doi:10.4149/neo_2016_616

Comparison of the combination therapy of bacillus Calmette-Guérin and mitomycin C with the monotherapy for non-muscle-invasive bladder cancer: a meta-analysis

Y. LAN[1,2,‡], D. LIU[1,3,‡], M. LIN[1,*]

[1]*Department of Urology, The First Affiliated Hospital Of Shantou University Medical College, Shantou, Guangdong, China;* [2]*Department of Urology, Minimally Invasive Surgery center, The First Affiliated Hospital of Guangzhou Medical University Guangzhou, Guangdong, China;* [3]*Department of Urology, The 150th Center Hospital of Chinese People`s Liberation Army, Luoyang, Henan, China*

**Correspondence: me_lin2000@163.com*
‡Contributed equally to this work.

Received March 27, 2016 / Accepted June 17, 2016

Urinary bladder cancer is one of the most frequent cancers worldwide. Non-muscle-invasive bladder carcinoma (NMIBC) has a very low curative rate after resection. The meta-analysis aims to compare efficiency of the combination therapy of bacillus Calmette-Guérin (BCG) and mitomycin C (MMC) with each monotherapy on NMIBC treatment. Articles were retrieved in relevant databases up to May, 2016. The Cochrane Collaboration Risk of Bias Tool was used to assess quality of the included studies. Risk ratio (RR) and the 95% confidence interval (CI) were used as the effect size to calculate pooled result. Funnel plot and Egger's test were applied to examine publication bias. Sensitive analysis was performed. Eight randomized controlled trials were included in this meta-analysis. As a result, the BCG+MMC combination therapy had a significantly decreased recurrence rate in NMIBC patients, compared with monotherapy of BCG or MMC (RR = 0.81, 95% CI: 0.72 to 0.92, $P < 0.001$). However, there were no obvious differences between the two regimens regarding to progression rate, overall mortality and disease-specific mortality ($P > 0.050$). Subgroup analysis indicated the combination therapy was more advantageous than BCG (RR = 0.73, 95% CI: 0.61 to 0.87) but not MMC monotherapy ($P > 0.050$), on the reduced recurrence rate. 81mg/week BCG + 30 mg/week MMC had a significant lower progression rate than BCG (RR = 0.44, 95%CI: 0.24 to 0.82). In conclusion, BCG+MMC combination therapy is more advantageous than BCG to NMIBC patients with reduced recurrence rate.

Key words: non-muscle-invasive bladder carcinoma, bacillus Calmette-Guérin, mitomycin C, recurrence rate, meta-analysis

Urinary bladder cancer is one of the most frequent cancers with high prevalence in the world [1]. It is derived from the epithelial lining of the urinary bladder. Reportedly, approximately 30% bladder cancer patients are muscle-invasive and closely associated with high risk of metastases-related death, and the remaining 70% are identified as superficial tumors [2], namely non-muscle-invasive tumors. Although not as serious as muscle-invasive bladder carcinoma (MIBC), non-MIBC (NMIBC) has a very low curative rate after resection, and most of NMIBC patients would recur. In addition, several NMIBC patients would develop into MIBC over time [3].

Instillation therapies are clinically demonstrated to be effective for the treatment of NMIBC, such as the intravesical immunotherapy, bacillus Calmette-Guérin (BCG) [4]. Reportedly, BCG could result in a 67% reduction on recurrence rate, compared with resection alone [5]. On the other hand, it is found that intravesical chemotherapies, such as mitomycin C (MMC), are effective options when BCG is failing or patients are unsuitable [6]. Many studies have been conducted to compare efficiency between the two therapies, especially on the control of recurrence. For instance, a study finds that BCG achieves a lower recurrence during a long-term administration, compared with MMC [7]. Böhle et al also support the superiority of BCG over MMC in preventing recurrence [8]. Despite these advantages, BCG is demonstrated to be poorly tolerant in patients with a long-term maintenance [5]. Thereafter, a large number of studies have focused on the combination of BCG with MMC, to reduce the BCG dose and diminish the toxicity. Di et al indicate that patients assigned sequential BCG and electromotive mitomycin have a lower recurrence

rate than those assigned with BCG only [9]. By contrast, several studies suggest that there are no significant differences between NMIBC patients treated with MMC plus BCG and those treated with BCG alone, regarding to the recurrence rate [10, 11]. Meta-analysis is a statistical analysis that combines data from several individual studies to provide a quantitative summary of the studies. Compared with the less quantitative review methods, meta-analysis has the advantages to enhance statistical power, provide a more rigorous generalizability of results and have a profound understanding of the nature of relationships among variables [12-14]. Meta-analysis also has disadvantages as follows: (1) All the studies are observational studies instead of clinical trials; (2) There might be heterogeneities across different studies, however, we can select different models based the heterogeneity result, and a random-effects model is utilized when heterogeneity presents; otherwise the fixed-effects model is used [15]. To resolve these inconsistent results regarding to MMC+BCG combination therapy and monotherapy, a previous meta-analysis has been carried out and finds that maintenance BCG is superior to MMC for prophylaxis of recurrence, but has a comparable effect on progression, overall survival, and cancer-specific survival with MMC [16]. However, combination therapy of BCG with MMC is not concerned. In addition, toxicity is not evaluated.

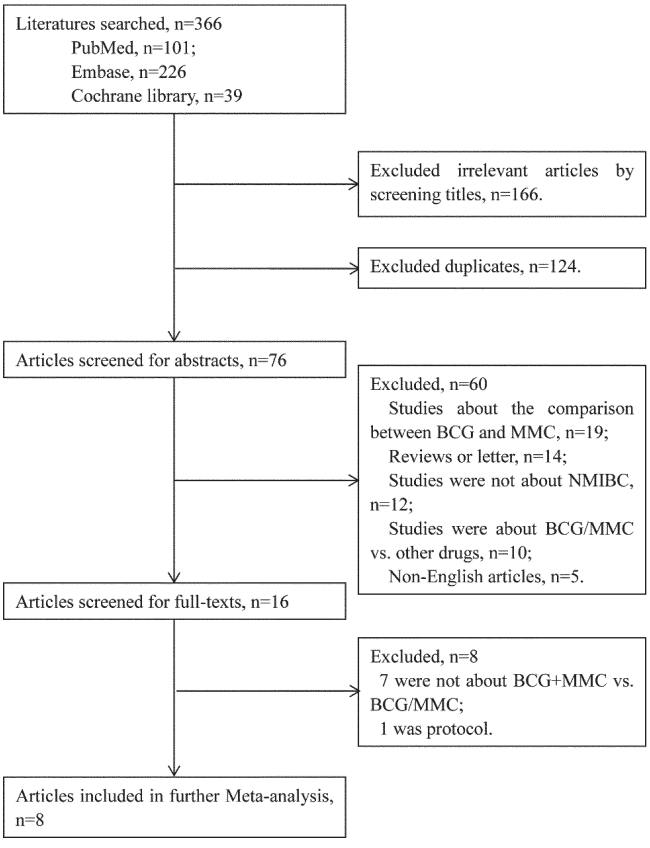


Figure 1. Flow chart of the study selection

Therefore, we performed this meta-analysis by retrieving electronic databases up to May, 2016, to include only randomized controlled trails (RCTs) and mainly compared the combination therapy with the two monotherapies and took the adverse effects into consideration. We attempt to provide a comprehensive evaluation and solid evidence for the optimum treatment of NMIBC.

Methods

Literature search and study selection. We retrieved PubMed, Embase and Cochrane library to select the eligible studies up to May, 2016. The relevant RCTs were obtained using the key searching terms of "bacillus Calmette-Guérin", "mitomycin C", "instillation therapy" and "bladder cancer". The searching strategy was ((bacillus Calmette-Guérin) OR BCG) AND (mitomycin C) AND ((instillation therapy) OR intravesical) AND (bladder cancer) AND (random* OR (randomized controlled trial)).

Two investigators independently selected the study basing on the predefined criteria. When disagreements appeared, a discussion with a third investigator was conducted to reach a consensus.

Inclusion and criteria. Studies were included if they met with the following criteria: (1) the study was a RCT comparing the combination therapy (BCG+MMC) with BCG or MMC monotherapy for NMIBC treatment; (2) instillation therapy of the study included both of induction therapy and maintenance therapy; (3) the study contained at least one of the four outcomes: recurrence, progression, overall mortality and disease-specific mortality; (4) for the duplicated publications based on the same dataset, only the study with the best quality and most complete outcomes was included; (5) the study was an English publication. On the other hand, studies were excluded if they were letters, conference abstracts reviewers; or they compared the differences of BCG+MMC combination therapy with other agents.

Quality assessment and data extraction. The Cochrane Collaboration Risk of Bias Tool was used to assess quality of the included studies [17]. Likewise, two investigators independently evaluated quality of the included studies, and then extracted the following data information: first author name, publication year, disease status, drug strategies (drug and their dosage in trial group and control group, respectively), sample size (male/female), age (mean±sd) and the outcomes including recurrence rate, progression rate, overall mortality, disease-specific mortality and adverse events.

Statistical analysis. Risk ratio (RR) and the 95% confidence interval (CI) were used as a measure of effect size to calculate the pooled results. Heterogeneity across the studies was determined by Cochran based Q statistical and I^2 test [18]. $P < 0.05$ or $I^2 > 50\%$ indicated a significant heterogeneity and then the random-effects model was selected. Otherwise, if there did not detect significant heterogeneity ($P > 0.05$ or $I^2 \leq 50\%$), the fixed-effects model was applied. For outcomes as

recurrence rate, progression rate, overall mortality and disease-specific mortality, subgroup analyses stratified by different control groups (BCG or MMC) and BCG or MMC dosage were performed. Funnel plot and Egger's test were applied to examine the publication bias [19]. All the statistical analyses were completed using RevMan 5.3 software (Cochrane Collaboration, http://ims.cochrane.org/revman).

Sensitive analysis. To evaluate whether a single study would influence the combined results, sensitive analysis by removing a study at one time was carried out. If a reverse result appeared after eliminating a study, it indicated that result of the meta-analysis was instable. The software of Stata 12.0 (STATA, College Station, TX, USA) was used for the analysis.

Results

Eligible studies. Through preliminary retrieval, a set of 366 articles were obtained (101 in PubMed, 226 in Embase and 39 in Cochrane library). Then 124 duplicated publications and 166 irrelevant studies were eliminated. The remaining 76 studies were further examined by reading abstract, and another 60 articles were excluded, including 14 reviewers and letters; 5 non-English publications; 10 studies that were about BCG/MMC vs. other drugs; 19 studies that involved comparison of BCG vs. MMC; and 12 studies that did not enroll NMIBC patients as the cases. Through full-text reading, 8 of the remaining 16 studies were excluded (7 did not involve comparison of BCG+MMC vs.

Table 1. Characteristics of the included articles

Study	Country	Period	Disease	Follow-up	Group	Treatment schedules	No. (M/F)	Age, y
Di Stasi 2006	Italy	1994.01-2002.06	Stage pT1 bladder cancer	88 (IQR: 63-110) m	BCG+MMC	BCG: 81 mg/week, 120 min, 2 weeks; MMC: 40 mg/week, 3 week	107 (87/20)	66 (56-73)[1]
					BCG	BCG: 81 mg/week, 120 min, 6 weeks	105 (86/19)	67 (61-73)
Gulpinar 2012	Turkey	2004.11-2006.05	NMIBC, stage Ta, T1 urinary bladder cancer	41.3 (8-64) m	BCG+MMC	BCG: $5*10^8$ colony-forming units in 50 mL saline, at least 15 days from TURBT MMC: 40 mg MMC in 40 mL saline, within 6 hours of surgery	25 (21/4)	58.2
				40.9 (6-68) m	BCG	BCG: $5*10^8$cfu in 50 mL saline, once a week, 6 weeks	26 (20/6)	58
Jarvinen 2012	Finland	1987-1992	patients with CIS, NMIBC	7.2 (range 0.8-19.5) y	BCG+MMC	alternating MMC and BCG instillations during the first year and every third month during the second year. BCG Pasteur strain F 75 mg or $6*10^8$cfu in 50 ml saline	28 (24/4)	66 (36-83)
					MMC	monthly installations of MMC alone	40 (31/9)	68 (40-80)
Kaasinen 2003	Finland	1992.12-17.12	primary, secondary, and concomitant CIS	56 m	BCG+MMC	MMC: 40 mg, 6 weeks; alternating monthly instillations of BCG 120 mg and MMC for one year.	159 (125/34)	71
					BCG	monthly instillations of BCG 120 mg	145 (119/26)	69.9
Oosterlinck 2011	Belgium	2001.06-2005.02	patients with primary/secondary/ concurrent CIS of the urinary bladder	4.7 y	BCG+MMC	MMC: 40 mg/week, 6 weeks; BCG: TICE $5*10^8$cfu/week, 6 weeks	48 (44/4)	68 (42-83)[2]
					BCG	BCG: TICE $5*10^8$cfu/week, 6 weeks Then, followed by 3 wk of rest and then by 3 wk of BCG.	48 (42/5) 1 missing	70 (55-83)
Rintala 1996	Finland	1987-1992	patients with rapidly recurring stage Ta or T1 cancer	34 m	BCG+MMC	MMC: 40 mg, BCG: 2.75 mg ($6*10^8$cfu) of Pasteur strain F immune BCG in 50 ml.	95 (71/24)	68
					MMC	20 to 40 mg depending on the bladder capacity	93 (71/22)	69
Solsona 2014	Spain	1993.01-1994.11	papillary NMIBC, TaG2 multiple tumors, TaG3 or T1G1-3 tumors, and Tis	7.1 y	BCG+MMC	BCG: 81 mg (1.5-$5*10^8$ CFU) in 50 ml 0.9% saline, weekly intravesical BCG instillation for 6 wk; MMC: 30 mg in 50 ml 0.9% saline.	211 (192/19)	65 (57-71) [1]
					BCG		196 (174/22)	66 (59-72)
Witjes 1998	The Netherlands	1991.01-1993.11	papillary superficial bladder cancer and carcinoma in situ	32 m (range 2-65)	BCG+MMC	MMC: 40 mg/week, 4 weeks; BCG: 6 weekly instillations with	90	
					MMC	MMC: 10 weekly instillations	92	

Abbreviations: NMIBC: non-muscle-invasive bladder carcinoma; BCG: bacillus Calmette-Guérin; MMC: mitomycin C; CFU: colony-forming units; m: months; y: year; M: male; F: female. IQR: interquartile range.
1 represented Medium (IQR); 2 represented Medium (range)

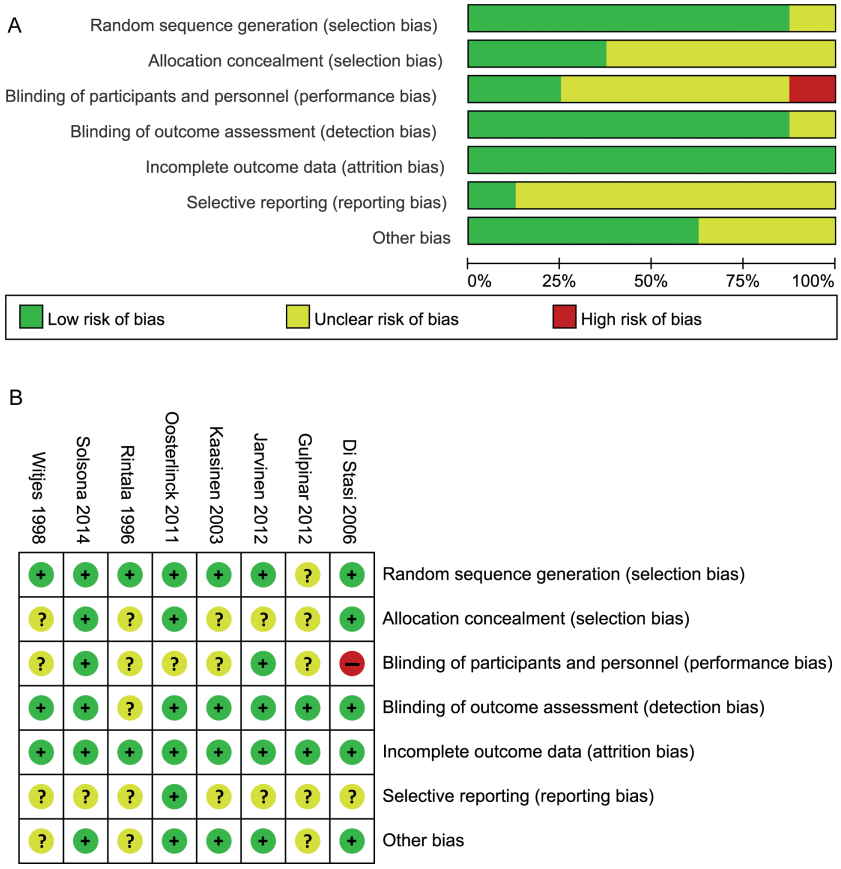


Figure 2. Assessment of risk of bias.A: Methodological quality graph: authors' judgment about each methodological quality item presented as percentages across all included studies; B: Methodological quality summary: authors' judgment about each methodological quality item for each included study, "+" low risk of bias; "?" unclear risk of bias; "-" high risk of bias.

BCG/MMC, and 1 was protocol). Finally, 8 RCTs [9-11, 20-24] were included in the meta-analysis. Detailed procedures of study selection are presented in Figure 1.

Characteristics of the included studies. As listed in Table 1, the 8 studies were all RCTs, containing a total of 1502 NMIBC cases. Five studies were about the comparison of BCG+MMC vs. BCG, and the BCG+MMC group contained 550 cases, while BCG group had 520 cases. Three studies involved the comparison of BCG+MMC vs. MMC, and 210 cases were distributed in BCG+MMC group, while 222 were in MMC group. These studies were conducted in different countries such as Italy, Turkey and Finland. The mean follow-up times varied from 32 months to 7.2 years, and the average ages in different studies were 58-71 years. Quality assessment indicated that as a whole, risk of the selection bias, detection bias and attrition bias were low in all the included studies. Two studies carried out by Oosterlinck et al. [11] and Solsona et al. [23] had a relatively high quality (Figure 2).

Outcome comparisons. The main outcomes of the present meta-analysis included recurrence rate, progression rate, overall mortality and disease-specific mortality.

Recurrence rate. There were 7 studies reported the recurrence of patients after different regimens. The fixed-effects model was used due to a lack of significant heterogeneity ($P = 0.120$, $I^2 = 41\%$). The pooled result indicated that combination therapy of BCG+MMC achieved a significantly reduced recurrence rate of NMIBC, compared with monotherapy of BCG or MMC (RR = 0.81, 95% CI: 0.72 to 0.92, $P < 0.001$, Figure 3A). No obvious publication bias was detected among these studies (Egger's test: $P = 0.513$).

Progression rate. Seven studies reported the disease progression after application of these different therapies. As there was no significant heterogeneity across studies ($P = 0.110$, $I^2 = 41\%$), the fixed-effect model was selected. As a result, there were no significant differences between different treatments (RR = 0.94, 95% CI: 0.71 to 1.23, $P = 0.650$, Figure 3B). Likewise, there did not observe any publication bias (Egger's test: $P = 0.502$).

Overall mortality. Five studies involved the outcome of overall mortality. A fixed-effects model was applied due to significant homogeneity ($P = 0.250$, $I^2 = 26\%$). As expected, there were no significant differences between combination therapy and any monotherapy (RR = 0.90, 95% CI: 0.74 to

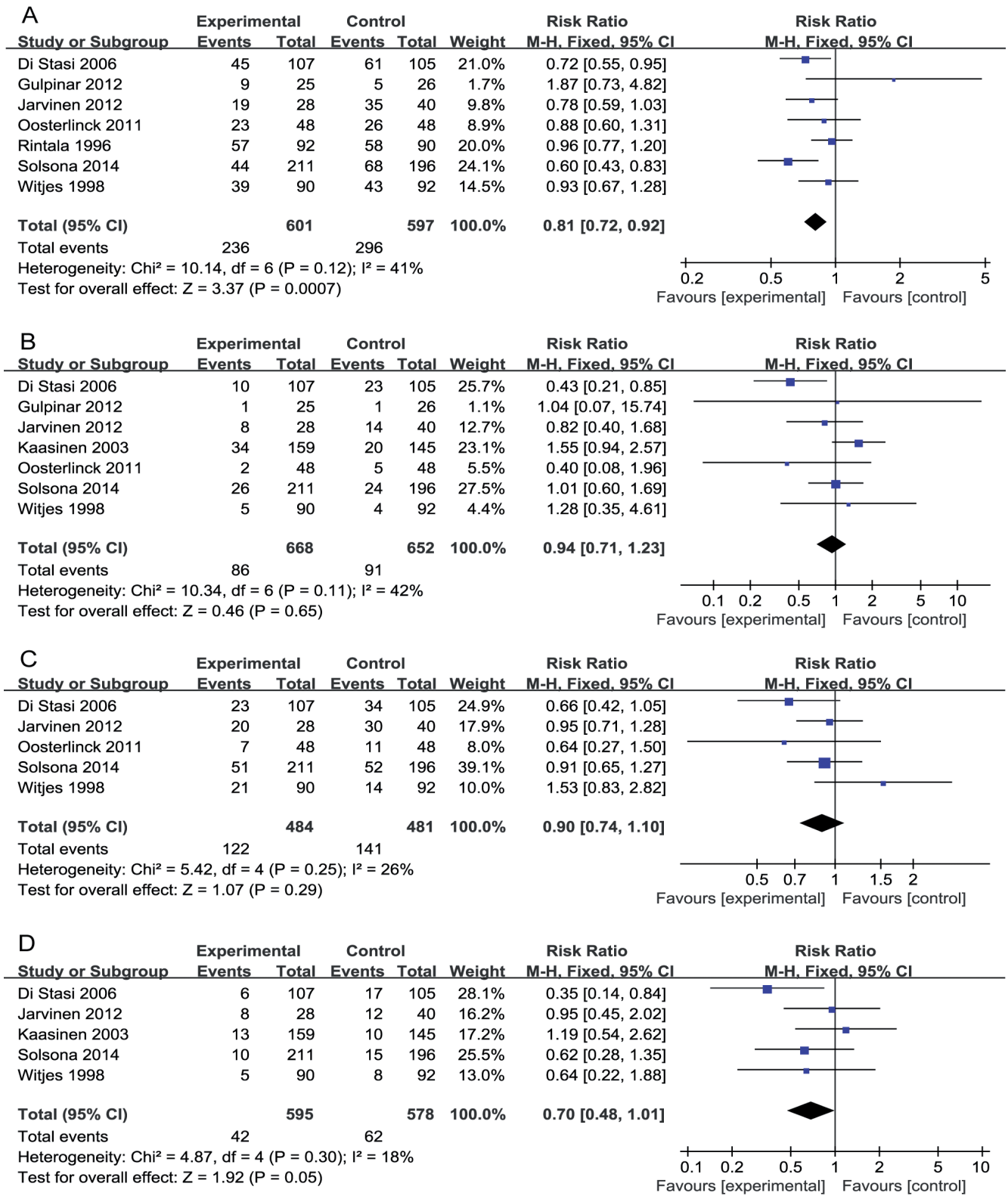


Figure 3. Forest plot of comparisons between the combination therapyof bacillus Calmette-Guérin (BCG) and mitomycin C (MMC) and the monotherapy of BCG or MMC on four outcomes. A: Recurrence rate; B: Progression rate; C: Overall mortality; D: Disease-specific mortality.

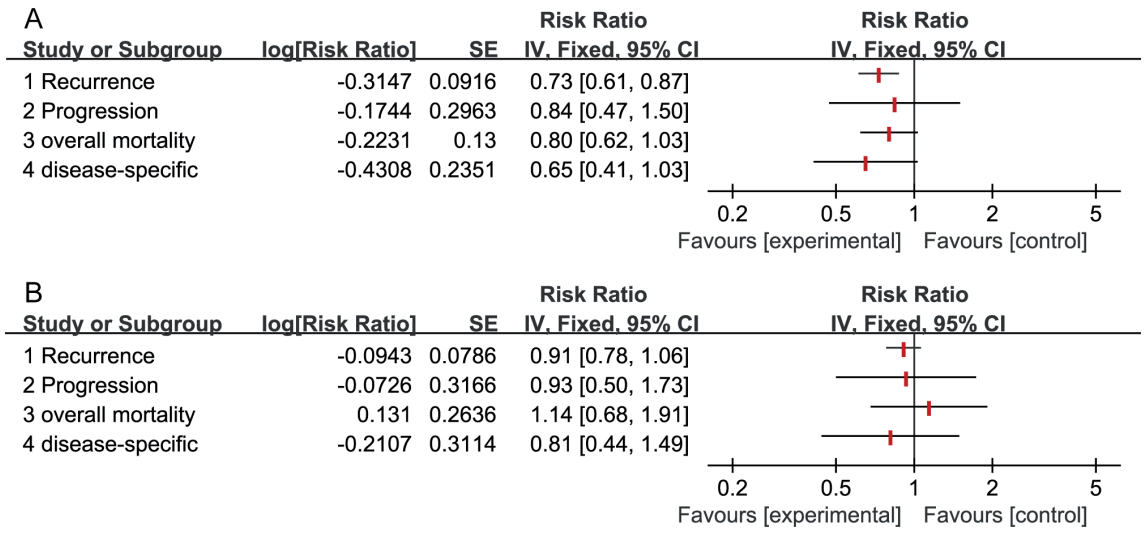


Figure 4. Subgroup analysis stratified by the monotherapy of bacillus Calmette-Guérin (BCG) and mitomycin C (MMC) with regard to recurrence rate. A: BCG+MMC vs BCG; B: BCG+MMC vsMMC.

1.10, P = 0.290, Figure 3C). No significant publication was observed (Egger's test: P = 0.903).

Disease-specific mortality. A set of five studies involved the disease-specific mortality after application of two regimens. Since there lacked significant heterogeneity across the studies (P = 0.300, I^2 = 18%), a fixed-effects model was used. The pooled RR was 0.70 (95% CI: 0.48 to 1.01, Figure 3D), indicating a lower disease-specific mortality with the combination therapy than with monotherapy, however without statistical significance (P > 0.050). There also did not detect any publication bias (Egger's test: P = 0.458).

Subgroup analysis. When stratified by different control groups (BCG/MMC), it indicated that the combination therapy of BCG+MMC significantly reduced the recurrence rate of NMIBC patients, compared with BCG monotherapy (RR = 0.73, 95% CI: 0.61 to 0.87, Figure 4); while in the comparison of BCG+MMC vs. MMC, there did not observe any significant difference between these two regimens.

When stratified by different BCG/MMC dosage, the result suggested that 81mg/week BCG in combination with 30 mg/week MMC had a significant lower progression rate than BCG monotherapy (RR = 0.44, 95%CI: 0.24 to 0.82, P = 0.008, Figure 5C). Likewise, 81mg/week BCG and 30 mg/week MMC reduced the recurrence rate, however, without statistical significance (P = 0.110, Figure 5D). As only three studies involved the comparison of BCG+MMC with MMC, we did not further perform subgroup analysis stratified by dosage, compared with MMC.

Adverse events. As the evaluation indexes of adverse events were different in different studies, we did not combine the result with regard to these outcomes.

The study of Di Stasi et al. [9] believed that there were not significant differences between combination therapy and BCG monotherapy on adverse events. Likewise, Gulpinar et al. [10] suggested that monotherapy had a comparable incidence of adverse events with combination therapy (P = 0.457). Kaasinen et al. [21] revealed that alternative therapy with BCG and MMC had a significant lower incidence of local and systemic adverse events at 3 months and 12 months, than BCG monotherapy.

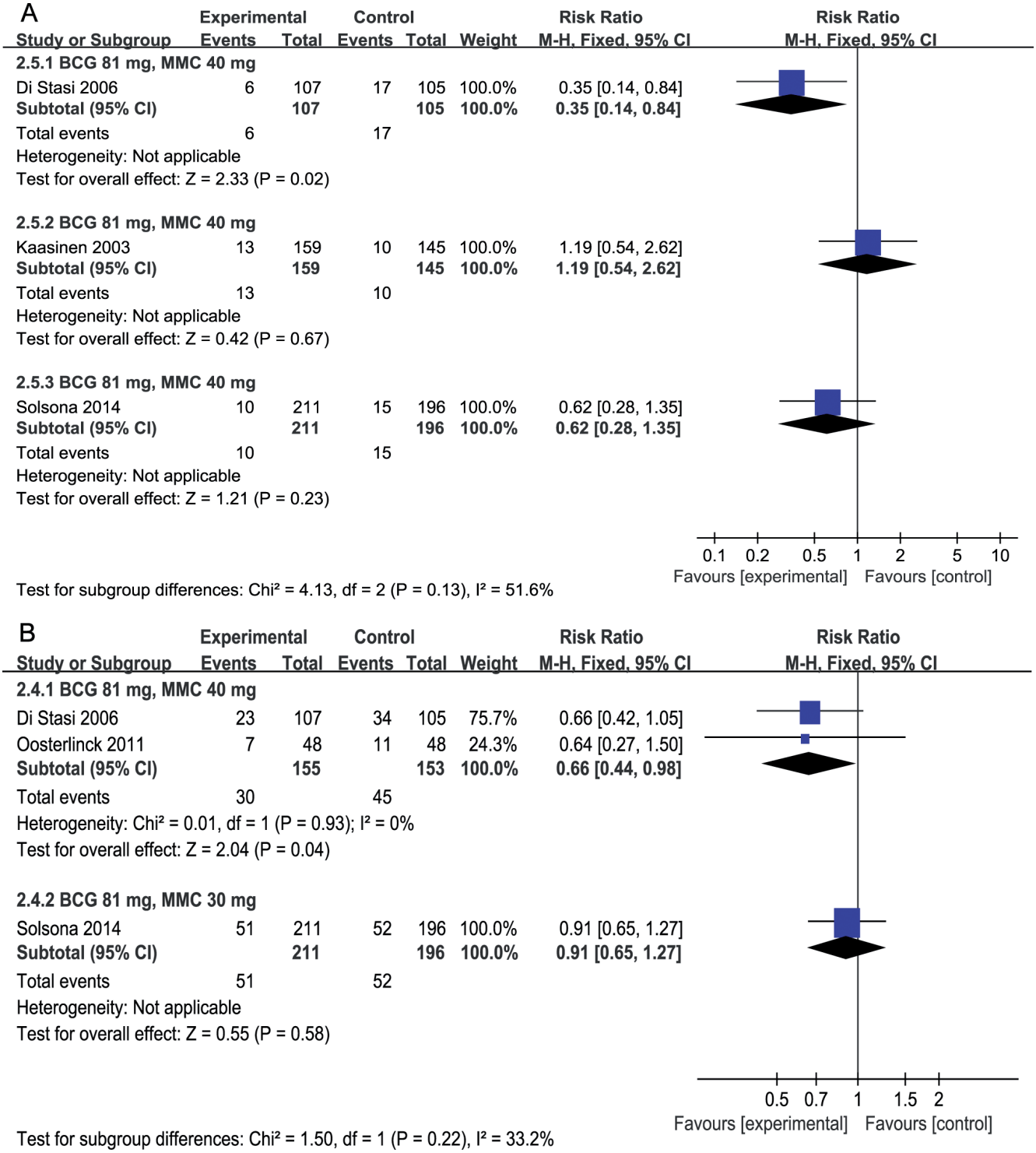
Sensitive analysis. As expected, with regard to the above four outcomes, the newly combined results after removal of a single study did not show a reverse result. This result indicated a reliability of the meta-analysis.

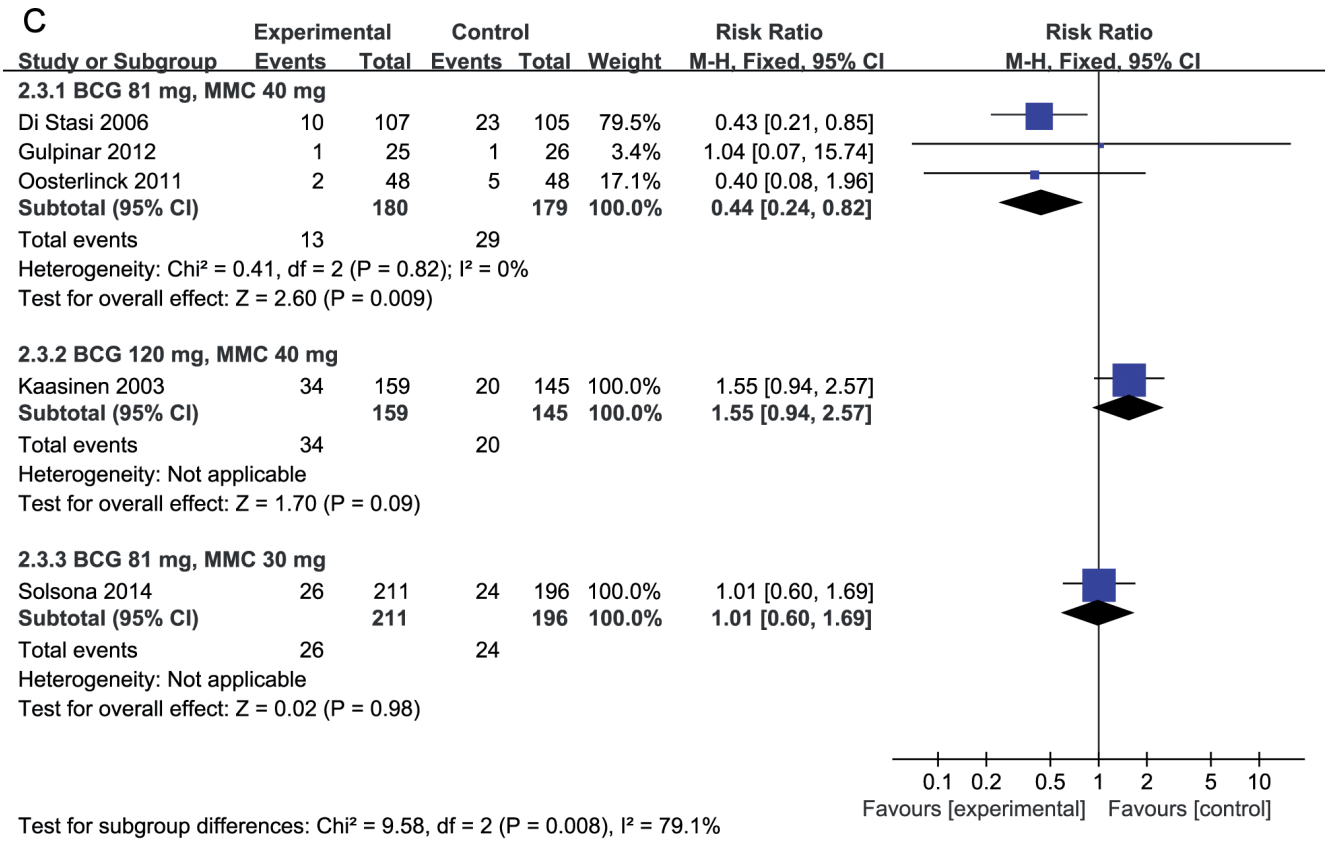
Discussion

The meta-analysis included a total of 8 RCTs containing 1502 NMIBC cases. As expected, the BCG+MMC combination therapy showed a significantly decreased recurrence rate in NMIBC patients, compared with monotherapy of BCG or MMC. However, there were no obvious differences between the two regimens with regard to progression rate, overall mortality and disease-specific mortality. Subgroup analysis indicated the combination therapy was more advantageous than the monotherapy of BCG but not MMC, with the decreased recurrence rate. Moreover, subgroup analysis stratified by BCG/MMC dosage suggested that 81mg/week BCG and 30 mg/week MMC had a significant lower progression rate than BCG monotherapy. Several studies showed a comparable adverse effects caused by the two regimens, and a study indicated a lower incidence of local and systemic adverse events with the combination therapy than monotherapy [21].

BCG is a common intravesical immunotherapy for NMIBC management. However, about a half of patients will develop recurrence during a long period after BCG application [25].

MMC is a chemotherapy that has been used as the most common intravesical cytotoxic drug [26]. Combination of MMC and BCG could reduce the dosage of BCG, and thus alleviate the toxicity of BCG. Di Stasi et al point out that patients treated with sequential BCG and electromotive MMC therapy achieve a lower recurrence rate than BCG monotherapy (41.9% vs 57.9%) [9]. The possible explanation is that the inflammation induced by BCG might increase the permeability of the bladder mucosa, and thus contribute to the subsequent MMC chemotherapy [27]. However, another meta-analysis stresses





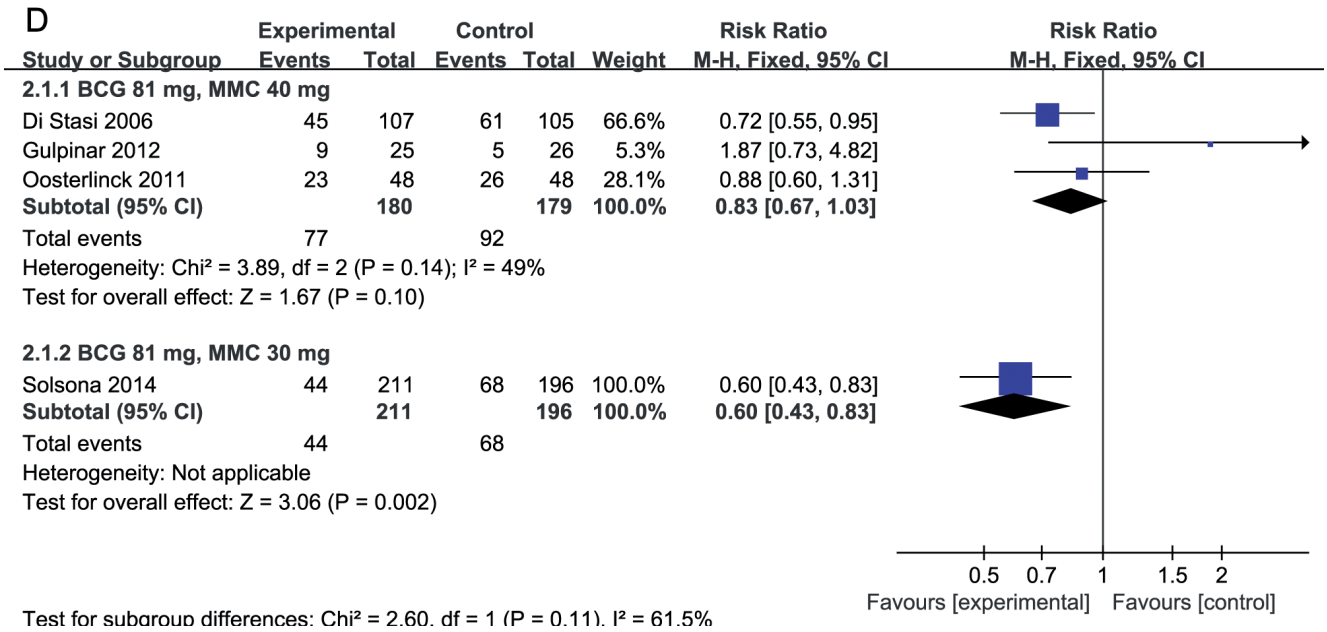


Figure 5. Subgroup analysis stratified by dosage of Calmette-Guérin (BCG) and mitomycin C (MMC). A: BCG+MMC vs. BCG on disease-specific mortality; B: BCG+MMC vs. BCG-overall mortality; C: BCG+MMC vs. BCG on progression rate; D: BCG+MMC vs. BCG on recurrence.

that reduced recurrence of NMIBC is not observed when adding chemotherapy to maintenance BCG [28]. Oosterlinck and Decaestecker further explore the correct sequence of chemotherapy and BCG but fail to make a conclusion, because they find the synergistic effect is only effective within 24 h [29]. It might be the reason for the failure of detecting decreased recurrence rate that chemotherapy is given at least one week before BCG in most of the included studies in their meta-analysis [28]. In addition, a large scale, randomized phase III trial is designed to seek the definitive evaluation of the two regimens [30]. In our study, although we found the combination therapy of BCG+MMC resulted in a reduced recurrence rate, the sequence of the two therapies and time duration was not concerned. Therefore, based on our results, we could just speculate that the combination therapy has the potential to reduce recurrence rate of NMIBC, compared with BCG monotherapy. Subgroup analysis indicated that the combination was not superior to MMC, suggesting that MMC chemotherapy might be sufficient for NMIBC treatment. Actually, MMC is often applied when BCG is failed in NMIBC patients [6]. Moreover, based on the subgroup analysis stratified by dosage, 81mg/week BCG and 30 mg/week MMC might be the optimal dosage for the combination therapy.

However, the combination therapy of BCG+MMC showed a comparable effect with the monotherapy on progression rate, overall mortality and disease-specific mortality. In the comparison of BCG with MMC, Malmström et al show the same result [16]. Interferon (IFN)-α2b is another immunotherapy. A prospective randomized FinnBladder-4 study compared the long-term (medium follow-up time: 10.3 years) outcome of MMC+BCG and MMC+BCG/IFN (alternating BCG or IFN) regimens on frequently recurrent NMIBC patients, and find no significant differences in the probability of progression, disease-free mortality, or overall survival [31]. These results collectively indicate that there might be no obvious differences between chemotherapy and immunotherapy, regarding to outcomes such as progression, overall mortality and disease-specific mortality. Therefore, it is understandable that combination therapy achieved a comparable result with monotherapy on the three outcomes.

With regard to the side effects, Solsona et al state that sequential combination of MMC and BCG is superior to BCG monotherapy, but more toxic than BCG [23]. In the included studies in our meta-analysis, only one study observed that BCG, in combination with MMC, resulted in a significant reduced local and systemic adverse events at 3 months and 12 months, compared with BCG alone [21]. As we did not combine the adverse events due to different evaluation indexes, result of this outcome needed to be interpreted carefully.

In the present study, all the included studies were RCTs, and the lack of extensive heterogeneity across the included studies strengthened the reliability of the pooled results. However, despite these obvious advantages, several limitations were presented. The overall quality of the included studies was relatively low. In addition, we did not consider duration as a risk factor for subgroup analysis, which might cause deviation of the results. Moreover, sequences of BCG and MMC in the combination therapy were not concerned, which might also influence the summary result. Therefore, more large scale RCTs are required to confirm our findings.

In conclusion, BCG in combination with MMC is more advantageous than BCG monotherapy for NMIBC treatment with reduced recurrence rate, and 81mg/week BCG and 30 mg/week MMC might be the optimal dosage. However, the effect on progression rate, overall mortality and disease-specific mortality were not different between the two regimens.

References

[1] PLOEG M, ABEN KK, KIEMENEY LA. The present and future burden of urinary bladder cancer in the world. World J Urol 2009; 27: 289–293. http://dx.doi.org/10.1007/s00345-009-0383-3

[2] KAUFMAN DS, SHIPLEY WU, FELDMAN AS. Bladder cancer. Lancet 2009; 374: 239–249. http://dx.doi.org/10.1016/S0140-6736(09)60491-8

[3] DYRSKJ T L, ZIEGER K, REAL FX, MALATS N, CARRATO A et al. Gene expression signatures predict outcome in non–muscle-invasive bladder carcinoma: a multicenter validation study. Clin Cancer Res 2007; 13: 3545–3551. http://dx.doi.org/10.1158/1078-0432.CCR-06-2940

[4] CHADE DC, SHARIAT SF, DALBAGNI G. Intravesical therapy for urothelial carcinoma of the urinary bladder: a critical review. Int Braz J Urol 2009; 35: 640–651. http://dx.doi.org/10.1590/S1677-55382009000600002

[5] HILTON WM, ERCOLE B, PAREKH DJ, SONPAVDE G, GHOSH R et al. Efficacy of combined intravesical immunotherapy and chemotherapy for non-muscle invasive bladder cancer. Expert Rev Antic Anc 2011; 11: 949–957. http://dx.doi.org/10.1586/era.11.69

[6] SHELLEY MD, MASON MD, KYNASTON H. Intravesical therapy for superficial bladder cancer: a systematic review of randomised trials and meta-analyses. Cancer Treat Rev 2010; 36: 195–205. http://dx.doi.org/10.1016/j.ctrv.2009.12.005

[7] J RVINEN R, KAASINEN E, SANKILA A, RINTALA E, GROUP F. Long-term efficacy of maintenance bacillus Calmette-Guérin versus maintenance mitomycin C instillation therapy in frequently recurrent TaT1 tumours without carcinoma in situ: a subgroup analysis of the prospective, randomised FinnBladder I study with a 20-year follow-up. Eur Urol 2009; 56: 260–265. http://dx.doi.org/10.1016/j.eururo.2009.04.009

[8] B HLE A, JOCHAM D, BOCK P. Intravesical bacillus Calmette-Guerin versus mitomycin C for superficial bladder cancer: a formal meta-analysis of comparative studies on recurrence and toxicity. J Urology 2003; 169: 90–95. http://dx.doi.org/10.1016/S0022-5347(05)64043-8

[9] DI STASI SM, GIANNANTONI A, GIURIOLI A, VALENTI M, ZAMPA G et al. Sequential BCG and electromotive mitomycin versus BCG alone for high-risk superficial bladder cancer: a randomised controlled trial. Lancet Oncol 2006; 7: 43–51. http://dx.doi.org/10.1016/S1470-2045(05)70472-1

[10] G LPINAR O, HALILIOGLU AH, G K E MI, G G Ş Ç, BALTACI S. The value of perioperative mitomycin C instillation in improving subsequent bacillus calmette-guerin instillation efficacy in intermediate and high-risk patients with non-muscle invasıve bladder cancer: a prospective randomized study. Int Braz J Urol 2012; 38: 474–479.

[11] OOSTERLINCK W, KIRKALI Z, SYLVESTER R, DA SILVA FC, BUSCH C et al. Sequential intravesical chemoimmunotherapy with mitomycin C and bacillus Calmette-Guerin and with bacillus Calmette-Guerin alone in patients with carcinoma in situ of the urinary bladder: results of an EORTC genito-urinary group randomized phase 2 trial (30993). Eur Urol 2011; 59: 438–446. http://dx.doi.org/10.1016/j.eururo.2010.11.038

[12] THACKER SB. Meta-analysis: a quantitative approach to research integration. Jama 1988; 259: 1685–1689. http://dx.doi.org/10.1001/jama.1988.03720110047033

[13] SPIX C, ANDERSON HR, SCHWARTZ J, VIGOTTI MA, LETERTRE A et al. Short-term effects of air pollution on hospital admissions of respiratory diseases in Europe: a quantitative summary of APHEA study results. Arch Environ Health 1998; 53: 54–64. http://dx.doi.org/10.1080/00039899809605689

[14] SULLIVAN PF, NEALE MC, KENDLER KS. Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiat 2000;

[15] HEDGES LV, VEVEA JL. Fixed-and random-effects models in meta-analysis. Psychological methods 1998; 3: 486. http://dx.doi.org/10.1037/1082-989X.3.4.486

[16] MALMSTR M P-U, SYLVESTER RJ, CRAWFORD DE, FRIEDRICH M, KREGE S et al. An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus bacillus Calmette-Guérin for non–muscle-invasive bladder cancer. Eur Urol 2009; 56: 247–256. http://dx.doi.org/10.1016/j.eururo.2009.04.038

[17] HIGGINS JPT, GREEN S, editors. Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series. The Cochrane Collaboration, published online 2008, ISBN (online) 978–0-4707–1218-4.

[18] JIANG Q, JIANG XH, ZHENG MH, CHEN YP. l-Ornithine-l-aspartate in the management of hepatic encephalopathy: A meta-analysis. J Gastroen Hepatol 2009; 24: 9–14. http://dx.doi.org/10.1111/j.1440-1746.2008.05582.x

[19] ZHANG C, SUN A, ZHANG P, WU C, ZHANG S et al. Aspirin for primary prevention of cardiovascular events in patients with diabetes: A meta-analysis. Diabetes Res Clin Pr 2010; 87: 211–218. http://dx.doi.org/10.1016/j.diabres.2009.09.029

[20] J RVINEN R, KAASINEN E, RINTALA E, GROUP TF. Long-term results of maintenance treatment of mitomycin C or alternating mitomycin C and bacillus Calmette–Guérin instillation therapy of patients with carcinoma in situ of the bladder: A subgroup analysis of the prospective FinnBladder 2 study with a 17-year follow-up. Scand J Urol Nephrol 2012; 46: 411–417. http://dx.doi.org/10.3109/00365599.2012.694906

[21] KAASINEN E, WIJKSTR M H, MALMSTR M P-U, HELLSTEN S, DUCHEK M et al. Alternating mitomycin C and BCG instillations versus BCG alone in treatment of carcinoma in situ of the urinary bladder: a Nordic study. Eur Urol 2003; 43: 637–645. http://dx.doi.org/10.1016/S0302-2838(03)00140-4

[22] RINTALA E, JAUHIAINEN K, KAASINEN E, NURMI M, ALFTHAN O. Alternating mitomycin C and bacillus Calmette-Guerin instillation prophylaxis for recurrent papillary (stages Ta to T1) superficial bladder cancer. J Urology 1996; 156: 56–60. http://dx.doi.org/10.1016/S0022-5347(01)65936-6

[23] SOLSONA E, MADERO R, CHANTADA V, FERNANDEZ JM, ZABALA JA et al. Sequential combination of mitomycin C plus bacillus Calmette-Guérin (BCG) is more effective but more toxic than BCG alone in patients with non–muscle-invasive bladder cancer in intermediate-and high-risk patients: final outcome of CUETO 93009, a randomized prospective trial. Eur Urol 2015; 67: 508–516. http://dx.doi.org/10.1016/j.eururo.2014.09.026

[24] WITJES J, CARIS C, MUNGAN N, DEBRUYNE F, WITJES W. Results of a randomized phase III trial of sequential intravesical therapy with mitomycin C and bacillus Calmette-Guerin versus mitomycin C alone in patients with superficial bladder cancer. J Urology 1998; 160: 1668–1672. http://dx.doi.org/10.1016/S0022-5347(01)62377-2

[25] DOWNS TM, LEE DJ, SCHERR DS Management of BCG Recurrent Bladder Cancer. pp 245–263. In: Konety BR, Chang SS, editors. Management of Bladder Cancer: A Comprehensive Text With Clinical Scenarios. Springer New York 2015 ISBN (online) 978–1-4939–1881-2.

[26] PORTEN SP, LEAPMAN MS, GREENE KL. Intravesical chemotherapy in non-muscle-invasive bladder cancer. Indian J Urol 2015; 31: 297–303. http://dx.doi.org/10.4103/0970-1591.166446

[27] ZARGAR H, ANING J, ISCHIA J, SO A, BLACK P. Optimizing intravesical mitomycin C therapy in non-muscle-invasive bladder cancer. Nat Rev Urol 2014; 11: 220–230. http://dx.doi.org/10.1038/nrurol.2014.52

[28] HOUGHTON BB, CHALASANI V, HAYNE D, GRIMISON P, BROWN CS et al. Intravesical chemotherapy plus bacille Calmette-Guérin in non-muscle invasive bladder cancer: a systematic review with meta-analysis. BJU Int 2013; 111: 977–983. http://dx.doi.org/10.1111/j.1464-410X.2012.11390.x

[29] OOSTERLINCK W, DECAESTECKER K. The Correct Sequence of Intravesical Chemotherapy and Bacillus Calmette-Guérin for Non–Muscle-invasive Bladder Cancer. Eur Urol 2015; 67: 517–518. http://dx.doi.org/10.1016/j.eururo.2014.11.028

[30] HAYNE D, STOCKLER M, MCCOMBIE SP, CHALASANI V, LONG A et al. BCG+ MMC trial: adding mitomycin C to BCG as adjuvant intravesical therapy for high-risk, non-muscle-invasive bladder cancer: a randomised phase III trial (ANZUP 1301). BMC cancer 2015; 15: 432. http://dx.doi.org/10.1186/s12885-015-1431-6

[31] J RVINEN R, MARTTILA T, KAASINEN E, RINTALA E, AALTOMAA S et al. Long-term Outcome of Patients with Frequently Recurrent Non–muscle-invasive Bladder Carcinoma Treated with One Perioperative Plus Four Weekly Instillations of Mitomycin C Followed by Monthly Bacillus Calmette-Guérin (BCG) or Alternating BCG and Interferon-α2b Instillations: Prospective Randomised FinnBladder-4 Study. Eur Urol 2015; 68: 611–617. http://dx.doi.org/10.1016/j.eururo.2015.02.022