Original Paper

Assessing the Feasibility of Replacing Standard-Dose Bacillus Calmette–Guérin Immunotherapy with Other Intravesical Instillation Therapies in Bladder Cancer Patients: A Network Meta-Analysis

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Key Words

Intravesical instillation therapies • Bacillus Calmette–Guérin • Mitomycin C • Epirubicin • Interferon-Alpha • Gemcitabine • Tumor recurrence • Tumor progression • Pairwise/network meta-analysis • Heterogeneity • Consistency

Abstract

Background: Bacillus Calmette–Guérin (BCG) immunotherapy plays a key role in patients with bladder cancer. The shortage of intravesical BCG has motivated researchers to seek alternatives with equivalent efficacy. If other alternative intravesical agents have equivalent efficacy compared to BCG, then it may be feasible to replace standard BCG with alternative options.

Methods: We searched all relevant evidence in multiple sources and key data was extracted from included studies. Conventional and network meta-analysis were conducted so that pooled odds ratios (ORs) for the event of tumor recurrence and progression can be computed. The relative efficacy of different intravesical instillation procedures was computed by pooled odds ratios and their 95% confidence or credible intervals. Besides, several key model assumptions were evaluated in our analysis. **Results:** Three intravesical instillation procedures have the potential for preventing tumor recurrence: standard-dose BCG (BCG_SD), Epirubicin (EPI) and Mitomycin C (MMC) (ORs < 1). Patients with BCG_SD also exhibited a decreased risk of tumor recurrence and progression compared to those with EPI. No significant difference in the risk of tumor recurrence or progression was detected between patients treated with BCG_SD and those with low-dose BCG (BCG_LD). Results of SUCRA indicated that BCG_EPI, BCG_MMC and BCG_SD had higher rankings with respect to tumor recurrence and progression. **Conclusions:** BCG_SD, EPI and MMC exhibited established efficacy for preventing tumor recurrence in postoperative BC patients. The efficacy of BCG may not be significantly reduced if standard dose was reduced to a lower level. However, there is no consensus suggesting that intravesical BCG with standard dose can be replaced by alternating or sequentially combined intravesical instillation therapies.

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Introduction

Bladder cancer (BC) is generally classified as starting from the urothelium. Although the exact cause of BC has not yet been identified, it is still associated with exposure to certain aromatic chemicals such as aniline dyes and benzidine compounds [1]. The survival rate of bladder cancer patients varies significantly with tumor stages. According to the American Cancer Society (ACS), the five-year survival rate decreased dramatically from 88% (stage I) to 15% (stage IV).

If tumors are diagnosed through pathological examinations, transurethral resection of bladder tumor (TURBT) will be performed. Treatment selection is determined by several factors: pathological classification, tumor staging and metastatic status. Immunotherapy using intravesical delivery of Bacillus Calmette-Guérin (BCG) plays a pivotal role in bladder cancer since it is effective in BC treatment and tumor recurrence prevention after surgical resection in a certain degree [1].

There is a potential shortage of intravesical BCG due to its increasing demand together with insufficient supplies [2]. Two potential solutions can be provided as treatment supplementary, particularly for patients with non-muscle-invasive bladder cancer. One typical approach is to use alternative intravesical agents instead, such as Mitomycin C (MMC), Epirubicin (EPI), Interferon-Alpha (INF) and Gemcitabine (GEM), which can be quite controversial in the meanwhile because it is believed immunotherapy of BCG can overcome short remissions resulted from intravesical chemotherapeutic agents [3, 4]. However, it can still be improved. For instance, intravesical BCG can be combined with other intravesical agents to enhance its efficacy in the long term. The second approach comes from the hypothesis that a lower dose of intravesical BCG has no significant influence on the overall efficacy [5]. This inevitably increases the complexity of evidence.

If the shortage of intravesical BCG production continues and the number of bladder cancer patients keeps increasing, evaluating the two solutions mentioned above will become an urgent task. Besides that, preventing the abuse of intravesical BCG is highly advocated, particularly for the non-muscle invasive bladder cancer (NMIBC) patients [6]. This network meta-analysis (NMA) was designed to compare the long-term efficacy of different intravesical instillation therapies. Several intravesical instillation therapies with different features (immunotherapy of intravesical BCG: standard dosage or reduced dosage; other intravesical instillation agents: MMC, EPI, INF, GEM; single, sequentially combined or alternating) are considered throughout the research protocol, systematic review and NMA.

Material and Methods

Research protocol: systematic review and planning

We designed a study protocol to ensure the accuracy and feasibility of our study. The corresponding study protocol concerned about specific study populations, interventions, comparators and outcomes (PICOS). Besides that, a few items were discussed by the researchers in the protocol: search strategy, predefined study inclusion criteria, data extraction process, quality assessment, risk of bias and statistical approaches. Also, the implementation of our network meta-analysis was guided by the research protocol. A few meta-analyses were reviewed for reference. We also planned for some potential changes during the course of our research.

Evidence searching

An initial search was conducted in the current literature to ascertain that our research topics have not been studied. Multiple sources were identified and selected for preventing selection and reporting bias: Embase, PubMed, Cochrane Library and China National Knowledge Infrastructure (CNKI). Preliminary searching terms and strings were developed using the following key words: Urinary Bladder Neoplasms; Bladder Instillations; BCG Vaccine; Mutamycin; Epilem; Interferons; gemcitabine.. The entire searching strategy was conducted iteratively and the corresponding searching results were peer viewed for the purpose of quality control. Apart from the initial search, evidence searching was updated at the final stage.

Eligibility criteria and study selection

Eligibility criteria were clearly defined before study selection. The corresponding eligibility criteria consider four key elements in order to ensure the validity of the upcoming network meta-analysis: types of studies, types of participants, types of interventions and types of outcomes. 1) Types of studies: randomized clinical trials (RCTs) comparing the efficacy or safety of intravesical agents for bladder cancer patients; trials were conducted between the year of 1986 and 2016 with a minimum follow-up duration of six months. 2) types of participants: postoperative (TUR) adult patients with proven evidence of non-muscle-invasive bladder cancer (with or without carcinoma in situ), superficial bladder cancer, recurrent bladder cancer, superficial bladder carcinoma patients with increased risk of tumor recurrence or progression, patients with previous BCG treatment or chemotherapy or radiation therapy, patients with severe infection or active tuberculosis, patients with other neoplastic diseases, lower urinary tract diseases or major concomitant diseases were excluded. 3) Types of interventions: instillation therapy with BCG (standard dose: 80 mg; low dose: 40 mg), MMC (10 mg, 30 mg, 40 mg), EPI (20 mg, 40 mg, 50 mg, 80 mg), IFN (50 million units) and GEM (2,000 mg); trials with single, combined or alternating instillation therapy were all eligible. 4) Types of outcomes: trials that assessed intravesical instillation therapy by using tumor recurrence or tumor progression. The above eligibility criteria were also reviewed by senior researchers. Discussion was held in a group meeting if there was any disagreement.

Data collection process

We developed a preliminary data extraction sheet and identified a list of essential variables for our network meta-analysis. Then, a pilot data extraction was conducted by drawing a random sample from the eligible list. The initial data extraction was refined to reflect the nature of our network meta-analysis and the quality of included studies. The refined data extraction sheet covers three types of information for each eligible study: basic study information (author, publication year, average age of patients, the proportion of male patients, the following-up duration), comparators and outcomes (instillation therapy, sample size in each group, the number or proportion of patients who experienced tumor recurrence or progression by the end of the following-up period) and quality of eligible studies (appropriate randomization techniques, blinding procedures and disclosure of withdrawals). All study variables were clearly coded before data extraction. Eligible studies with missing variables were not removed in order to prevent selection bias. Missing study variables were not imputed (NR: Not Reported) if they cannot be estimated or computed from the original study. Data collection results were verified by two independent reviewers. All inconsistency was resolved by consensus before the commencement of statistical analysis.

Quality of included studies

The eligible study list was reviewed by our review team and the content for each study was carefully examined. Each included study was discussed based on the following topics: the adequacy of randomization, blinding procedures, the issue of loss to follow-up and the degree of heterogeneity among included studies. Then, the Jadad scale was used by two independent reviewers to quantify the quality of studies. Some potential sensitivity or subgroup analysis was also planned in this stage.

Statistical analysis

The efficacy of intravesical instillation therapies was compared by using the endpoint of tumor recurrence and progression. First, our reviewers performed a pairwise meta-analysis based on the fixed-effect model. The statistic of odds ratio (OR) for the event of tumor recurrence or progression was produced in each included study. Then, a weighted odds ratio together with its 95% confidence interval (95% CI) was computed by the fixed-effect model for each direct comparison. Study heterogeneity within each direct comparison was measured by the statistics of I^2 . The assumption of homogeneous effect size was tested by the Cochran's Q statistics. Study heterogeneity is significant if $I^2 > 50\%$ or P -value for the hypothesis testing of homogeneous effect < 0.1 . After that, an NMA (random-effects model, Bayesian Framework) along with the Markov Chain Monte Carlo (MCMC) simulation was carried out to synthesize all relevant evidence. Summary OR and its 95% credible interval (95% CrI) for the event of tumor recurrence or progression were produced for comparison. Evidence inconsistency for each pair of comparison was assessed by the node-splitting method [7]. Evidence was significantly inconsistent if the P -value of the node-splitting method < 0.05 . Intravesical instillation therapies were compared according to their surface under the cumulative

ranking curve (SUCRA) values. Finally, funnel plots were created for detecting asymmetry patterns which are typical signs for publication bias. All of the above data manipulation and statistical analysis was implemented by using the statistical computing software R (The R Project for Statistical Computing, R version 3.2.5). The GEMTC package was also loaded into R software for Bayesian network meta-analysis and MCMC simulation.

Results

Literature search results

We initially identified 2,226 literature records from a variety of sources. All identified records were retrieved and imported into the bibliography management software (Endnote 7). Then, 248 duplicated or overlapped records were removed from the bibliography software. By reviewing the title and abstract of the remaining 1978 articles, we further excluded 1,909 studies that were not related to our research topics or did not fulfill the predefined eligibility criteria. As a result, only 69 studies were remained for full-text assessment. We identified and excluded 12 studies without full-text content or sufficient data during the course of full-text review. The above steps were performed by two independent literature searchers who did not conduct the previous literature search. Any discrepancy of the literature search results was discussed with caution (Fig. 1).

Characteristics of included studies and structures of network

In total, we included 57 RCTs [8-64] conducted between 1988 and 2016 (Table 1). All included studies were followed up for a minimum and maximum duration of 0.9 and 9.2 years, respectively. The 57 eligible studies included a total of 12,943 patients who were diagnosed with superficial bladder cancer, carcinoma in site or non-muscle invasive bladder cancer. There appeared to be significant variation in the demographic features of patients in each included study. For instance, the average age of patients ranged from 55 to 71.9 and some studies did not report the average age of patients. A vivid network demonstrating the pattern of evidence and comparisons is displayed in Fig. 2. The structure of evidence was formed by a total of 9 intravesical instillation therapies: BCG_SD (standard dose), BCG MMC, BCG_LD (low dose), BCG_EPI, MMC, IFN, GEM and EPI. As shown in the network plot, the sample size for each intravesical instillation therapy varied remarkably.

Pairwise meta-analysis

The following groups of patients were exhibited a lower risk of tumor recurrence compared to those with placebo: BCG_SD (OR = 0.48, 95% CI = 0.34-0.70), EPI (OR = 0.76, 95% CI = 0.62-0.94) and MMC (OR = 0.65, 95% CI = 0.48-0.88; Table 2). Direct evidence also revealed that postoperative BC patients who received BCG MMC exhibited a reduced risk of tumor recurrence than those with BCG_SD (OR = 0.74, 95% CI = 0.54-0.99). By contrast, patients with EPI exhibited an elevated risk of tumor recurrence in relation to those with BCG_SD (OR = 1.53, 95% CI =

Fig. 1. Flow chart of the study selection.

Table 1. The main characteristics of the included clinical trials. * NR: Not reported; BCG_SD: Bacille Calmette Guerin standard dose; BCG_LD: Bacille Calmette Guerin low dose; MMC: Mitomycin C; GEM: Gemcitabine; EPI: Epirubicin; IFN: Interferon

First author, year	Age	Male (%)	Follow-up (year)	Comparison	Treatments and outcomes			Quality assessment		
					Size	Tumor recurrence	Tumor progression	Random	Blind	Withdraw
Mondal, 2016 [43]	NR	90	0.9	BCG_SD/MMC	21/19	0/2	NR	2	\	\
Solsona, 2015 [55]	67	89.9	7.1	BCG_MM/BCG_SD	211/196	44/68	26/24	2	\	1
Inamoto, 2013 [27]	71.9	81.6	1.4	BCG_SD/BCG_LD	20/18	5/5	NR	2	\	\
Gontero, 2013 [23]	67.4	85.8	1	BCG_LD/GEM	47/41	14/16	3/5	2	\	1
Oddens, 2013 [45]	68	81.1	7.1	BCG_LD/BCG_SD	657/659	311/276	56/53	2	\	\
Järvinen, 2012 [29]	68	80.9	7.2	MMC/BCG_MM	40/28	35/19	14/8	2	\	\
Gülpınar, 2012 [25]	58.1	80.3	5	BCG_MM/BCG_SD	25/26	9/5	1/1	2	\	\
Oosterlinck, 2011 [47]	69	86.5	4.7	BCG_MM/BCG_SD	48/48	23/26	2/5	2	\	\
Hinotsu, 2011 [26]	NR	90.4	2	BCG_SD/EPI	83/32	19/22	3/7	2	\	\
De Nunzio, 2011 [16]	60.8	68.6	7.5	MMC/Placebo	97/105	10/46	0/1	2	\	\
Bandary, 2011 [11]	56.2	NR	0.9	GEM/BCG_SD	40/40	10/12	NR	2	\	\
O'Brien, 2011 [44]	70	NR	NR	MMC/Placebo	105/115	21/31	NR	2	\	1
Sylvester, 2010 [56]	67	NR	9.2	EPI/BCG_SD	267/266	147/103	24/19	2	\	\
Porena, 2010 [50]	69.4	84.4	3.7	BCG_SD/GEM	32/32	9/17	5/10	2	\	1
Di Lorenzo, 2010 [118]	70.4	61.2	1.3	GEM/BCG_SD	40/40	21/35	7/13	2	\	\
Addeo, 2010 [8]	66.4	85.3	3	MMC/GEM	55/54	22/15	10/6	2	\	\
Wu, 2010 [63]	65	46.9	4.6	EPI/MMC/Placebo	31/27/145	9/7/57	NR	\	\	\
Gudjonsson, 2010 [24]	NR	NR	2.9	EPI/Placebo	102/117	63/90	NR	2	\	1
Bohle, 2009 [13]	66	79.8	2	GEM/Placebo	124/124	49/48	3/1	2	2	\
Yoneyama, 2008 [64]	66.7	75.3	5.6	BCG_SD/BCG_LD	85/65	29/21	NR	\	\	\
Cai, 2008 [14]	NR	85.7	1.3	BCG_EPI/BCG_SD	80/81	34/40	2/4	2	2	\
Ojeda, 2007 [46]	64.5	87	4.4	BCG_LD/MMC	281/149	88/58	32/14	2	\	1
Friedrich, 2007 [22]	67.4	80.2	2.9	BCG_LD/MMC	163/332	41/62	NR	2	\	\
El-Ghohashy, 2007 [21]	62.2	80.2	2.9	MMC/Placebo	31/32	12/17	1/1	2	\	\
Di Stasi, 2006 [19]	67	81.6	7.3	BCG_SD/BCG_MM	105/107	61/45	23/10	2	\	1
de Reijke, 2005 [17]	NR	92	5.6	BCG_SD/EPI	84/84	9/21	NR	2	\	\
Cheng, 2005 [15]	69.9	71.2	5.1	BCG_SD/EPI	102/107	30/59	9/16	2	\	\
Peyromaur, 2004 [49]	68.4	81	4.4	BCG_LD/MMC/Placebo	57/10/7	24/8/2	13/1/0	\	\	\
Irie, 2003 [28]	61.9	85	1.7	BCG_SD/BCG_LD	39/41	5/11	2/1	\	\	1
Di Stasi, 2003 [20]	NR	73	3.6	BCG_SD/MMC	36/72	19/46	6/14	2	\	\
March, 2003 [38]	NR	NR	2.8	MMC/BCG_LD	139/263	46/49	9/15	2	\	\
Librenjak, 2003 [35]	64	78.8	5.3	BCG_LD/Placebo	80/90	36/68	12/28	\	\	\
Martinez-Pineiro, 2002 [39]	63.5	90.2	5.8	BCG_SD/BCG_LD	252/257	71/76	29/33	2	\	1
Kumar, 2002 [33]	56.3	88.5	2	BCG_SD/BCG_LD	13/13	4/5	1/1	2	\	\
Kolodziej, 2002 [31]	NR	NR	1.9	BCG_SD/Placebo	102/53	20/29	8/12	2	\	1
Rajala, 2002 [51]	65.4	72	6	IFN/EPI/Placebo	66/68/66	45/31/48	NR	2	\	1
van der Meijden, 2001 [60]	66	77	3.5	EPI/BCG_SD	279/281	142/98	19/9	2	\	\
Tozawa, 2001 [59]	66.3	87.5	3	BCG_SD/BCG_EPI	50/23	27/13	NR	\	\	1
Bilen, 2000 [12]	55	95.1	1.5	BCG_SD/BCG_EPI	21/20	4/3	2/1	2	\	\
Witjes, 1999 [62]	NR	NR	2.7	BCG_MM/MMC	90/92	39/42	5/4	2	\	\
Malmström, 1999 [37]	NR	NR	5.3	MMC/BCG_SD	125/125	83/66	27/20	2	\	\
Ali-El-Dein, 1999 [10]	58.2	77.4	2.5	BCG_EPI/BCG_SD	66/58	7/12	3/5	2	\	\
Rajala, 1999 [52]	NR	72	NR	EPI/IFN/Placebo	66/68/66	42/23/40	NR	2	\	\
Solsona, 1999 [54]	61	92.4	7.8	MMC/Placebo	57/64	23/35	1/1	2	\	\
Jimenez-Cruz, 1997 [30]	NR	84.4	NR	BCG_SD/IFN	61/49	24/34	6/7	2	\	\
Ali-El-Dein, 1997 [9]	55.7	70.8	2.7	EPI/Placebo	114/54	28/28	5/5	2	\	\
Rintala, 1996 [53]	68	75.5	2.8	MMC/BCG_MM	90/92	58/57	3/3	2	\	1
Melekos a, 1996 [41]	NR	NR	2.9	BCG_SD/EPI	46/48	16/22	5/7	2	\	\
Melekos b, 1996 [42]	NR	88.2	3.6	EPI/BCG_SD	61/58	34/26	10/7	2	\	\
Krege, 1996 [32]	NR	79.8	1.7	BCG_SD/MMC/Placebo	102/112/122	26/30/56	NR	2	\	1
Lundholm, 1996 [36]	68	84	3.3	MMC/BCG_SD	130/131	43(125)/62(125)	17/16	2	\	\
Vegt, 1995 [61]	NR	NR	3	MMC/BCG_SD	148/289	58/137	8/15	2	\	\
Takashi, 1995 [57]	64.7	83.8	2.6	BCG_SD/BCG_LD	37/37	1/3	0/2	\	\	\
Lamm, 1995 [34]	67	83	2.5	BCG_LD/MMC	225/222	77/101	15/25	2	\	\
Oosterlinck, 1993 [48]	NR	NR	2	EPI/Placebo	194/205	41/49	7/5	2	\	\
Melekos, 1993 [40]	NR	83.2	NR	EPI/BCG_SD/Placebo	67/62/32	27/20/19	6/4/7	2	\	\
Tolley, 1988 [58]	NR	NR	1	MMC/Placebo	267/130	137/84	NR	2	\	1

Fig. 2. Network geometry of clinical trials of postoperative intravesical instillation for efficacy in bladder cancer. * BCG_SD: Bacille Calmette Guerin standard dose; BCG_LD: Bacille Calmette Guerin low dose; MMC: Mitomycin C; GEM: Gemcitabine; EPI: Epirubicin; IFN: Interferon.

1.30-1.82). Postoperative BC patients with EPI also appeared to have a higher risk of tumor progression compared to those with BCG_SD (OR = 1.64, 95% CI = 1.16-2.33). As suggested by pairwise meta-analysis, BCG_SD was the only one that was likely to inhibit the risk of tumor progression (OR = 0.33, 95% CI = 0.15-0.71). No significant study heterogeneity was identified for the above results.

Table 2.

Pair-wise meta-analyses of direct comparisons between different treatments. * P_H P value of heterogeneity; OR: Odds ratio; CI: Confidential interval; BCG_SD: Bacille Calmette Guerin standard dose; BCG_LD: Bacille Calmette Guerin low dose; MMC: Mitomycin C; GEM: Gemcitabine; EPI: Epirubicin; IFN: Interferon

Endpoints	Direct comparisons	I^2	P_H values	OR (95% CI)	P_{OR} values
Tumor Recurrence	GEM vs. BCG_LD	-	-	1.31 (0.57, 3.01)	0.524
	MMC vs. BCG_LD	53.10%	0.074	1.26 (0.93, 1.70)	0.141
	BCG+EPI vs. BCG_SD	0.00%	0.748	0.82 (0.55, 1.23)	0.347
	BCG_LD vs. BCG_SD	0.00%	0.895	1.12 (0.95, 1.32)	0.164
	BCG+MMC vs. BCG_SD	11.10%	0.338	0.74 (0.54, 0.99)	0.049
	EPI vs. BCG_SD	0.00%	0.537	1.53 (1.30, 1.82)	<0.001
	GEM vs. BCG_SD	45.70%	0.158	0.93 (0.48, 1.82)	0.831
	IFN vs. BCG_SD	-	-	1.76 (0.93, 3.36)	0.084
	MMC vs. BCG_SD	14.70%	0.32	0.97 (0.77, 1.22)	0.767
	IFN vs. EPI	83.00%	0.015	0.90 (0.33, 2.47)	0.834
	BCG+MMC vs. MMC	0.00%	0.881	0.92 (0.67, 1.26)	0.605
	EPI vs. MMC	-	-	1.12 (0.37, 3.41)	0.842
	GEM vs. MMC	-	-	0.69 (0.33, 1.48)	0.345
	BCG_LD vs. Placebo	6.40%	0.301	0.66 (0.38, 1.16)	0.146
	BCG_SD vs. Placebo	0.00%	0.565	0.48 (0.34, 0.70)	<0.001
	EPI vs. Placebo	0.00%	0.594	0.76 (0.62, 0.94)	0.01
	GEM vs. Placebo	-	-	1.02 (0.64, 1.63)	0.931
Tumor Progression	IFN vs. Placebo	36.20%	0.211	0.74 (0.45, 1.23)	0.246
	MMC vs. Placebo	39.30%	0.117	0.65 (0.48, 0.88)	0.005
	GEM vs. BCG_LD	-	-	1.91 (0.43, 8.49)	0.395
	MMC vs. BCG_LD	0.80%	0.388	1.13 (0.75, 1.69)	0.566
	BCG+MMC vs. BCG_SD	13.40%	0.326	0.69 (0.41, 1.16)	0.163
	BCG_LD vs. BCG_SD	0.00%	0.951	1.08 (0.79, 1.46)	0.645
	EPI vs. BCG_SD	0.00%	0.587	1.64 (1.16, 2.33)	0.006
	GEM vs. BCG_SD	63.30%	0.099	1.00 (0.28, 3.62)	0.998
	BCG+EPI vs. BCG_SD	0.00%	0.999	0.52 (0.19, 1.44)	0.209
	MMC vs. BCG_SD	0.00%	0.956	1.18 (0.80, 1.74)	0.41
	IFN vs. BCG_SD	-	-	1.45 (0.46, 4.60)	0.526
	BCG+MMC vs. MMC	0.00%	0.871	0.96 (0.47, 1.97)	0.912
	GEM vs. MMC	-	-	0.61 (0.21, 1.80)	0.371
	MMC vs. Placebo	0.00%	0.998	1.01 (0.25, 4.14)	0.993
	GEM vs. Placebo	-	-	3.00 (0.31, 29.24)	0.344
	BCG_LD vs. Placebo	23.10%	0.254	0.63 (0.22, 1.77)	0.375
	BCG_SD vs. Placebo	0.00%	0.845	0.33 (0.15, 0.71)	0.004
	EPI vs. Placebo	27.00%	0.254	0.67 (0.30, 1.51)	0.335

Table 3. The efficacy of different treatments according to the network meta-analysis using ORs and corresponding 95% CrIs. * OR: Odds ratio; CrI: Credible interval; BCG_SD: Bacille Calmette Guerin standard dose; BCG_LD: Bacille Calmette Guerin low dose; MMC: Mitomycin C; GEM: Gemcitabine; EPI: Epirubicin; IFN: Interferon

Tumor Recurrence									
BCG_EPI	1.48 (0.68, 3.29)	1.11 (0.47, 2.59)	1.38 (0.68, 2.77)	2.75 (1.26, 5.99)	1.62 (0.66, 3.90)	2.77 (1.05, 7.32)	1.84 (0.87, 4.01)	4.18 (1.92, 9.21)	
0.68 (0.30, 1.48)	BCG_LD	0.75 (0.42, 1.31)	0.93 (0.64, 1.34)	1.86 (1.16, 2.97)	1.09 (0.59, 1.97)	1.88 (0.89, 3.94)	1.26 (0.87, 1.82)	2.83 (1.84, 4.35)	
0.90 (0.39, 2.12)	1.34 (0.76, 2.36)	BCG_MMC	1.25 (0.76, 2.01)	2.51 (1.40, 4.44)	1.48 (0.72, 2.94)	2.51 (1.12, 5.64)	1.68 (1.02, 2.77)	3.82 (2.18, 6.62)	
0.73 (0.36, 1.46)	1.07 (0.75, 1.57)	0.80 (0.50, 1.31)	BCG_SD	2.01 (1.42, 2.83)	1.17 (0.68, 2.03)	2.01 (1.03, 3.97)	1.35 (0.98, 1.88)	3.06 (2.16, 4.35)	
0.36 (0.17, 0.79)	0.54 (0.34, 0.86)	0.40 (0.23, 0.71)	0.50 (0.35, 0.70)	EPI	0.59 (0.32, 1.07)	1.01 (0.52, 1.95)	0.67 (0.44, 1.03)	1.52 (1.05, 2.20)	
0.62 (0.26, 1.51)	0.91 (0.51, 1.70)	0.68 (0.34, 1.39)	0.85 (0.49, 1.48)	1.70 (0.93, 3.16)	GEM	1.72 (0.74, 4.01)	1.14 (0.65, 2.05)	2.59 (1.46, 4.66)	
0.36 (0.14, 0.95)	0.53 (0.25, 1.13)	0.40 (0.18, 0.90)	0.50 (0.25, 0.97)	0.99 (0.51, 1.93)	0.58 (0.25, 1.35)	IFN	0.67 (0.33, 1.36)	1.51 (0.77, 2.94)	
0.54 (0.25, 1.15)	0.79 (0.55, 1.15)	0.59 (0.36, 0.98)	0.74 (0.53, 1.02)	1.49 (0.97, 2.25)	0.88 (0.49, 1.54)	1.49 (0.73, 3.03)	MMC	2.27 (1.58, 3.19)	
0.24 (0.11, 0.52)	MMC vs. BCG_SD	0.26 (0.15, 0.46)	0.33 (0.23, 0.46)	0.66 (0.45, 0.95)	0.39 (0.21, 0.68)	0.66 (0.34, 1.30)	0.44 (0.31, 0.63)	Placebo	
Tumor Progression									
BCG_EPI	2.2 (0.76, 7.54)	1.57 (0.49, 5.53)	2.05 (0.73, 6.69)	3.63 (1.22, 12.3)	2.32 (0.7, 8.94)	3.22 (0.66, 17.64)	2.46 (0.84, 8.41)	4.62 (1.51, 16.6)	
0.45 (0.13, 1.31)	BCG_LD	0.69 (0.41, 1.21)	0.93 (0.66, 1.26)	1.63 (1.00, 2.56)	1.04 (0.56, 1.99)	1.46 (0.41, 5.26)	1.11 (0.77, 1.55)	2.08 (1.25, 3.49)	
0.64 (0.18, 2.03)	1.45 (0.83, 2.44)	BCG_MMC	1.32 (0.85, 2.05)	2.34 (1.31, 4.10)	1.49 (0.76, 3.29)	2.10 (0.56, 8.00)	1.60 (0.89, 2.59)	3.00 (1.57, 5.87)	
0.49 (0.15, 1.38)	1.07 (0.79, 1.52)	0.76 (0.49, 1.17)	BCG_SD	1.77 (1.22, 2.53)	1.14 (0.61, 2.10)	1.58 (0.47, 5.58)	1.19 (0.87, 1.67)	2.25 (1.39, 3.67)	
0.28 (0.08, 0.82)	0.61 (0.39, 0.99)	0.43 (0.24, 0.76)	0.57 (0.39, 0.82)	EPI	0.64 (0.31, 1.31)	0.90 (0.25, 3.25)	0.68 (0.42, 1.11)	1.28 (0.76, 2.23)	
0.43 (0.11, 1.42)	0.96 (0.50, 1.79)	0.67 (0.30, 1.32)	0.88 (0.48, 1.63)	1.57 (0.76, 3.22)	GEM	1.40 (0.35, 5.37)	1.06 (0.55, 1.93)	2.01 (0.95, 4.06)	
0.31 (0.06, 1.52)	0.68 (0.19, 2.46)	0.48 (0.12, 1.79)	0.63 (0.18, 2.14)	1.11 (0.31, 3.97)	0.71 (0.19, 2.89)	IFN	0.75 (0.21, 2.75)	1.43 (0.38, 5.31)	
0.41 (0.12, 1.20)	0.90 (0.64, 1.30)	0.63 (0.39, 1.13)	0.84 (0.60, 1.15)	1.48 (0.90, 2.36)	0.94 (0.52, 1.80)	1.34 (0.36, 4.76)	MMC	1.88 (1.09, 3.35)	
0.22 (0.06, 0.66)	0.48 (0.29, 0.80)	0.33 (0.17, 0.64)	0.44 (0.27, 0.72)	0.78 (0.45, 1.32)	0.50 (0.25, 1.05)	0.70 (0.19, 2.66)	0.53 (0.30, 0.91)	Placebo	

Network meta-analysis

The efficacy of different intravesical instillation therapies was also assessed by using indirect evidence. Patients with seven intravesical instillation therapies benefited from a

Fig. 3. Odds ratio and 95% credible interval for tumor recurrence. * OR: Odds ratio; CrI: Credible interval; BCG_SD: Bacille Calmette Guerin standard dose; BCG_LD: Bacille Calmette Guerin low dose; MMC: Mitomycin C; GEM: Gemcitabine; EPI: Epirubicin; IFN: Interferon.

Fig. 4. Odds ratio and 95% credible interval for tumor progression. * OR: Odds ratio; CrI: Credible interval; BCG_SD: Bacille Calmette Guerin standard dose; BCG_LD: Bacille Calmette Guerin low dose; MMC: Mitomycin C; GEM: Gemcitabine; EPI: Epirubicin; IFN: Interferon.

reduced risk of tumor recurrence compared to those with placebo (BCG_EPI, BCG_LD, BCG_MMC, BCG_SD, EPI, GEM and MMC) (all ORs < 1, Table 3, Fig. 3). Patients with BCG_EPI, BCG_LD, BCG_MMC and BCG_SD appeared to have a decreased risk of tumor recurrence compared to those with EPI (all ORs < 1). Also, three intravesical instillation therapies were associated with a suppressed risk of tumor recurrence compared to IFN: BCG_EPI, BCG_MMC and BCG_SD (all ORs < 1). Patients with BCG_EPI, BCG_LD, BCG_MMC and BCG_SD were associated with a reduced risk of tumor progression compared to EPI (all ORs < 1, Table 3, Fig. 4). Besides that, five intravesical instillation therapies (BCG_EPI, BCG_LD, BCG_MMC, BCG_SD, and MMC) were likely to inhibit the risk of tumor progression (all ORs < 1). The cumulative probability of being a specific rank was displayed in Fig. 5. BCG_EPI, BCG_MMC and BCG_SD exhibited the three highest SUCRA values in regards of tumor recurrence (BCG_EPI = 0.88, BCG_MMC = 0.86, BCG_SD = 0.71) and tumor progression (BCG_EPI = 0.92, BCG_MMC = 0.84, BCG_SD = 0.65).

Fig. 5. Ranking of treatments in terms of different criteria. * BCG_SD: Bacille Calmette Guerin standard dose; BCG_LD: Bacille Calmette Guerin low dose; MMC: Mitomycin C; GEM: Gemcitabine; EPI: Epirubicin; IFN: Interferon.

Fig. 6. Comparison adjusted funnel plot for assessing publication bias. * A: Placebo; B: Bacille Calmette Guerin standard dose; C: Bacille Calmette Guerin low dose; D: Mitomycin C; E: Gemcitabine; F: Epirubicin; G: Interferon; H: Bacille Calmette Guerin/ Mitomycin C; I: Bacille Calmette Guerin/ Epirubicin.

Model assumption assessments

Results of the node splitting method are depicted in Table 4. The consistency assumption in the NMA and MCMC simulation was not violated since inconsistency in the corresponding evidence was not significant (all P -value > 0.05). Besides that, small-study effects and publication bias was visually examined by funnel plots (Fig. 6). Since no asymmetry patterns were observed in the funnel plots, we concluded that there was no strong evidence of publication bias.

Discussion

Overall, some consistent evidence was provided by our pairwise MA and NMA. A reduced risk of tumor recurrence was observed in postoperative patients with BCG_SD, EPI or MMC. Besides that, both MA and NMA confirmed that BCG_SD was more effective than EPI

Table 4. Comparison of direct and indirect evidences. * BCG_SD: Bacille Calmette Guerin standard dose; BCG_LD: Bacille Calmette Guerin low dose; MMC: Mitomycin C; GEM: Gemcitabine; EPI: Epirubicin; IFN: Interferon

Endpoints	Comparisons	OR (95% CI or CrI)	P values	Endpoints	Comparisons	OR (95% CI or CrI)	P values
Tumor Recurrence	BCG_SD vs BCG_LD			Tumor Progression	direct	1.90 (0.90, 4.70)	
	direct	0.79 (0.46, 1.30)			indirect	0.79 (0.24, 2.80)	0.220
	indirect	1.10 (0.68, 1.90)			network	1.50 (0.79, 3.00)	
	network	0.93 (0.63, 1.30)	0.310		Placebo vs MMC		
	GEM vs BCG_LD				direct	2.00 (1.20, 3.20)	
	direct	1.50 (0.40, 5.90)			indirect	2.90 (1.60, 5.10)	0.320
	indirect	0.99 (0.47, 2.00)	0.583		network	2.30 (1.60, 3.10)	
	network	1.10 (0.58, 2.00)			BCG_SD vs BCG_LD		
	MMC vs BCG_LD				direct	0.91 (0.60, 1.30)	
	direct	1.50 (0.92, 2.60)			indirect	0.97 (0.58, 1.60)	0.891
	indirect	1.10 (0.64, 1.90)	0.376		network	0.91 (0.67, 1.30)	
	network	1.30 (0.86, 1.80)			GEM vs BCG_LD		
	Placebo vs BCG_LD				direct	2.10 (0.45, 11.0)	
	direct	2.30 (0.78, 5.90)			indirect	0.94 (0.45, 2.00)	0.395
	indirect	2.80 (1.80, 4.50)	0.744		network	1.00 (0.56, 1.90)	
	network	2.80 (1.80, 4.30)			MMC vs BCG_LD		
	BCG_SD vs BCG_MMC				direct	1.10 (0.69, 1.70)	
	direct	1.50 (0.79, 2.60)			indirect	1.10 (0.67, 1.80)	0.945
	indirect	0.97 (0.44, 2.20)	0.441		network	1.10 (0.78, 1.60)	
	network	1.30 (0.76, 2.00)			Placebo vs BCG_LD		
	MMC vs BCG_MMC				direct	1.80 (0.79, 3.80)	
	direct	1.40 (0.68, 3.10)			indirect	2.40 (1.20, 4.80)	0.560
	indirect	2.00 (1.00, 4.10)	0.516		network	2.10 (1.30, 3.40)	
	network	1.70 (1.00, 2.80)			BCG_SD vs BCG_MMC		
	EPI vs BCG_SD				direct	1.60 (0.94, 2.70)	
	direct	2.30 (1.50, 3.40)			indirect	0.81 (0.33, 1.90)	0.219
	indirect	1.60 (0.88, 3.00)	0.349		network	1.30 (0.86, 2.00)	
	network	2.00 (1.40, 2.80)			MMC vs BCG_MMC		
	GEM vs BCG_SD				direct	1.00 (0.50, 2.30)	
	direct	0.70 (0.32, 1.70)			indirect	2.00 (1.10, 3.90)	0.180
	indirect	1.80 (0.82, 3.70)	0.124		network	1.60 (0.99, 2.60)	
	network	1.20 (0.68, 2.00)			EPI vs BCG_SD		
	IFN vs BCG_SD				direct	1.80 (1.20, 2.70)	
	direct	3.60 (1.00, 13.00)			indirect	1.80 (0.55, 5.80)	0.994
	indirect	1.60 (0.71, 3.50)	0.280		network	1.70 (1.20, 2.50)	
	network	2.00 (1.00, 3.90)			GEM vs BCG_SD		
	MMC vs BCG_SD				direct	0.94 (0.41, 2.20)	
	direct	1.10 (0.65, 1.80)			indirect	1.40 (0.63, 3.50)	0.488
	indirect	1.60 (1.10, 2.50)	0.191		network	1.10 (0.63, 2.10)	
	network	1.40 (0.98, 1.90)			MMC vs BCG_SD		
	Placebo vs BCG_SD				direct	1.20 (0.74, 1.90)	
	direct	3.40 (1.70, 7.30)			indirect	1.20 (0.76, 1.90)	0.999
	indirect	3.00 (2.00, 4.60)	0.766		network	1.20 (0.88, 1.70)	
	network	3.10 (2.20, 4.40)			Placebo vs BCG_SD		
	IFN vs EPI				direct	3.80 (1.70, 9.20)	
	direct	0.86 (0.37, 1.90)			indirect	1.70 (0.92, 3.00)	0.111
	indirect	1.90 (0.47, 6.20)	0.339		network	2.30 (1.40, 3.70)	
	network	0.99 (0.51, 1.90)			Placebo vs EPI		
	MMC vs EPI				direct	1.60 (0.74, 3.50)	
	direct	0.83 (0.18, 4.20)			indirect	1.10 (0.49, 2.30)	0.534
	indirect	0.66 (0.43, 1.00)	0.809		network	1.30 (0.80, 2.20)	
	network	0.67 (0.45, 1.10)			MMC vs GEM		
	Placebo vs EPI				direct	1.80 (0.52, 6.30)	
	direct	1.90 (1.20, 2.90)			indirect	0.83 (0.36, 1.70)	0.266
	indirect	1.00 (0.55, 1.90)	0.128		network	1.10 (0.56, 2.00)	
	network	1.50 (1.10, 2.20)			Placebo vs GEM		
	MMC vs GEM				direct	0.29 (0.01, 4.70)	
	direct	1.70 (0.49, 6.10)			indirect	2.50 (1.20, 5.40)	0.119
	indirect	1.00 (0.55, 2.00)	0.474		network	2.10 (0.97, 4.10)	
	network	1.10 (0.66, 2.10)			Placebo vs MMC		
	Placebo vs GEM				direct	1.00 (0.18, 6.90)	
	direct	0.95 (0.34, 2.80)			indirect	2.20 (1.20, 4.00)	0.403
	indirect	3.80 (2.00, 7.50)	0.024		network	1.90 (1.10, 3.20)	
	network	2.60 (1.50, 4.70)					
	Placebo vs IFN						

considering the risk of tumor recurrence and progression. On the other hand, BCG_SD was the only intravesical instillation agent which may suppress the risk of tumor progression in postoperative BC patients. Although results provided by NMA are more informative than those provided by MA, ranking various intravesical instillation agents remains challenging. Results of SUCRA indicate that BCG_EPI, BCG_MMC and BCG_SD outperformed others with respect to tumor recurrence and progression.

The bladder is able to trigger strong immune responses and animal models indicated that the effect of BCG was maximized if there was close contact between BCG and cancer [65, 66]. BCG immunotherapy has not been widely accepted for BC patients until the study which was conducted by the Southwest Oncology Group in 1980 [67]. The corresponding

results revealed that BC patients with BCG immunoprophylaxis after local surgery exhibited decreased tumor recurrence rate and increased median time to recurrence. Results of our study appear to support the above conclusions since post-surgery patients with BCG_SD exhibited lower risk of tumor recurrence and progression than those with placebo. This convinces us that BCG has specific efficacy for preventing tumor recurrence and progression in BC patients. On the other hand, intravesical chemotherapy prophylaxis for tumor recurrence, progression or mortality did not exhibit strong efficacy in the long term [4]. This disadvantage may be overcome by BCG immunotherapy since the average short-term reduction in tumor recurrence among BC patients treated by BCG is about 40% and the corresponding benefits can persist for 5 to 10 years [68]. Clinical trials have compared BCG immunotherapy with other forms of intravesical chemotherapies. In our study, BCG_SD was compared with EPI, GEM and MMC. However, pooled evidence demonstrated that only patients treated by BCG_SD exhibited a lower risk of tumor recurrence and progression than those with EPI. Therefore, the dispute of whether BCG immunotherapy is more efficacious than intravesical chemotherapies in postoperative BC patients should be studied further. Despite the convincing performance of BCG_SD in our study, using BCG immunotherapy for BC patients has some inevitable drawbacks. First, predicting whether a specific BC patient will respond to BCG immunotherapy cannot be achieved since no significant prognostic factors have been discovered [68]. As a result, clinicians will not be able to know in advance whether BCG immunotherapy can provide adequate efficacy given a specific BC patient. Several issues may come after this, for instance, if clinicians believed that BCG the optimal option for preventing tumor recurrence and progression based on empirical evidence, abuse of BCG immunotherapy and waste of resources may occur in BC patients with different tumor classifications or stages. It has been verified that BCG is not appropriate for muscle-invasive BC or for tumors that lie deep within the prostate or in the upper urinary tract [1]. Thus, the selection of an appropriate intravesical instillation therapy should be carefully planned after pathological classification and tumor staging.

Another major issue associated with BCG immunotherapy is its side effects such as cystitis, dysuria, occasional haematuria and BCG sepsis [1]. Recently, studies investigating the feasibility of BCG dose reduction appeared to flourish in the current literature. These studies suggest that standard dose of BCG immunotherapy can be halved in most circumstances, resulting in a reduction in side effects without any significant loss of efficacy [1]. The above hypothesis was also tested and partially verified by our analysis in which BCG immunotherapy with standard dose was compared to that with low dose. In our study, BC patients with BCG_SD or BCG_LD had the same level of tumor recurrence/progression risk. The SUCRA value of BCG_LD is marginally lower than that of BCG_SD, suggesting the two may have approximately the same level of efficacy for preventing tumor recurrence and progression. Evidence also indicated that a three-fold decrease in the dose of BCG immunotherapy is as effective as the standard dose against the risk of tumor progression but with significantly less toxicity [69]. According to the above evidence, we suspected that the relationship between the dose of BCG immunotherapy and BC patients' responses to BCG is not linear; therefore reducing the dose of BCG immunotherapy is likely to maintain and even enhance responses in vivo. However, the above hypothesis together with the reduction in toxicity was not verified by our study and should be confirmed by ongoing researches.

Our study also investigated the potential benefits of alternating or sequentially combined intravesical instillation therapies in BC patients. This strategy has three potential advantages: reducing the use of intravesical BCG, reducing the toxicity resulted from intravesical BCG and enhancing the corresponding efficacy. Two alternating or sequentially combined intravesical instillation therapies were included and compared with other standard approaches: BCG_MMC and BCG_EPI. Both pairwise MA and NMA suggest no significant difference in the risk of tumor recurrence or progression between patients with BCG_EPI and BCG_SD. This finding was verified by an individual study which suggested that the combination therapy of BCG_EPI should not be recommended to high risk patients with superficial BC [70]. Instead, this combination therapy led to a higher incidence of side-effects without any additional

benefits compared to standard BCG. A similar trend between patients with BCG_MMC and those with BCG_SD was suggested by our analysis. Although BCG_EPI or BCG_MMC exhibited a larger SUCRA value than BCG_SD, it is still unclear whether alternating or sequentially combined instillation therapies are more efficacious than BCG.

Our study enhanced the level of evidence by incorporating a large number of studies and patients. Nevertheless, heterogeneity of included studies may impact on the above conclusions. For instance, variation in patient age, follow-up duration, dose and particularly the classification of BC in each study reflects a high degree of heterogeneity which cannot be addressed in the process of evidence. Besides that, we did not include any unpublished articles or studies and this may result in potential biased results. Thirdly, the proportion of male BC patients is substantially larger than that of female BC patients in each included study. If gender is a significant risk factor for tumor recurrence or progression, then unbalanced distribution of male or females in the study may cause biased results. In conclusion, BCG_SD, EPI and MMC appeared to have established efficacy for preventing tumor recurrence in postoperative BC patients. The efficacy of BCG may not be significantly reduced if standard dose was reduced to a lower level. However, we may experience pressing challenges in the future when increasing BC patients accompanied with shortage of intravesical BCG continue since there is no unanimous agreement suggesting that standard intravesical BCG can be replaced by alternating or sequentially combined intravesical instillation therapies.

Disclosure Statement

The authors declare no conflict of interest.

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