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Comparison of intravesical bacillus Calmette-Guerin and mitomycin C administration for non-muscle invasive bladder cancer: A meta-analysis and systematic review

SHANG-JUN JIANG, LI-YIN YE and FAN-HUA MENG

Department of Urinary Surgery, The People's Hospital of Fuyang, Hangzhou, Zhejiang 311400, P.R. China

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Abstract. The aim of the present meta-analysis was to compare the benefits of Bacillus Calmetter-Guerin (BCG) and mitomycin C in the treatment of patients with superficial bladder cancer. The present meta-analysis analyzed the benefits of BCG and mitomycin C in the treatment of patients with superficial bladder cancer by comparing progression-free survival (PFS) rates in patients treated with either of the drugs following transurethral resection. The Medline, Cochrane and EMBASE databases were searched between January 1966 and August 31, 2014 for studies that investigated the efficacy of the intravesical instillation of chemotherapy in patients with non-muscle invasive bladder cancer who had been treated with transurethral resection. Search terms included: 'Urinary bladder neoplasms', 'superficial bladder cancer' and 'non-muscle invasive bladder cancer'; 'bacillus Calmette-Guerin' or 'BCG'; 'mitomycin C'; and 'intravesical administration'. Sensitivity and data quality analyses were performed. A total of 6 randomized controlled studies were included with 1,289 patients. Complete 5-year PFS data for patients who received intravesical resection and were treated with mitomycin C or BCG was provided for 3 of the 6 studies, which were therefore included in the meta-analysis. The overall analysis revealed a significant benefit of BCG compared with mitomycin C in terms of 5-year PFS rate (odds ratio, 0.53; 95% confidence interval, 0.38-0.75; P<0.001), indicating that BCG was superior to mitomycin C therapy in patients with non-muscle invasive bladder cancer following transurethral resection.

Correspondence to: Dr Shang-Jun Jiang, Department of Urinary Surgery, The People's Hospital of Fuyang, 2-4 Osmanthus Road, Fuchun Streets, Fuyang, Hangzhou, Zhejiang 311400, P.R. China
E-mail: jiangshangjun09@yeah.net

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Introduction

Bladder cancer is the ninth most commonly occurring cancer globally. In total, 70-80% of all bladder cancer patients initially present with superficial disease (i.e., non-muscle invasive) (1). Non-muscle invasive bladder cancers [Ta, T1 or carcinoma *in situ* (CIS)] are a heterogeneous group of tumors that vary in terms of oncological outcome (2,3).

Generally, the initial approach to managing non-muscle invasive bladder cancer is cystoscopic observation followed by transurethral resection. The recurrence rate in non-muscle invasive bladder cancer is high following resection and the disease can progress to muscle invasive cancer, which has a poor prognosis (4).

Since there is considerable risk for the recurrence and/or progression of tumors following transurethral resection, adjuvant intravesical therapies are recommended for all patients at an intermediate to high risk of recurrence (5). Current treatment guidelines recommend that patients at risk of recurrence should be treated with adjuvant intravesical immunotherapy with bacillus Calmette-Guerin (BCG) or adjuvant intravesical chemotherapy with mitomycin C, epirubicin or doxorubicin (5). The time to the initial cancer recurrence, but not disease progression, is reduced by intravesical chemotherapy, and the treatment is associated with minor side-effects (6). BCG appears to be superior to intravesical chemotherapy with regard to the rate of recurrence, the response rate and the percentage of patients remaining tumor-free; however BCG is more toxic than chemotherapy (5-11).

Although evidence suggests that BCG is superior to the majority of chemotherapies, its superiority with respect to mitomycin C is less clear. Two prior meta-analyses found that tumor recurrence was reduced with maintenance BCG compared with mitomycin C (9,12). Another meta-analysis found that the superiority of BCG over mitomycin C for tumor recurrence was only apparent in a subgroup of patients at high risk for tumor recurrence (13). A different meta-analysis found that BCG was superior to chemotherapy (mitomycin C, adriamycin, epirubicin and gemcitabine) with regard to achieving a complete response or disease-free survival; however, the evidence did not indicate that one agent was superior to the others with regard to overall survival (14). The study did, however, find that the immediate post-operative use of mitomycin or epirubicin was effective in reducing tumor recurrence (14).

The present meta-analysis further investigated the benefits of BCG and mitomycin C in the treatment of patients with superficial bladder cancer by comparing progression-free survival (PFS) rates in patients treated with either mitomycin C or BCH following transurethral resection.

Materials and methods

Search strategy. This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (15). The Medline (www.ncbi.nlm.nih.gov/pubmed/), Cochrane (www.cochranelibrary.com/) and EMBASE (www.embase.com/)databases were searched between January 1966 and August 31, 2014 for studies that investigated the efficacy of the intravesical instillation of chemotherapy in patients with non-muscle invasive bladder cancer who had been treated with transurethral resection. Search terms included: 'Urinary bladder neoplasms', 'superficial bladder cancer' and 'non-muscle invasive bladder cancer'; 'bacillus Calmette-Guerin' or 'BCG'; 'mitomycin C'; and 'intravesical administration'. A list of potentially relevant studies was identified by two independent reviewers. A third reviewer was consulted for any discrepancies.

Included studies had to be randomized controlled trials that investigated subjects who were ≥18 years of age and who had been diagnosed with non-muscle invasive bladder cancer [stage Ta, T1 or carcinoma *in situ* (CIS)]. Included studies also had to have reported the numerical data of interest (i.e., PFS rate) for intravesical BCG and intravesical mitomycin C administration. Non-English publications, letters, comments, editorials and case reports were excluded.

Data extraction. Data were extracted by two independent reviewers and a third reviewer was consulted in the case of any uncertainties or disagreements. The following information was extracted from studies that met the inclusion criteria: The name of the first author, year of publication, study design, demographic data of subjects, regimen of intervention, PFS rate, recurrence-free survival rate and adverse events.

Quality assessment. The quality of the studies and included data was evaluated using the Cochrane Risk of Bias Tool (16). Similar to the method for study inclusion and data extraction, two independent reviewers performed the quality assessment and a reviewer was consulted for any disagreements.

Statistical analysis. The primary outcome for this meta-analysis was the 5-year PFS rate. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for binary outcomes for each individual study and for those studies combined. An OR of <1 indicated that the BCG group was favored. A χ^2-based test of homogeneity was performed and the inconsistency index (I^2) and Q statistics were determined. If the I^2 statistic was >50%, a random-effects model (DerSimonian-Laird method) was used. Otherwise, a fixed-effects model (Mantel-Haenszel method) was employed. Combined effects were calculated and a two-sided P-value of <0.05 was considered to indicate statistical significance. Sensitivity analysis was performed using the leave one-out approach.

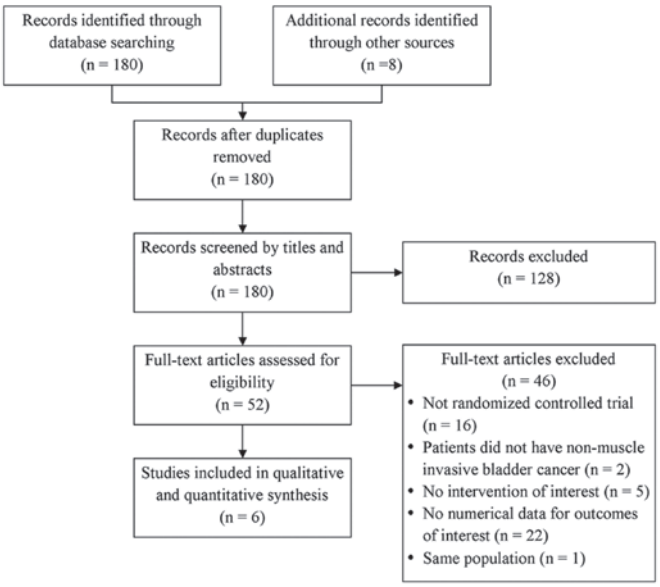

Figure 1. Flowchart of study selection.

Publication bias was not assessed as >5 studies are required to detect funnel plot asymmetry (17). All analyses were performed using Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ, USA).

Results

Literature search. The database search identified 180 studies and a hand-search identified an additional 8 studies (Fig. 1). Of the 188 studies, 8 studies were excluded as they were duplicates and 128 were excluded as they were clearly irrelevant. Another 46 studies were excluded as they were not randomized control trials (n=16), the patients did not have non-muscle invasive bladder cancer (n=2), the studies did not report interventions of interest (n=5), the studies did not quantitatively report data of interest (n=22) or the studies included the same population of patients as another included study (n=1). A total of 6 randomized controlled studies were included in the final analysis (18-23).

Study characteristics. A total of 1,289 patients were encompassed by all 6 studies (Table I). Overall, the studies were similar with respect to the distributions of age and gender between patients who received intravesical mitomycin C or BCG (Table I); ages ranged from 63.5-68 years and the majority of patients were male (range, 71-88%). Dosing regimens across the included studies varied and all the intravesical regimens were applied subsequent to surgery.

Across the studies, PFS rate ranged from 34-75% for mitomycin C and from 47-81% for BCG (Table II). Recurrence-free survival rate was higher for mitomycin C compared with BCG (range, 37-88.3% for mitomycin C and 21-68.5% for BCG). Common adverse events reported across studies for the two treatments were hematuria, fever and cystitis.

5-year PFS rate. Only 3 (19-21) of the 6 studies provided complete 5-year PFS data for patients who received

Table I. Study characteristics of the included studies.

First author, year	Study type	Type of patients	Comparison	Dosage of intervention	Cases, n	Age, years	Male,%	(Ref.)
Friedrich *et al*, 2007	RCT	Intermediate-risk superficial bladder cancer	MMC	20 mg weekly for 6 weeks followed by monthly instillations for 3 years	153	67	87	(18)
			BCG	RIVM $2x10^8$ CFU weekly for 6 weeks	163	67	80	
Ojea *et al*, 2007	RCT	Intermediate-risk superficial bladder cancer	MMC	30 mg weekly for 6 weeks followed by instillations every 2 weeks for 12 weeks	149	64	87	(19)
			BCG	27 mg weekly for 6 weeks followed by instillations every 2 weeks for 12 weeks	142	65	88	
Di Stasi *et al*, 2003	RCT	High-risk superficial bladder cancer	MMC	40 mg electromotive MMC instillation with 20-mA electric current for 30 min/40 mg passive MMC with a dwell time of 60 min	72	67	72	(20)
			BCG	81 mg BCG with a dwell time of 120 min	36	67	75	
Malmström *et al*, 1999	RCT	Superficial bladder cancer	MMC	40 mg MMC for 2 years	125	NA	NA	(21)
			BCG	20 mg BCG for 2 years	125	NA	NA	
Krege *et al*, 1996	RCT	Superficial bladder cancer	MMC	20 mg in 150 ml sodium chloride every 2 weeks during year 1 followed by monthly instillations during year 2	113	68	84	(22)
			BCG	120 mg in 50 ml sodium chloride weekly for 6 weeks and once a month for 4 months	102	64	80	
Rintala *et al*, 1991	RCT	Frequent1y recurrent superficial bladder cancer	MMC	20-40 mg weekly for 1st month flowed by monthly instillations for 2 years	58	67	71	(23)
			BCG	$6x10^8$ CFU weekly during the first month, and once a month for a 2-year period	51	68	76	

Age values have been rounded off. BCG, bacillus Calmette-Guerin; NA, not available; RIVM, commercially available BCG strain (Medac GmbH, Wedel, Germany); MMC, mitomycin C; RCT, randomized controlled trial; CFU, colony-forming units.

intravesical mitomycin C or BCG, and hence, were included in the meta-analysis. No heterogeneity was observed among the 3 studies, therefore, a fixed-effects model was used (Q statistic, 0.74; I^2<0.00%; P=0.690). The overall analysis revealed a significant difference in 5-year PFS rate between the mitomycin C and BCG groups (OR, 0.53; 95% CI, 0.38-0.75; P<0.001) and indicated that BCG was superior to mitomycin C therapy in patients with non-muscle invasive bladder cancer following transurethral resection (Fig. 2).

Sensitivity analysis. Sensitivity analyses were performed using the leave-one-out approach in which the meta-analysis of the 5-year PFS rate was performed with each study removed in turn. The direction and magnitude of combined estimates did not vary markedly with the removal of the studies (Fig. 3), indicating that the meta-analysis had good reliability and that the data was not overly affected by any one study.

Quality assessment. As shown in Fig. 4A and B, the data from the 6 studies were of good quality, although performance and detection biases were also present. The studies indicated either that the patients and personnel were blinded to randomization, or that randomization was not reported within the study.

Table II. Summary of outcome measurements and adverse events/toxicity.

First author, year	Comparison	Progression-free survival rate, %	Recurrence-free survival rate, %	Adverse events/toxicity, % cases	(Ref.)
Friedrich *et al*, 2007	MMC vs. BCG	NA	(2-year) 88.3 vs. 68.5 (3-year) 86.1 vs. 65.5	Dysuria: 20.5 vs. 17.3; hematuria: 9.4 vs. 17.6; fever: 2.4 vs. 9.3	(18)
Ojea *et al*, 2007	MMC vs. BCG	(5-year) 58 vs. 75	NA	Local toxicity: 30.2 vs. 65.4; systemictoxicity: 4.6 vs. 11.2	(19)
Di Stasi *et al*, 2003	MMC vs. BCG	(5-year) 75 vs. 81	(5-year) 37 vs. 21	Hematuria: 19.4 vs. 72.2; fever: 0.0 vs. 19.4; cystitis: 30.6 vs. 66.7; urinary frequency: 18.1 vs. 58.3; general malaise: 1.4 vs. 30.5; allergic reactions: 6.9 vs. 0.0	(20)
Malmström *et al*, 1999	MMC vs. BCG	(5-year) 34 vs. 47	NA	In 6 patients (2.4%) a contracted bladder developed (<100 ml); after MMC in 3 patients and BCG in 1 patient, and after crossover to BCG in 2 patients	(21)
Krege *et al*, 1996	MMC vs. BCG	NA	(3-year) 46.7 vs. 59.6	Haematuria: 3 vs. 6; fever: 0 vs. 18; cystitis: 16 vs. 34; skin alteration: 6 vs. 0; epididymitis: 3 vs. 10	(22)
Rintala *et al*, 1991	MMC vs. BCG	(1-year) 39 vs. 72	NA	Cystitis: 2 vs. 9; eczema: 5.2 vs. 0.0	(23)

BCG, bacillus Calmette-Guerin; NA, not available; MMC, mitomycin C.

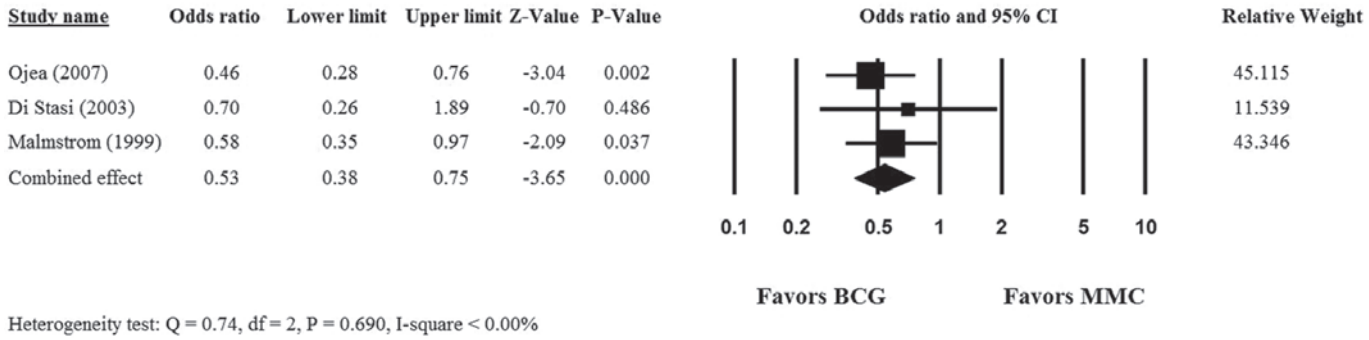

Figure 2. Meta-analysis of the effect of treatment on 5-year progression-free survival rate when comparing mitomycin C (MMC) and bacillus Calmette-Guerin (BCG). CI, confidence interval.

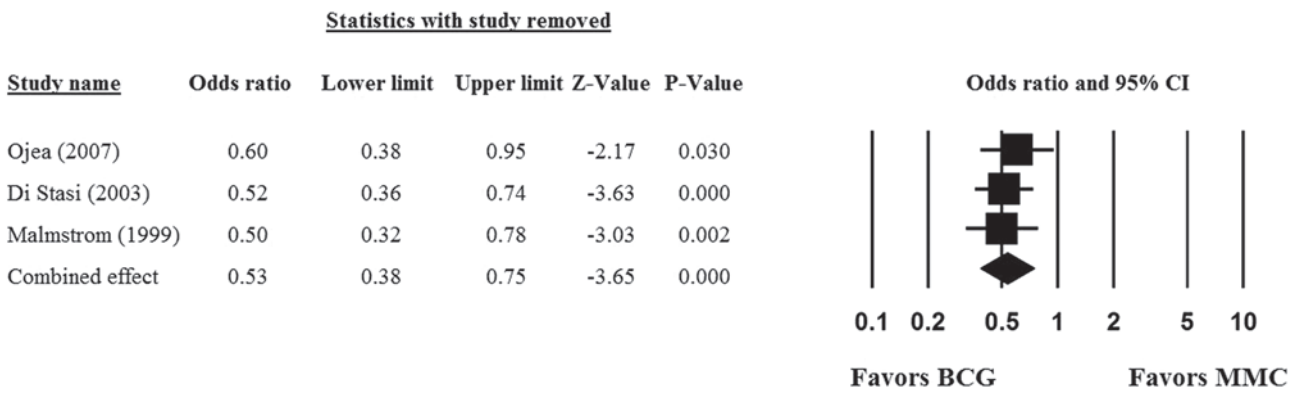

Figure 3. Sensitivity analysis for the effect of treatment on 5-year progression-free survival rate when comparing mitomycin C (MMC) and bacillus Calmette-Guerin (BCG). CI, confidence interval.

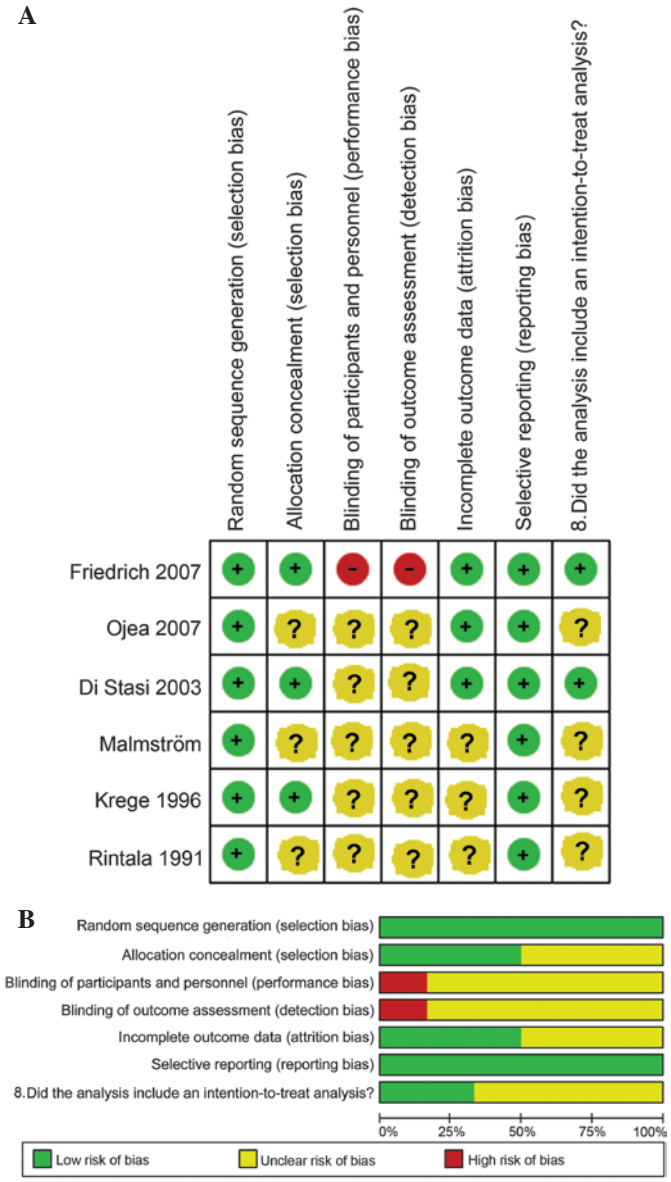

Figure 4. Results of quality assessment of included studies. (A) Potential risk of bias of individual included study. (B) Summarized risk of included studies.

Discussion

The present meta-analysis evaluated the benefit of BCG compared with mitomycin C in the treatment of patients with superficial bladder cancer by analyzing PFS rate in patients treated with either of these drugs following transurethral resection. It was found that BCG was superior to mitomycin C with regard to 5-year PFS rate (P<0.001).

The present meta-analysis differed from several prior meta-analyses (4,14,24) in that the present study quantitatively evaluated a head-to-head comparison of BCG and mitomycin C using only randomized controlled studies. The present analysis did not include studies that evaluated combination (i.e., BCG plus mitomycin C) therapies.

Two previous meta-analyses assessed the benefit of BCG compared with mitomycin C in patients with non-muscle invasive bladder cancer (10,25). The study by Sylvester *et al* (2002) included 9 randomized trials with 700 CIS patients and compared BCG to either mitomycin C, epirubicin, adriamycin, or sequential dosing of mytomycin C and Adriamycin. Although the difference in the long-term benefit of BCG compared with mitomycin C was smaller compared with other chemotherapies, BCG was superior to mitomycin C in trials with maintenance BCG with regard to disease recurrence (OR, 0.57; P<0.04) (10). The study concluded that compared with chemotherapy, BCG significantly lowered the risk of short- and long-term treatment failure in patients with superficial bladder cancer.

Malmström *et al* (2009) performed a meta-analysis that compared the efficacy of BCG and mitomycin C using individual patient data from randomized trials (25). The analysis included 9 studies with 2,820 patients. At 4.4 years post-initiation of treatment, 43% of the patients exhibited tumor recurrence. In general, there was no difference in the time to first recurrence between BCG and mitomycin C therapy (P=0.09). However, with BCG maintenance therapy, there was a 32% reduction in the risk of recurrence with BCG compared with mitomycin C (P<0.0001). No significant difference was found between BCG and mitomycin C with regard to bladder cancer-related mortality, overall survival or disease progression. The difference between the findings of Malmström *et al* (2009) and the present analysis may reflect the differences in the studies included and analyses performed (25).

The present study did not evaluate the type of regimen (i.e., co-administration, dose and maintenance therapy vs. induction therapy). Prior studies found BCG to be more effective at reducing recurrence when used as maintenance therapy, but that a sole induction course was not superior to mitomycin C (10,11,14,24). It was also found that maintenance BCG therapy was associated with greater adverse events, but a lower recurrence rate, compared with other therapies. It has been proposed that the benefit of the reduced rate of recurrence outweighs the risk of complications, particularly in patients that are at a high risk of recurrence (24). Prior studies have not clarified if the dose of BCG affects the outcome (24,26-28). Also, one prior meta-analysis did not find a significant difference in terms of recurrence-free survival and PFS between patients who received BCG plus mitomycin C compared with those who received BCG or mitomycin C alone (24). The present analysis did not assess the addition of mitomycin C to BCG therapy, or the effect of the timing or dose of either therapy on reducing the rate of recurrence or PFS. Future studies are required to further evaluate the effect of dose and combination therapy on recurrence rate and PFS in patients with superficial bladder cancer following transurethral resection.

Several limitations of the present study should be considered when interpreting the results. The analysis used a small sample size and there was heterogeneity in the types of treatment regimens used across the studies; these factors may have biased the results. In addition, the patients and the study personal were not blinded to the treatment, which also could have affected the analysis.

In summary, the present meta-analysis found that BCG was superior to mitomycin C with regard to 5-year PFS rate in patients with non-muscle invasive bladder cancer following transurethral resection.

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