrading
Martinez-Pineiro (c) [26]	2015	Spain	1999-2007	68, 30-86	367/30	397	386	77	Muscle invasion or metastasis
Nakai [25]	2016	Japan	2004-2008	NA, 20-79	76/12	95	88	51, 9-86	Muscle invasion, metastasis or tumor in the upper urinary tract
Strain									
Witjes [35]	1996	Netherland	1987-1990	NA	NA	289	251	36, 2-81	Increase of stage
Sengiku [34]	2013	Japan	2004-2012	NA	107/22	178	129	28.5	NA
Rentsch [33]	2014	Europe	1998-2010	NA, 46-96	111/20	142	131	NA	Increase of stage or grade

FU=follow-up, NA=not available.

Table 2. Treatment characteristics of the eligible studies

Study	Inclusion criteria	Group	Dose (mg)	Regimen	Strain
Dose					
Morales [24]	Ta, T1 or CIS	A	60	One weekly for 6 weeks	Pasteur
		B	120	One weekly for 6 weeks	Pasteur
Yalcinkaya [23]	Ta/T1	A	54	One weekly for 6 weeks	Connaught
		B	81	One weekly for 6 weeks	Connaught
Martinez-Pineiro (a) [22]	TaG2-3, T1G1-3, CIS or recurrent TaG1	A	27	One weekly for 6 weeks + once every 2 weeks, 6 times	Connaught
		B	81	One weekly for 6 weeks + once every 2 weeks, 6 times	Connaught
Irie [21]	Ta/T1	A	40	One weekly for 6 weeks	Tokyo 172
		B	80	One weekly for 6 weeks	Tokyo 172
Martinez-Pineiro (b) [20]	T1HG or CIS	A	27	One weekly for 6 weeks + once every 2 weeks, 6 times	Connaught
		B	81	One weekly for 6 weeks + once every 2 weeks, 6 times	Connaught
Vijjan [19]	>G1, >Ta, >1cm, multiple or recurrent	A	40 or 80	One weekly for 6 weeks	Danish 1331
		B	120	One weekly for 6 weeks	Danish 1331
Argawal [18]	Ta/T1 except CIS	A	40 or 80	One weekly for 6 weeks + once monthly for 1 year	Danish 1331
		B	120	One weekly for 6 weeks + once monthly for 1 year	Danish 1331
Oddens (A) [17]	Single T1G3 or multiple Ta/T1G1-3	A	1/3D	One weekly for 6 weeks + every week for 3 weeks on 3, 6 and 12 months	OncoTice
		B	FD (5×10^8 CFU)	One weekly for 6 weeks + every week for 3 weeks on 3, 6 and 12 months	OncoTice
Oddens (B) [17]	Single T1G3 or multiple Ta/T1G1-3	A	1/3D	One weekly for 6 weeks + every week for 3 weeks on 3, 6, 12, 18, 24, 30 and 36 months	OncoTice
		B	FD (5×10^8 CFU)	One weekly for 6 weeks + every week for 3	OncoTice

Study	Inclusion criteria	Group	Dose (mg)	Regimen	Strain
				weeks on 3, 6, 12, 18, 24, 30 and 36 months	
Duration					
Badalament [32]	Ta, T1 or CIS	A	120	One weekly for 6 weeks	Pasteur
		B	120	One weekly for 6 weeks + once monthly for 2 years	Pasteur
Gruenwald [31]	≥ 3 tumors, ≥ 3 prior recurrences or recurrence within 12 month, CIS, T1 or G3	A	120	One weekly for 6 weeks	Pasteur
		B	120	One weekly for 12 weeks	Pasteur
Lamm [30]	Recurrent Ta/T1 (2 tumors within 1 year or 3 recurrences in recent 6 months) and/or CIS	A	81	One weekly for 6 weeks	Connaught
		B	81	One weekly for 6 weeks + every week for 3 weeks on 3, 6, 12, 18, 24, 30 and 36 months	Connaught
Palou [29]	Primary or recurrent Ta/T1G3 or isolated CIS or CIS with G2	A	81	One weekly for 6 weeks	Connaught
		B	81	One weekly for 6 weeks + 6 weekly instillations every 6 months for 2 years	Connaught
Koga [28]	Ta, T1 or CIS	A	80	One weekly for 8 weeks	Tokyo 172
		B	80	One weekly for 8 weeks + single instillation at 3, 6 and 12 months	Tokyo 172
Hinotsu [27]	Recurrent Ta/T1: ≥ 3 tumors, ≥ 3 prior recurrences or recurrence within 12 months	A	81	One weekly for 6 weeks	Connaught
		B	81	One weekly for 6 weeks + every week for 3 weeks at 3, 6, 12 and 18 months	Connaught
Martinez-Pineiro (c) [26]	TaG3, T1G3 or CIS	A	$6.6-19.2 \times 10^8$ CFU	One weekly for 6 weeks	Connaught
		B	$6.6-19.2 \times 10^8$ CFU	One weekly for 6 weeks + every 3 month for 3 years	Connaught
Nakai [25]	Multiple or recurrent Ta/T1 or CIS	A	81	One weekly for 6 weeks	Connaught
		B	81	One weekly for 6 weeks + every week for 3 weeks at 3, 6, 12 and 18 months	Connaught

Study	Inclusion criteria	Group	Dose (mg)	Regimen	Strain
Strain					
Witjes [35]	Ta/T1 or CIS	A	5×10^8 CFU	One weekly for 6 weeks	OncoTice
		B	5×10^8 CFU	One weekly for 6 weeks	RIVM
Sengiku [34]	Ta/T1, CIS, multiple and a recurrence-free period of 3 months or less	A	80	One weekly for 6-8 weeks	Tokyo 172
		B	81	One weekly for 6-8 weeks	Connaught
Rentsch [33]	HG, LG with ≥2 recurrences within 2 years or CIS	A	$2-8 \times 10^8$ CFU	One weekly for 6 weeks	OncoTice
		B	$6.6-19.2 \times 10^8$ CFU	One weekly for 6 weeks	Connaught

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

Table 3. Relative risk according to the strain of bacillus Calmette–Guerin

			Strain A		Strain B		
	Strain A	Strain B	No. events	No. total	No. events	No. total	RR (95% CI)
Recurrence							
Witjes [35]	OncoTice	RIVM	75	140	62	149	1.29 (1.01–1.64)
Sengiku [34]	Tokyo 172	Connaught	42	86	45	92	1.00 (0.74–1.35)
Rentsch [33]	OncoTice	Connaught	31	60	18	71	2.04 (1.28–3.25)
Progression							
Witjes [35]	OncoTice	RIVM	7	140	8	149	0.93 (0.35–2.50)
Rentsch [33]	OncoTice	Connaught	7	60	4	71	2.07 (0.64–6.74)
Cancer–specific mortality							
Rentsch [33]	OncoTice	Connaught	0	60	5	71	0.11 (0.01–1.90)
All–cause mortality							
Rentsch [33]	OncoTice	Connaught	4	60	11	71	0.43 (0.14–1.28)

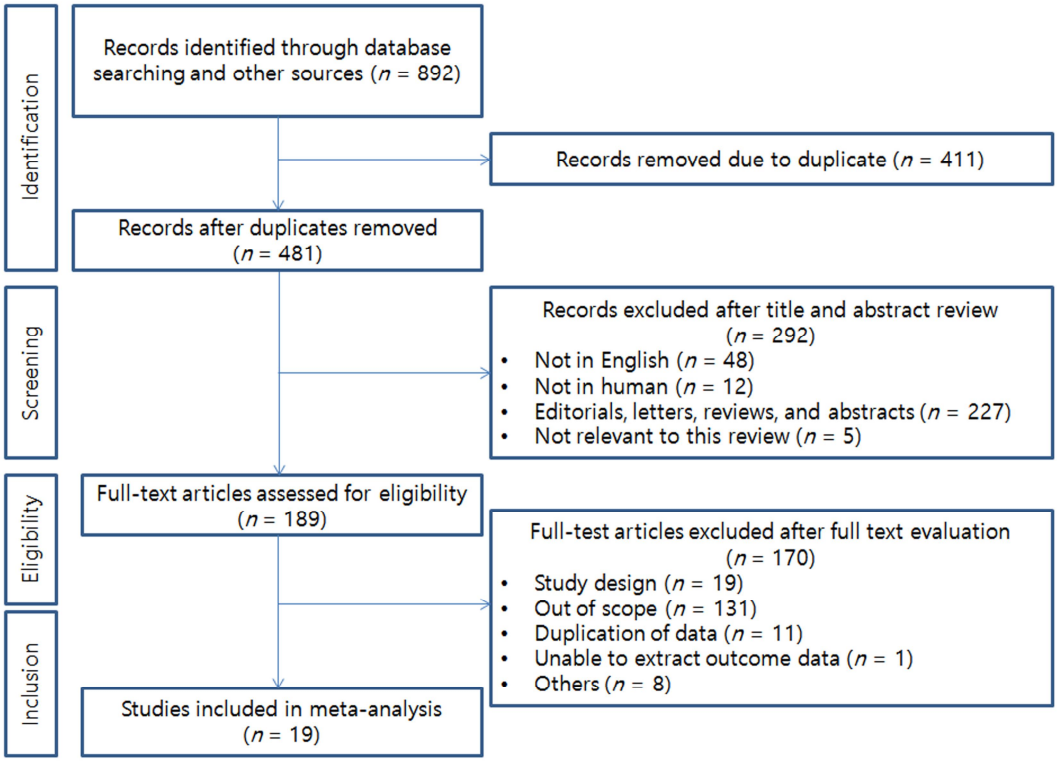

Figure 1. Flow chart of the literature search.

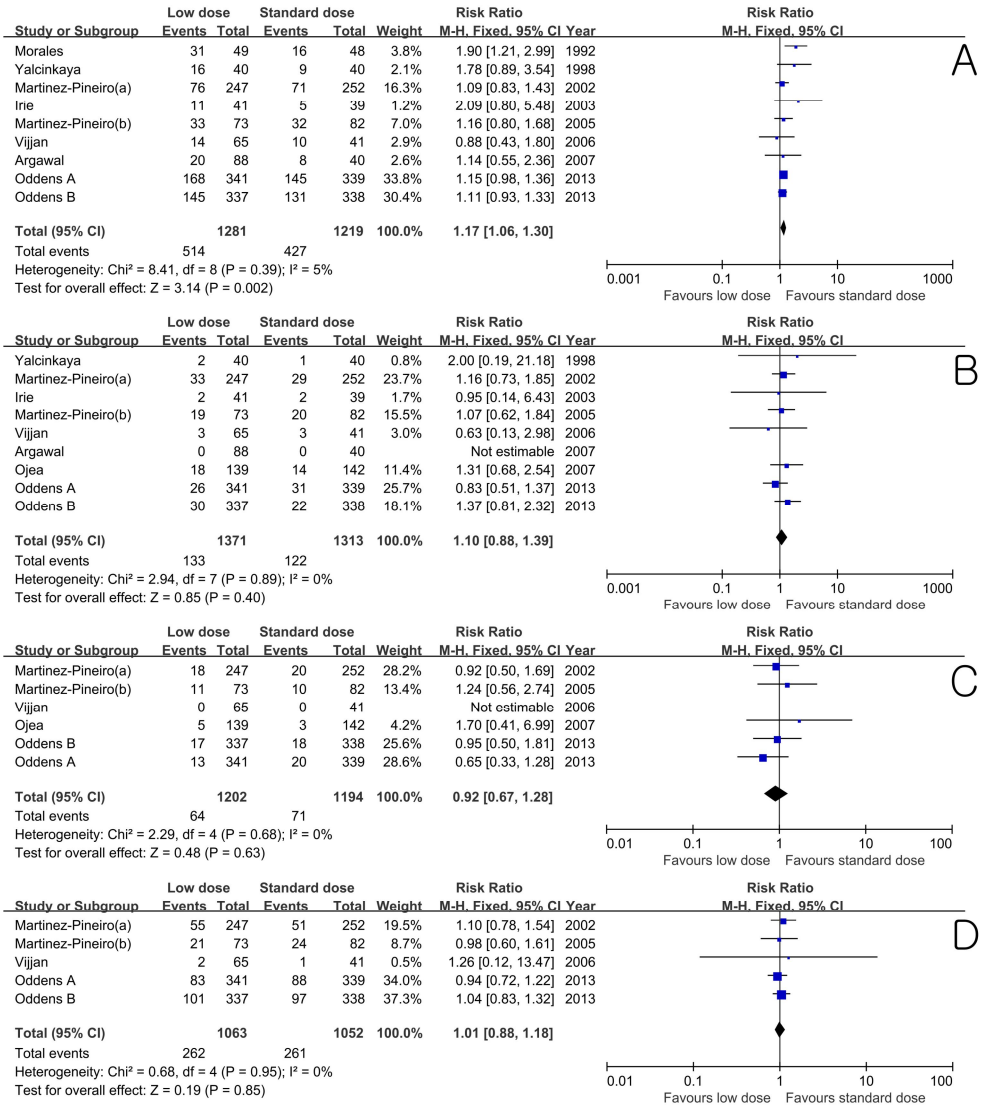

Figure 2. Forest plots of the prognosis of BCG dose. The horizontal lines correspond to the study-specific hazard ratio and 95% confidence interval, respectively. The area of the squares reflects the study-specific weight. The diamond represents the results for pooled hazard ratio and 95% confidence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

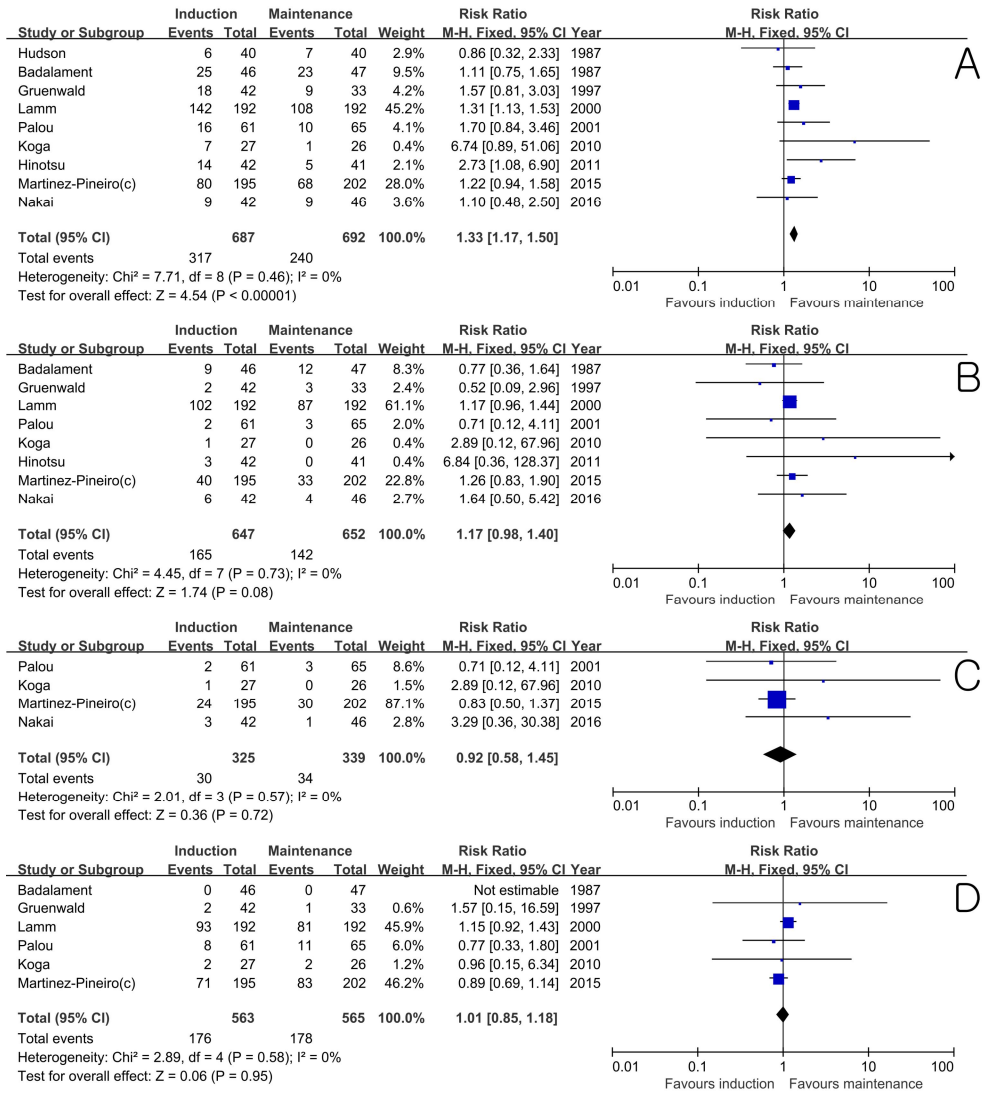

Figure 3. Forest plots of the prognosis of BCG duration. The horizontal lines correspond to the study-specific hazard ratio and 95% confidence interval, respectively. The area of the squares reflects the study-specific weight. The diamond represents the results for pooled hazard ratio and 95% confidence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

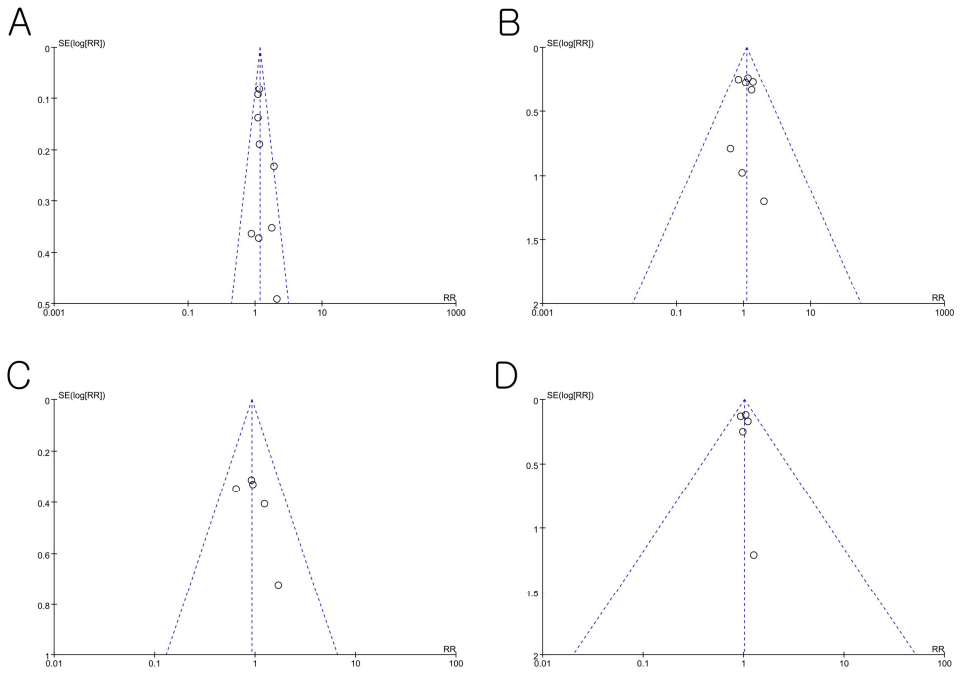

Figure 4. Funnel plots for publication bias test of prognosis in BCG dose. Each point represents a separate study for the indicated association. Vertical line represents the mean effects size. (A) recurrence-free survival, (B) progression-free survival, (C) cancer-specific survival, (D) overall survival.

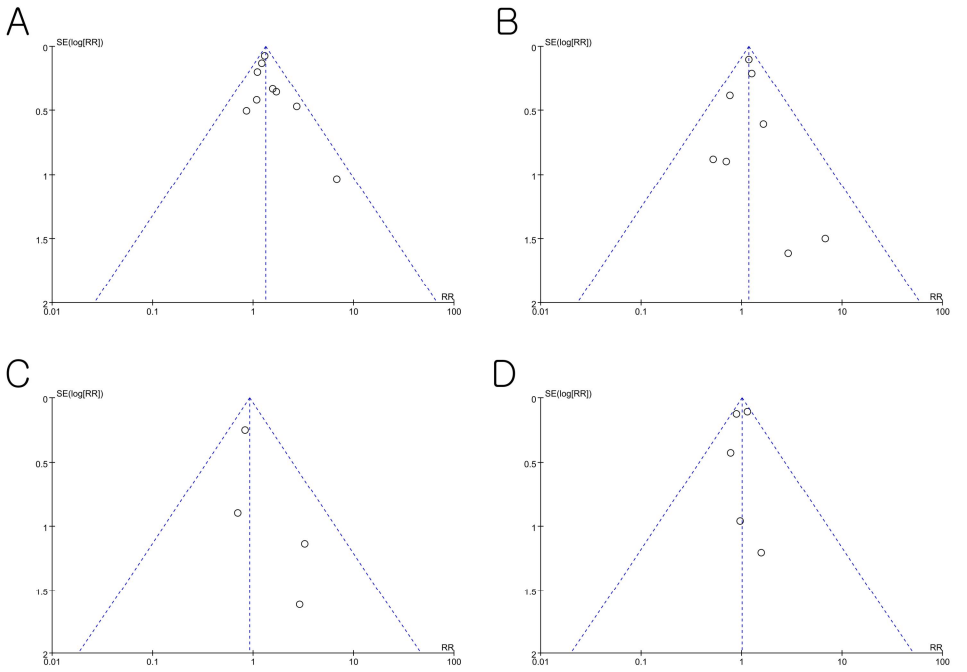

Figure 5. Funnel plots for publication bias test of prognosis in BCG duration. Each point represents a separate study for the indicated association. Vertical line represents the mean effects size. (A) recurrence-free survival, (B) progression-free survival, (C) cancer-specific survival, (D) overall survival.

국문초록

비근침윤성 방광암 환자에서 Bacillus Calmette-Guerin 치료의 투여량, 투여시간, 균종에 대한 연구: 무작위 임상시험 결과에 대한 체계적 문헌고찰과 메타분석

서론: Bacillus Calmette-Guerin (BCG)은 약독화한 우생결핵균으로서 비근침윤성 방광암 환자가 경요도방광종양절제술을 받은 후 보조치료로 매우 널리 쓰이고 있다. 지금까지 임상에서 BCG치료의 투여량, 투여시간, 균종에 대하여 모두 종합하고 분석한 연구는 없다. 본 연구는 BCG치료의 무작위 임상시험 결과에 대한 체계적 문헌고찰과 메타분석을 통하여 비근침윤성 방광암 환자에서 BCG보조치료의 투여량, 투여시간, 균종에 따른 임상결과를 분석하고자 하였다.

방법: 본 연구는 Cochrane Collaboration와 Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA)지침에 따라 Embase, Scopus, PubMed databases 등의 데이터베이스에서 2016년 10월 31일까지 영어로 발표된 논문을 사용하였다. 비근침윤성 방광암 환자에서 BCG치료의 투여량, 투여시간, 균종에 따른 종양의 재발률, 진행률, 암특이적사망률과 전체사망률을 분석하였고 생존결과는 위험비 (RRs) 및 95% 신뢰구간 (CI)로 나타내었다.

결과: 최종적으로 19편의 논문을 대상으로 분석을 진행하였다. 무재발생존률의 비교에서 BCG치료의 저용량 (RR, 1.17; 95% CI 1.06-1.30)과 유도요법 (RR, 1.33; 95% CI 1.17-1.50)은 더욱 높은

위험비를 보여주었다. 하지만 무진행생존률, 암특이성생존률, 전체생존률 등 지표들의 비교결과, BCG 용량, 혹은 BCG 투여시간에서 모두 유의미한 차이가 없었다. Chi-square-based Q statistic test 와 Higgins I-squared statistic test 결과 모든 비교에서 연구간 이질성이 존재하지 않았다. 균종에 대한 연구결과를 분석해보면 무재발생존률의 비교에서 OncoTice는 RIVM (RR, 1.29; 95% CI 1.01-1.64), 혹은 Connaught (RR 2.04; 95% CI 1.28-3.25)에 비교하여 더 높은 위험비를 보여주었다. Funnel plots를 이용하여 분석한 결과 모든 연구에서 유의미한 출간오류는 없었다.

결론: 본 연구결과 비근침윤성 방광암 환자에서 BCG치료의 표준용량과 유지요법은 환자의 재발률을 억제하는데 도움이 될 수 있음을 보여주었다. 비근침윤성 방광암 환자에서 경요도방광종양절제술 치료를 받은 후 BCG보조치료에 대한 좀 더 정확한 임상결과를 얻기 위해서는 향후 더욱 잘 디자인된 대규모 무작위 전향적 연구가 필요하다고 생각된다.

주요어: Bacillus Calmette-Guerin, 방광암, 재발

학 번: 2015-30883