

Can intravesical bacillus Calmette-Guérin reduce recurrence in patients with non-muscle invasive bladder cancer? An update and cumulative meta-analysis

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Abstract Approximately 70% of newly diagnosed bladder tumors are non-muscle invasive bladder cancer (NMIBC). NMIBC accounts for approximately 80% of total bladder cancer cases. Bacillus Calmette-Guérin (BCG) instillation and maintenance is considered as the standard adjuvant treatment for superficial bladder cancer. A number of randomized studies have focused on the benefit of maintenance therapy following initial BCG induction. To provide further insights into the effect of intravesical instillation on recurrence in patients with NMIBC, we analyzed this relationship by conducting an updated detailed meta-analysis. Evidence suggested that adjuvant intravesical BCG with maintenance treatment is significantly effective for the prophylaxis of tumor recurrence in patients with NMIBC.

Keywords non-muscle invasive bladder cancer; bacillus Calmette-Guérin (BCG); meta-analysis

Introduction

Bladder cancer is one of the most common malignancies of the urinary tract [1]. Approximately 70% of newly diagnosed bladder tumors are non-muscle invasive bladder cancer (NMIBC) at diagnosis [1]. NMIBC also accounts for approximately 80% of total bladder cancer cases [2]. Bacillus Calmette-Guérin (BCG) instillation and maintenance is considered as the standard adjuvant treatment for superficial bladder cancer [3]. However, the five-year recurrence rates range from 16% to 59% after a single six-week course of intravesical immunotherapy after transurethral resection of bladder tumor (TURBT) is performed [4]. The European Association of Urology (EAU) guidelines recommend a second transurethral resection (TUR) two to six weeks after the initial resection [5]. Although instillations are administered according to a six weekly induction scheme proposed by Morales *et al.* [6], no consensus regarding the optimal maintenance scheme is established. The EAU recommends at least one year of BCG maintenance [7], but the American

Urological Association proposes three weekly instillations (i.e., each week for three weeks) at three and six months after induction and every six months thereafter for three years [4].

Randomized studies have focused on the benefits of maintenance therapy following initial BCG induction [8]. Our published meta-analysis [9] showed a 39% reduction in the risk of recurrence with BCG maintenance compared with chemotherapy and immunotherapy. We also showed that adjuvant intravesical BCG with maintenance treatment is effective for the prophylaxis of tumor recurrence in superficial bladder cancer. For patients with papillary carcinoma, adjuvant intravesical BCG with maintenance therapy should be administered as the treatment of choice. However, several studies [17,20,22,26] have revealed no benefit of maintenance therapy in the control of tumor recurrence or progression. Differences in the results are possibly caused by maintenance schedules. Maintenance schedules vary considerably and a weekly, monthly, quarterly, or six-month schedule for one to two years may be immunologically suboptimal [10].

Since the time we conducted our meta-analysis [9], relevant studies [10–32] on the association between BCG and NMIBC recurrence after TURBT have been published. These reports are from both prospective and retrospective studies and include approximately 6000 additional cases. To

Received November 18, 2013; accepted January 25, 2014

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provide further insights into the effect of intravesical instillation on recurrence in patients with NMIBC, we analyzed this relationship by conducting an updated detailed meta-analysis. This updated analysis expanded the discussion of possible implications and interpretations of findings.

Materials and methods

Retrieval of studies

MEDLINE and EMBASE were used to gather studies published from January 2005 to November 2012 and are related to both the exposure (BCG) and outcome (bladder cancer) of interest. The following medical subject heading terms and/or text words were used: “bladder cancer,” “superficial bladder cancer,” “non-muscle invasive bladder cancer,” “bladder carcinoma,” and “bladder neoplasm.” The abstracts of all possibly relevant studies were reviewed, and full manuscripts of relevant studies were obtained. We also reviewed the reference lists of these included articles to identify any other studies that were not obtained from the initial literature search. No language restrictions were imposed.

Inclusion and exclusion criteria

In this meta-analysis, case-control, cohort, or cross-sectional studies were considered, particularly those that evaluated the instillation of BCG and bladder cancer recurrence after TURBT. All of the available published data on the treatment results of patients with histologically confirmed superficial bladder cancer were selected for analysis if the following criteria were satisfied: (1) case-control or cohort studies that provided treatment results for patients with histologically confirmed Stage Ta or T1 of any grade or carcinoma *in situ* (CIS) bladder cancer; (2) trials that compared intravesical BCG plus TUR with TUR alone, TUR plus intravesical chemotherapy, TUR plus immunotherapy, or alternatively, intravesical chemotherapy/immunotherapy and BCG; and (3) studies with sufficient information that adequately estimated the odds ratio (OR) and 95% confidence interval (CI), i.e., crude data or adjusted estimates, CIs or *P* values to estimate cancer risk under instillation of BCG compared with instillation of chemotherapy and/or immunotherapy.

Studies were excluded (1) if they provided only an estimate of the effect with no specific means to calculate CI and (2) if they were based on bladder cancer cell lines or animal models. If multiple publications were obtained from the same population or cohort, only data from the most recent reports were included.

The primary endpoint criterion of this meta-analysis was the frequency of tumor recurrence within the follow-up period of the studies. Recurrence was defined as the reappearance of tumor at the same or lower stage and grade as the primary tumor.

In this meta-analysis, BCG maintenance therapy was defined as a six-week induction course of BCG and then three-weekly BCG instillations at three and six months and every six months thereafter for at least one year. Patients who only received six-week (or less than) induction courses of BCG were included in the non-BCG maintenance group.

We did not assess the methodological quality of the primary studies because quality scoring in meta-analysis of observational studies is controversial. Instead, we performed subgroup and sensitivity analyses that are widely recommended. Hence, no study was rejected because of methodological characteristics or any subjective quality criteria.

Data extraction

Data were independently abstracted in duplicate by two investigators using a standard protocol and data collection form. We extracted the following information from each publication: the first author's last name; publication year; study design; type of control (in case-control studies); study location; exposure and outcome definition; number of subjects; sample size (cases and controls or cohort size); and controlled variables in the analysis. Disagreement or uncertainty between two investigators was resolved by discussion. We also extracted the risk estimate adjusted for the greatest number of potential confounders from each study.

Statistical analysis

We examined the relationship between instillation of BCG after TUR and bladder cancer recurrence risk on the basis of the ORs and 95% CIs published in each study. A fixed-effect model using the Mantel-Haenszel method and a random-effect model using the DerSimonian and Laird method were used to pool the results. Heterogeneity was evaluated using Cochran's *Q* test and *I*-squared statistics. If the level of heterogeneity was acceptable ($P > 0.10$, or $P \leq 0.10$ but $I^2 \geq 50\%$), the meta-analysis was conducted using a fixed-effect model. If the significant heterogeneity was found ($P \leq 0.10$, $I^2 > 50\%$), a random-effect model was used for the meta-analysis.

Inverted funnel plots and Egger's test were used to assess publication bias. An asymmetric plot suggested possible publication bias. Funnel plot asymmetry was assessed by Egger's linear regression test. *t*-test was performed to determine the significance of the asymmetry and $P < 0.05$ indicated a significant publication bias.

A sensitivity analysis was performed to determine the potential risk bias in the overall results because studies that violated some of the eligibility criteria were included. Potential confounding effects were investigated by stratified meta-analysis. Sensitivity analyses were also conducted to identify trends among subpopulations within the overall study. The following subgroups were included: (1) BCG maintenance therapy; (2) instillation schedules, such as BCG

versus TUR alone/chemotherapy/immunotherapy and BCG plus chemotherapy/immunotherapy versus BCG alone; (3) BCG strains; and (4) types of different histological results.

A cumulative meta-analysis was conducted. This procedure evaluated the cumulative effect estimate over time. We also used the META-INF command in Stata to evaluate the influence of any study on the overall effect estimate. This analysis omitted one study at a time and determined the pooled effect estimate.

Stata 10 software (Stata, College Station, Tex., USA) was used for the statistical analyses.

Results

The characteristics of the trials included in the meta-analysis are summarized in Tables 1, 2, and 3. Our literature search yielded 1260 articles; among these studies, 198 satisfied the inclusion criteria for our overall systematic review of the antitumor effect of BCG on NMIBC recurrence from January 2005 to November 2012. Among these 198 articles, a total of 23 [10–32] new publications or abstracts were indentified since the time we conducted a previous meta-analysis [9]. Two [33,34] additional papers published in 2000 and 2002 were also included in our analysis. As a result, 48 studies (Fig. 1) satisfied the inclusion criteria of our meta-analysis and provided information regarding 9482 subjects with published estimates of BCG instillation and NMIBC. The trial publication dates covered 1997 to 2012. A wide range of control groups was noted, including TUR alone (10 trials), the use of different immunotherapy agents, such as interferon (two trials), and the use of different chemotherapy regimens, such as mitomycin C, thiotepa, doxorubicin, and epirubicin (28 trials), and BCG and chemotherapy/immunotherapy (11 trials). Some forms of BCG maintenance were used in 30 trials and no BCG maintenance was used in 18 trials (Table 1). In the 48 eligible clinical trials with a total of 9482 patients, the sample size ranged from 3 to 560 patients (Table 2). Hence, a total of 4952 patients were treated with BCG. These patients were then compared with 4530 patients treated without BCG.

The funnel plot showed the expected funnel shape (Fig. 2). The results of Begg's ($P = 0.21$) and Egger's tests ($P = 0.30$) suggested a low probability of publication bias in our analysis. To determine the degree of heterogeneity that existed among the 48 studies, we conducted Cochran's Q test. Cochran's Q test yielded $P < 0.01$ ($Q = 192.97$ on 56 df), indicating a high degree of heterogeneity in our analysis. As such, a random-effect model including all studies was chosen. In the follow-up period, 1900 (38.4%) of the 4952 BCG-treated patients and 2231 (49.2%) of 4530 patients treated without BCG developed tumor recurrence. In the combined analysis, a statistically significant difference in the recurrence rate between the two treatment groups was found. The randomized model-combined OR was 0.59 (95% CI 0.49 to

Table 1 Trial characteristics ($n = 48$)

Publication date	
Oldest	1997
Most recent	2012
Disease type	
Ta-1	13
CIS	4
Ta, T1, CIS	22
Others (T1G3 and T1)	9
Treatment comparisons	
BCG vs. transurethral resection only	10
BCG vs. BCG and chemotherapy/immunotherapy	11
BCG vs. immunotherapy	2
BCG vs. chemotherapy	28
BCG maintenance	
No	18
Yes	30
BCG strain	
Connaught	10
Tokyo	6
Pasteur	9
Tice	8
Danish	1
RIVM	2

0.71, $P < 0.0001$). Thus, the overall results of the 48 included studies were consistent with the statistically significant difference between BCG and non-BCG efficacy on tumor recurrence in the overall pooled data.

In this meta-analysis, patients who only received a six-week (or less than) induction course of BCG were included in the non-BCG maintenance group. A total of 6547 patients received BCG maintenance therapy for at least one year. In 18 studies with a total of 2935 patients, no maintenance therapy was administered. In the BCG maintenance subgroup, the combined random effect OR was 0.53 (95% CI = 0.43 to 0.65, $P = 0.000$). The results indicated a statistical significance of BCG versus non-BCG efficacy on tumor recurrence in the BCG maintenance subgroup. The non-BCG maintenance subgroup showed a combined random effect model OR of 0.70 (95% CI = 0.50 to 0.99, $P = 0.047$).

The combined random effect OR was 0.43 (95% CI = 0.26 to 0.72, $P = 0.001$) when BCG versus TUR alone was stratified. In the BCG versus chemotherapy subgroup comprising patients who received BCG versus patients who only received chemotherapy without immunotherapy or BCG, the combined random effect OR was 0.58 (95% CI = 0.45 to 0.75; $P = 0.000$). In the BCG plus chemotherapy/immunotherapy versus BCG alone subgroup, the combined randomized model OR was 0.87 (95% CI = 0.62 to 1.21, $P = 0.408$). In the BCG versus immunotherapy subgroup, the combined random effect OR was 0.44 (95% CI = 0.21 to 0.91,

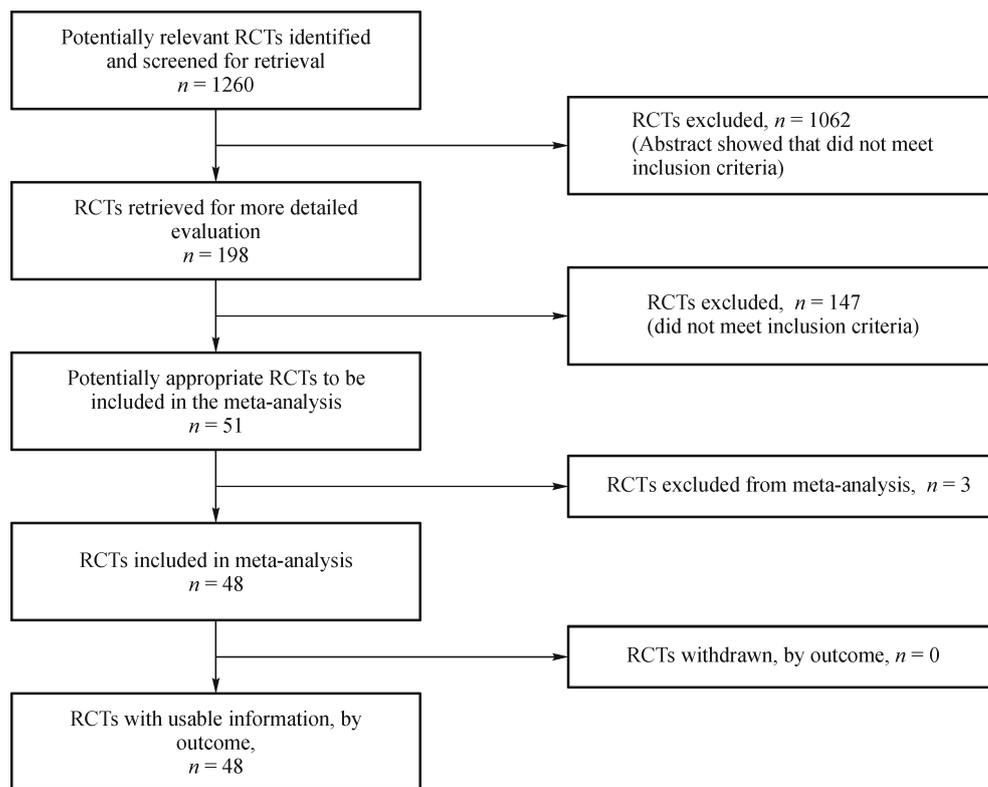


Fig. 1 PRISMA flow diagram for the trial. RCT, randomized clinical trial.

Table 2 Trial characteristics (*n* = 48)

Characteristics	<i>n</i> (%)
Evaluable	9482
No BCG	4530 (47.8)
BCG	4952 (52.2)
Treatment comparisons	8649
BCG vs. transurethral resection only	1242 (14.4)
BCG vs. BCG and chemotherapy/immunotherapy	1181 (13.8)
BCG vs. immunotherapy	360 (4.2)
BCG vs. chemotherapy	5866 (67.8)
BCG maintenance	9482
No	2935 (31.0)
Yes	6547 (69.0)
BCG strain	7701
Connaught	2629 (34.1)
Tokyo	313 (4.1)
Pasteur	1475 (19.2)
Others (Tice, Danish 1331, RIVM)	3284 (42.6)

P = 0.027). In the BCG maintenance therapy versus initial therapy subgroup, the combined random effect OR was 0.57 (95% CI = 0.32 to 0.99, *P* = 0.047).

In our study, several strains of BCG were used, including

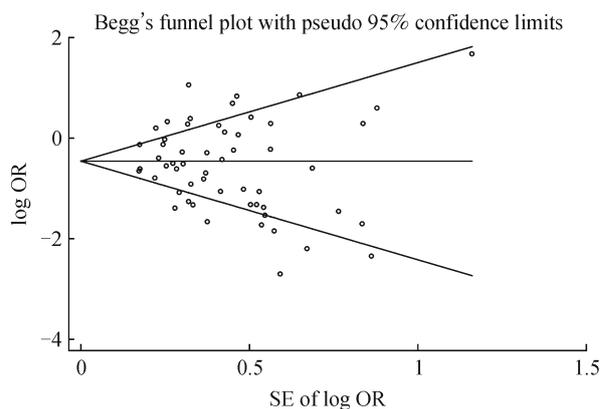


Fig. 2 Funnel plot of log OR of recurrent NMIBC according to the SEs of all studies in analysis. Begg's test (*P* = 0.21) and Egger test for publication bias (*P* = 0.30).

Connaught, Tokyo, Pasteur, Tice, Danish, and RIVM. The stratified meta-analysis did not show any statistically significant confounding effects on the results when stratified by a BCG strain. However, a statistically significant difference was found between BCG and non-BCG treatments in terms of tumor recurrence in the Ta-1 subgroup with a combined random effect OR of 0.63 (95% CI = 0.48 to 0.85, *P* = 0.002). The combined random effect OR of Ta, T1, and

Table 3 Descriptive characteristics of studies used in the meta-analysis

Study, year of publication	Location and year(s) of study	BCG <i>n/N</i>	No BCG <i>n/N</i>	Instillation schedules	Disease type	BCG strain
Yoo KH <i>et al.</i> , 2012	Korea, 2000–2009	33/92	21/34	BCG maintenance/BCG initiation therapy	Ta, T1, CIS	Tice
Gülpinar Ö <i>et al.</i> , 2012	Turkey, 2004–2006	9/25	5/26	BCG initiation therapy/BCG initiation therapy and perioperative MMC	Ta, T1, CIS	Not mentioned
Matsumoto K <i>et al.</i> , 2012	Japan, 1985–2008	48/119	19/24	BCG initiation therapy/chemotherapy	Ta, T1, CIS	Connaught
Cho IC <i>et al.</i> , 2012	Korea	48/119	23/40	BCG initiation therapy/TUR alone	TIG3	RIVM
Okamura T <i>et al.</i> , 2012	Japan, 1989–2006	16/53	15/54	BCG maintenance/MMC	Ta, T1, CIS	Tokyo
Chen CH <i>et al.</i> , 2012	China's Taiwan, 1996–2004	8/48	13/27	BCG maintenance/BCG initiation therapy	Ta, T1	Pasteur
Hinoitsu S <i>et al.</i> , 2011	Japan	22/62	36/65	BCG maintenance/doxorubicin	Ta, T1, CIS	Connaught
Oosterlinck W <i>et al.</i> , 2011	Turkey, Italy, etc., 2001–2005	22/62	66/114	BCG maintenance/MMC, doxorubicin, and cisplatin	Ta, T1, CIS	Connaught
Koga H <i>et al.</i> , 2010	Japan, 2002–2005	6/41	17/42	BCG maintenance/BCG initiation therapy	CIS	Tice
Porona M <i>et al.</i> , 2010	Italy, 2004–2006	6/41	23/32	BCG maintenance/Gemcitabine	Ta, T1, CIS	Tokyo
Di Lorenzo G <i>et al.</i> , 2010	Italy, 2006–2008	17/42	23/32	BCG maintenance/Gemcitabine	Ta, T1, CIS	Tice
Cho DY <i>et al.</i> , 2009	Korea, 2005–2006	26/48	23/48	BCG initiation therapy/BCG & Gemcitabine	Ta, T1	Connaught
Sylvester RJ <i>et al.</i> , 2010	Europe, 1992–1997	103/281	147/279	BCG maintenance/Epirubicin	Ta, T1, CIS	Tice
Duchek M <i>et al.</i> , 2010	Europe, 1999–2006	103/281	110/277	BCG maintenance/BCG & Isomiazid	Ta, T1	Tice
Riihka Järvinen <i>et al.</i> , 2009	Finland, 1984–1987	34/126	47/124	BCG maintenance/MMC	T1	Tice
Yi SH <i>et al.</i> , 2008	China, 2004–2007	26/44	36/45	BCG maintenance/MMC	Ta, T1, CIS	Pasteur
Cai T <i>et al.</i> , 2008	Italy, 2005–2007	3/21	0/24	BCG maintenance/BCG & Hydroxycamptothecin	Ta, T1, CIS	Not mentioned
Ojeda A <i>et al.</i> , 2007	CUETO, 1995–1998	40/81	34/80	BCG initiation therapy/BCG & Epirubicin	Ta, T1, CIS	Not mentioned
Friedrich MG <i>et al.</i> , 2007	Germany, 1995–2002	38/142	58/149	BCG maintenance (27 mg)/MMC	Ta, T1	Connaught
Hinoitsu S <i>et al.</i> , 2006	Japan, 1998–2002	50/139	58/149	BCG maintenance (13.5 mg)/MMC	Ta	RIVM
Di Stasi SM <i>et al.</i> , 2006	Italy, 1994–2002	41/163	46/179	BCG initial therapy/MMC 6 weeks	Ta	Tokyo
Startsev V <i>et al.</i> , 2005	Russia, 2002–2003	41/163	16/153	BCG initial therapy/MMC 3 years	Ta, T1	Tokyo
Cheng CW <i>et al.</i> , 2005	China, 1991–1999	21/40	13/40	BCG initial therapy/doxorubicin	Ta, T1, CIS	Connaught
de Reijke TM <i>et al.</i> , 2005	Netherlands, 1993–1999	26/105	38/107	BCG initial therapy/BCG & MMC	Ta, T1, CIS	Connaught
Yumura Y <i>et al.</i> , 2004	Japan	11/60	21/82	BCG initial therapy/chemotherapy	Ta, T1, CIS	Not mentioned
Peyromaure M <i>et al.</i> , 2004	France, 1991–2001	30/102	59/107	BCG maintenance/Epirubicin	Ta, T1, CIS	Connaught
Kaasinen E <i>et al.</i> , 2003	Nordic, 1992–1997	53/81	45/80	BCG maintenance/Epirubicin	Ta, T1, CIS	Connaught
Librenjak D <i>et al.</i> , 2003	Croatia, 1989–1994	4/19	8/15	BCG initial therapy/TUR alone	TIG3	Tokyo
Hara I <i>et al.</i> , 2003	Japan, 1995–1997	24/57	8/10	BCG maintenance/MMC	TIG3	Pasteur
Shahin O <i>et al.</i> , 2003	Switzerland	24/57	2/7	BCG maintenance/TUR alone	TIG3	Pasteur
		65/145	87/159	BCG maintenance/BCG & MMC	CIS	Connaught
		36/80	68/90	BCG maintenance/TUR alone	Ta, T1	Pasteur
		22/34	55/63	BCG initial therapy/chemotherapy	T1	Not mentioned
		64/92	46/61	BCG initial therapy/TUR alone	TIG3	Pasteur

(Continued)

Study, year of publication	Location and year(s) of study	BCG n/N	No BCG n/N	Instillation schedules	Disease type	BCG strain
Kaasinen E <i>et al.</i> , 2002	Finland, 1992–1996	48/102	64/103	BCG maintenance/BCG & IFN	Ta, T1	Tice
Patard JJ <i>et al.</i> , 2002	France, 1979–1996	25/50	27/30	BCG maintenance/TUR alone	T1G3	Pasteur
Kolodziej A <i>et al.</i> , 2002	Poland, 1996–2002	19/102	29/53	BCG maintenance/TUR alone	Ta, T1, CIS	Tice
Chepurov AK <i>et al.</i> , 2002	Russia	25/51	7/11	BCG maintenance/BCG initiation therapy	Ta, T1, CIS	Not mentioned
Kulkarni JN <i>et al.</i> , 2002	India, 1991–1999	32/69	8/22	BCG initiation therapy/TUR alone	T1G3	Danish
Sekine H <i>et al.</i> , 2001	Japan, 1998–1999	2/21	11/21	BCG initial therapy/chemotherapy	CIS	Not mentioned
van der Meijden AP <i>et al.</i> , 2001	Netherlands	91/281	131/279	BCG maintenance/chemotherapy	Ta, T1	Not mentioned
Tozawa K <i>et al.</i> , 2001	Japan, 1996–1999	16/50	6/23	BCG maintenance/BCG & Epirubicin	Ta, T1	Tokyo
Palou J <i>et al.</i> , 2001	Spain, 1989–1995	56/66	45/61	BCG maintenance/BCG initiation therapy	CIS	Connaught
Lamm DL <i>et al.</i> , 2000	USA	108/192	142/192	BCG maintenance/BCG initiation therapy	Ta, T1, CIS	Connaught
Altay B <i>et al.</i> , 2000	Turkey	16/61	10/40	BCG initiation therapy/TUR alone	Ta, T1	Not mentioned
		16/61	10/40	BCG initiation therapy/chemotherapy		
Bilen CY <i>et al.</i> , 2000	Turkey, 1994–1995	4/21	3/20	BCG initiation therapy/BCG & Epirubicin	Ta, T1, CIS	Connaught
Moyano Calvo JL <i>et al.</i> , 1999	Spain	43/111	89/124	BCG initiation therapy/TUR alone	Ta, T1	Not mentioned
Malmstrom PU <i>et al.</i> , 1999	Sweden	59/125	49/125	BCG maintenance/MMC	Ta, T1, CIS	Pasteur
Wijes JA <i>et al.</i> , 1998	Netherlands	35/90	42/92	BCG initiation therapy/MMC	Ta, T1, CIS	Not mentioned
Wijes JA <i>et al.</i> , 1998	EORTC, 1985–1986	76/159	72/168	BCG initiation therapy/MMC	Ta, T1, CIS	RIVM
Ayed M <i>et al.</i> , 1998	France	25/66	84/123	BCG maintenance/MMC	Ta, T1	Pasteur
Jimenez-Cruz JF <i>et al.</i> , 1997	Spain	24/61	34/49	BCG maintenance/INF	T1	Pasteur

MMC: Mitomycin C; INF: Interferon.

CIS subgroup was 0.55 (95% CI = 0.40 to 0.75, $P = 0.000$) and that of T1G3 was 0.50 (95% CI = 0.31 to 0.82, $P = 0.06$). Thus, BCG maintenance therapy and a papillary disease type in BCG versus non-BCG therapy against tumor recurrence were significantly associated. For CIS disease, the random effect OR was 0.80 (95% CI 0.34 to 1.85, $P = 0.595$). This result indicated that BCG therapy had no statistical significance compared with non-BCG therapy against CIS tumor recurrence.

A cumulative meta-analysis was conducted to evaluate the cumulative effect estimate over time. Since 2000, significantly lower OR between BCG instillation and bladder cancer has been found, specifically after 2005 when more publications were added cumulatively and resulted in the overall effect estimate of 0.60. In the sensitivity analysis, the overall homogeneity and effect size were calculated, but one study was removed at a time. The META-INF command in Stata was also used. The result of this analysis confirmed the stability of the inverse association between BCG instillation and bladder cancer. The range of the pooled OR when one study was removed was 0.55 to 0.70.

Discussion

Bladder cancer is a common disease in urologic oncology. NMIBC accounts for approximately 70% of bladder cancers. NMIBC is manifested as Ta, Tis, and T1 bladder cancers [35]. Among these cancers, the predominant histological type is transitional cell carcinoma accounting for > 90% of bladder tumors in Europe and USA. Approximately 75% to 85% of bladder cancers are superficial and confined to the mucosa (stage Ta) or submucosa (stage T1) [36]. CIS is a less common high-grade diffuse surface-spreading lesion confined to the urothelium (Ta), accounting for 1% to 4% of the primary tumors and occurs concomitantly with a papillary tumor in 13% to 20% of bladder cancer patients [37]. The standard primary treatment for NMIBC is TUR; however, the recurrence rates of TUR alone can be as high as 70%, in which a maximum of 30% progresses to muscle invasive disease requiring cystectomy [38].

For superficial urinary bladder cancer, one of the established treatment modalities involves the direct infusion of BCG into the bladder, and this procedure is recommended to those with intermediate or high risk of recurrence or stage progression [39]. For CIS, BCG is considered as the primary standard [39] and the only treatment option available.

High rates of recurrence and progression have prompted researchers to investigate various treatments to decrease the burden of this disease. Since the first therapeutic application of BCG in 1976 [6], intravesical BCG has been administered as the standard therapy for NMIBC and considered as superior to any other single chemotherapeutic agent for the reduction of recurrence and prevention of disease progression. Major efforts have also been devoted to elucidating the

antitumor mechanism. Typical complete response rates are 55% to 65% for papillary tumors and 70% to 75% for CIS; this result inversely indicates that 30% to 45% of patients likely suffer from BCG failures [39]. Among the complete responders, a maximum of 50% likely experience recurrence [40].

Many individual trials exhibit low capacities to detect medically plausible differences between two treatment regimens, particularly if both regimens have valid efficacy. One possible way to overcome this problem is to perform a combined analysis of the available materials by conducting a meta-analysis. Meta-analysis is a formal statistical method used to combine the results of separate, but similar, studies quantitatively; as such, the statistical power of the tests used to compare treatments is increased by considering evidence obtained from a larger number of controlled trials rather than only one controlled trial [41]. Meta-analytical techniques were also used to draw conclusions on the benefits of different therapeutic options for the adjuvant treatment of superficial bladder cancer. Our meta-analysis has shown that intravesical BCG after TUR reduces the risk of recurrence, particularly in papillary tumors, when maintenance BCG is used. Our meta-analysis confirmed that BCG plus chemotherapy/immunotherapy is not better than BCG alone; furthermore, BCG, particularly regimens with maintenance BCG, was more effective in the subgroup of patients with papillary tumors than other agents. In our study, the results indicated the statistical significance of BCG efficacy on tumor recurrence in the BCG maintenance subgroup. Grade 3 tumors likely undergo progression, and the treatment of these tumors remains controversial. In our study, the results indicated that BCG also yielded statistical significance against T1G3 tumors. Chemotherapy or immunotherapy agents can be instilled into the bladder directly by using a catheter; thus, the morbidity of systemic administration is prevented in most cases. In our study, mitomycin C, thiotepa, doxorubicin, epirubicin, interferon, interleukin-2, and BCG were included. However, our results did not show any statistically significant differences regarding the efficacy to prevent tumor recurrence.

The consideration of study bias is critical when observational data are subjected to meta-analysis. In our analysis, the funnel plot revealed the expected funnel shape (Fig. 2). The results of Begg's ($P = 0.21$) and Egger's tests ($P = 0.30$) suggested a low probability of publication bias. Therefore, we are confident that important publication bias caused by the preferential publication of large studies with significant findings unlikely occurred. However, Cochran's Q test results indicated a high degree of heterogeneity in our analysis. As a result, a random-effect model was used to include all studies. To identify the sources of heterogeneity, we stratified data into subgroups on the basis of study and performed sensitivity analysis. In the sensitivity analysis, the overall homogeneity and effect size were calculated, removing one study at a time. Excluding any study did not significantly change the pooled

OR. The range of pooled OR was 0.55 to 0.70 when one study was removed.

This formal and updated meta-analysis suggested that adjuvant intravesical BCG with maintenance treatment is significantly effective for the prophylaxis of tumor recurrence in patients with NMIBC. For patients with papillary bladder cancer, adjuvant intravesical BCG therapy with maintenance should be administered as the treatment of choice.

Compliance with ethics guidelines

Jiangang Pan, Mo Liu, and Xing Zhou declare that they have no conflict of interests. This article also does not contain any studies with human or animal subjects performed by any of the authors.

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