Systematic Review and Cumulative Analysis of the Combination of Mitomycin C plus Bacillus Calmette-Guérin (BCG) for Non–Muscle-Invasive Bladder Cancer

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This systematic review and cumulative analysis aimed to explore the efficacy and safety of the combination of intravesical mitomycin C (MMC) plus bacillus Calmette-Guerin (BCG) for non-muscle-invasive bladder cancer (NMIBC) patients. A comprehensive literature search using Pubmed, Embase, Medline, Cochrane Library, CBM, CNKI and VIP databases was performed to identify studies applying intravesical MMC plus BCG therapy on NMIBC patients up to June 2016. Summarized unadjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the efficacy and safety of the combination therapy. A total of 25 studies containing 2749 NMIBC patients were included in this systematic review. Compared with BCG monotherapy, the combination therapy could significantly reduce the tumor recurrence rate (OR = 0.64, 95% CI: 0.44–0.94, \( P = 0.02 \)) and cancer-specific mortality (OR = 0.54, 95% CI: 0.34–0.87, \( P = 0.01 \)), without more toxicities (OR = 0.58, 95% CI: 0.17–1.94, \( P = 0.37 \)). The combination therapy could also lead to significant lower tumor recurrence rate than MMC monotherapy (OR = 0.41, 95% CI: 0.24–0.69, \( P = 0.0009 \)). Our study indicates that the combination of MMC plus BCG instillation is an effective and safe adjuvant treatment for NMIBC patients.
Results

Eligible studies and characteristics. 25 studies containing 2749 NMIBC patients were included in this systematic review (Fig. 1). Baseline characteristics of all eligible studies were shown in Table 1. Among 25 included studies, 16 were randomized controlled trials (RCTs)10–13, 15–21, 24, 28, 31, 33, 34, 4 were retrospective comparative trials14, 26, 27, 29, 1 was retrospective cohort study30 and remaining 4 were clinical series22, 23, 32, 25.

In all studies, 1810–19, 24, 26–29, 31, 33, 34 were included in our cumulative analysis, comparing the efficacy of combined MMC plus BCG therapy with MMC or BCG monotherapy on NMIBC patients. Among them, MMC + BCG versus BCG alone was conducted in 10 studies10, 11, 13, 14, 16–18, 24, 27, 29, MMC + BCG versus MMC alone was referred in 7 studies12, 15, 19, 28, 31, 33, 34 and the rest 126 compared MMC + BCG with either MMC or BCG.

Quality assessments of included studies. Level of evidence (LOE) was accessed for all 25 included studies and results were listed in Table 1. Among 16 RCTs, 9 were in low risk of bias12, 13, 16, 20, 21, 24, 28, 33, 34, 6 were in moderate risk of bias10, 15, 17–19, 31 and the remaining one was in high risk of bias11 according to the quality assessment (Fig. 2). However, the risk of detection and attrition biases were low in all of them. Additionally, 7 RCTs were in relative high quality12, 13, 16, 20, 21, 33, 34.

Instillation regimens and prognoses of intravesical MMC plus BCG. 1361 NMIBC patients from 25 eligible studies received intravesical MMC plus BCG instillation as an adjuvant therapy besides surgery (Table 2). Combination regimens in these studies could be divided into four subtypes: single dose of perioperative MMC prior to BCG (combination regimen 1) was applied in 4 studies10, 14, 15, 25; sequential instillations with MMC and BCG (combination regimen 2) were used in 12 studies11, 16–23, 30–32; 7 studies12, 24–27, 33, 34 adopted alternating instillations with MMC and BCG (combination regimen 3); and last 2 studies13, 28 preferred mixed instillations with MMC plus BCG (combination regimen 4). Table 3 showed prognoses of patients receiving combination therapies in all included studies according to different instillation regimen and follow-up time.

MMC plus BCG instillation versus BCG alone. 11 studies compared the efficacy of MMC plus BCG with BCG alone instillation (Supplementary Table 1).

Recurrence. Tumor recurrence rate was compared between intravesical MMC plus BCG instillation and BCG alone treatment among NMIBC patients in all 11 studies. Slight heterogeneity was observed (I² = 57%, P = 0.009), and the recurrence rate in patients receiving MMC + BCG was significantly lower than BCG alone [odds ratio (OR) = 0.64, 95% confidence interval (CI): 0.44–0.94, P = 0.02] (Fig. 3). In subgroup analyses, patients in following subgroups also benefited more from MMC + BCG instillations significantly than BCG alone: retrospective comparative trials, combination regimen 2, combination regimen 4, short-term and long-term follow-ups, Asians
populations, therapeutic courses ≤ 1yr and > 2 yrs, and instillation numbers ≥ 24 (Supplementary Table 2). No publication bias was detected through both inverted funnel plot and Egger’s test ($t = -1.65, P = 0.138$).

In 3 studies, we reported multivariable adjusted hazard ratios (HRs) to prevent tumor recurrence of combined MMC and BCG instillation compared with BCG alone. No significant difference was found between two groups (HR = 0.86, 95% CI: 0.50–1.49, $P = 0.59$) with moderate heterogeneity ($I^2 = 80\%$, $P = 0.007$).

### Disease-free survival.

Number of disease-free patients during follow-up time was mentioned in 6 studies, and slight heterogeneity was found ($I^2 = 67\%$, $P = 0.01$). Although no significant difference was observed between MMC + BCG and BCG groups (OR = 1.16, 95% CI: 0.70–1.92, $P = 0.56$), patients receiving combination regimen 2 shared a significant higher disease-free survival rate than BCG alone (OR = 1.76, 95% CI: 1.11–2.79, $P = 0.02$) without heterogeneity ($I^2 = 0\%$, $P = 0.57$) (Supplementary Fig. 1). No publication bias was detected through the inverted funnel plot.

### Progression.

7 studies compared rate of tumor progression between MMC + BCG and BCG alone groups. No significant difference occurred (OR = 0.65, 95% CI: 0.33–1.29, $P = 0.22$) with slight heterogeneity ($I^2 = 63\%$, $P = 0.01$). However, subgroup analyses indicated that the application of combination regimen 2 could significantly reduce the risk of progression for NMIBC patients compared with BCG alone (OR = 0.32, 95% CI: 0.18–0.56).

### Table 1. The baseline characteristics of included studies.

| Combination regimen of MMC+BCG | Reference | Country | Ethnicity | Recruitment period | Study design | LOE | Tumor stage | No. of cases receiving MMC+BCG | Mean/median age(yr) | Mean/median follow-up time (mo) |
|--------------------------------|-----------|---------|-----------|-------------------|-------------|-----|-------------|-----------------------------|-------------------|--------------------------|
| A single dose of perioperative MMC prior to instillation with BCG | Badalato et al. | USA | mixed | 2000–2010 | Retrospective comparative trial | 3 | Ta, T1, Tis | 48 | 69.6 | 33 |
| | Gülpinar et al. | Turkey | Europeans | 2004–2006 | RCT | 2b | Ta, T1 | 25 | 58.2 | 41.3 |
| | Ye et al. | China | Asian | 1997–2002 | RCT | 2b | Ta, T1 | 50 | 57 | 32 |
| | Weiss et al. | USA | mixed | 1977–2009 | Retrospective comparative trial | 3 | Ta, T1, Tis | 23 | — | 54 |
| Sequential instillation with MMC and BCG | Di Stasi et al. | Italy | Europeans | 1994–2002 | RCT | 2b | T1, Tis | 107 | 66 | 91 |
| | Oosterlinck et al. | Multi-country in Europe | Europeans | 2001–2005 | RCT | 1b | Ta, T1, Tis | 41 | 68 | 56.4 |
| | He et al. | China | Asians | 2005–2009 | RCT | 2b | Ta, T1 | 40 | 61.2 | 21.2 |
| | Liu et al. | China | Asians | 2000–2003 | RCT | 2b | Ta, T1 | 59 | 55 | 35 |
| | Ma et al. | China | Asians | 1996–1998 | RCT | 2b | — | 29 | 52 | 37.9 |
| | Kaasinen et al. | Finland | Europeans | 1992–1996 | RCT | 2a | Ta, T1 | 102 | 68 | 30.7 |
| | Svatek et al. | USA | mixed | — | Case series | 4 | Ta, T1, Tis | 12 | 67 | 21.4 |
| | Cai et al. | China | Asians | 2007–2011 | Case series | 4 | Ta, T1 | 30 | 60.3 | 20.4 |
| | Gan et al. | UK | Europeans | 2009–2013 | Retrospective cohort study | | Ta, T1, Tis | 104 | 68 | 24 |
| | Witjes et al. | Netherlands | Europeans | 1991–1993 | RCT | 2a | Ta, T1, Tis | 90 | — | 32 |
| | Van der Meijden et al. | Netherlands | Europeans | 1990–1992 | Case series | 4 | Ta, T1 | 35 | 70 | 19.8 |
| Alternating instillation with MMC and BCG | Rintala et al. | Finland | Europeans | 1987–1992 | RCT | 2a | Ta, T1, Tis | 28 | 66 | 33 |
| | Kaasinen et al. | Finland, Norway and Sweden | Europeans | 1992–1997 | RCT | 2a | Ta, T1, Tis | 159 | 71 | 56.3 |
| | Zhang et al. | China | Asians | 1998–2006 | Retrospective comparative trial | 3 | Ta, T1 | 32 | 62.5 | 28 |
| | Bao et al. | China | Asians | 1999–2006 | Retrospective comparative trial | 3 | Ta, T1, Tis | 20 | 70 | 24 |
| | Rintala et al. | Finland | Europeans | 1987–1992 | RCT | 2a | Ta, T1 | 95 | 68.5 | 34 |
| Mixed instillation with MMC plus BCG | Solsona et al. | Spain | Europeans | 1993–1994 | RCT | 1b | Ta, T1, Tis | 211 | 65 | 85.2 |
| | Fang et al. | China | Asians | 1999–2000 | RCT | 2a | Ta, T1 | 21 | 67.5 | 23.4 |
0.18–0.60, \( P = 0.0004 \)) bearing no heterogeneity among these relevant studies (\( I^2 = 0\% \), \( P = 0.38 \)) (Fig. 4). The inverted funnel plot did not demonstrate any indication of publication bias.

**Cancer-specific mortality.** During the follow-up time, patients who died from bladder cancer were reported in 5 studies. Significant lower cancer-specific mortality was discovered in MMC + BCG compared with BCG group (\( OR = 0.54, 95\% CI: 0.34–0.87, P = 0.01 \)) sharing no heterogeneity (\( I^2 = 41\% \), \( P = 0.15 \)) (Supplementary Fig. 2). Furthermore, significant advantage was only tested in combination regimen 2 (\( OR = 0.24, 95\% CI: 0.10–0.59, P = 0.002 \)) after subgroup analyses were conducted. The inverted funnel plot showed no publication bias.

**Severe side-effects.** Toxicities of intravesical MMC + BCG versus BCG alone therapies were assessed in 5 studies with moderate heterogeneity (\( I^2 = 80\% \), \( P = 0.0004 \)). Combination of intravesical MMC + BCG instillation did not seem to bring fewer toxicities than BCG alone (\( OR = 0.58, 95\% CI: 0.17–1.94, P = 0.37 \)) (Supplementary Fig. 3). Nevertheless, subgroup analyses indicated that combination regimen 3 could significantly decrease the toxicity of combination therapy compared with BCG monotherapy (\( OR = 0.18, 95\% CI: 0.09–0.38, P < 0.00001 \)). No publication bias was detected through the inverted funnel plot.

**MMC + BCG instillation versus MMC alone.** 8 studies concentrated on the efficacy of intravesical MMC + BCG instillation versus MMC alone on NMIBC patients (Supplementary Table 3). Recurrence rate was compared in all 8 studies, and our results indicated that combined intravesical therapy was significantly more effective to decrease tumor recurrence than MMC alone (\( OR = 0.41, 95\% CI: 0.24–0.69, P = 0.0009 \)) with slight heterogeneity (\( I^2 = 47\% \), \( P = 0.07 \)) (Fig. 5). In addition, 5 studies compared the tumor progression rate between MMC + BCG and MMC alone groups with no significant difference (\( OR = 0.83, 95\% CI: 0.43–1.59, P = 0.57 \)) (Supplementary Fig. 4). No heterogeneity existed either (\( I^2 = 0\% \), \( P = 0.88 \)). Comparison of toxicities between two groups was also conducted in 5 studies and no significant difference was observed (\( OR = 1.18, 95\% CI: 0.63–2.19, P = 0.61 \)) (Supplementary Fig. 3). Cancer-specific mortality was only reported in 2 studies, and no significant difference was discovered.

**Discussion**

This systematic review aimed to evaluate the efficacy and safety of combined intravesical MMC plus BCG instillation as a novel adjuvant therapy for NMIBC. Our analyses concluded that, compared with BCG or MMC monotherapy, the combination therapy could reduce the recurrence rate of NMIBC significantly without causing more toxicities. As a result, all evidences we have achieved till now support that combined intravesical MMC plus BCG instillation may be a better choice for NMIBC patients.

Previous studies have shown that the adherence to bladder wall of BCG is an important step for immunotherapy\(^{35,36}\). Chemical disruption of the bladder urothelium induced by MMC could enable BCG to attach more efficiently to bladder wall and then improve the immune response and antitumor activity\(^{37}\). Furthermore, MMC instillation could also promote BCG uptake and activate related immune effector cells\(^{38–40}\). Therefore, an enhanced antitumor effect could be achieved by combined intravesical MMC and BCG instillation.
A single dose of perioperative MMC prior to instillation with BCG.

| Combination regimen of MMC + BCG | Reference | No. of case receiving MMC + BCG | Mean/median age(yr) | Mean/median follow-up time (mos) | During follow-up time | 5-year recurrence-free survival rate (%) | 3-year severe side-effects (%) |
|----------------------------------|-----------|---------------------------------|--------------------|-------------------------------|-----------------------|------------------------------------------|-------------------------------|
|                                  |           |                                 |                    |                               | No. recurrence (%) | No. disease-free case (%) | No. progression (%) | No. death from any causes (%) | No. death from bladder cancer (%) | No. death from any causes (%) | No. death from recurrence-free survival rate (%) | No. severe side-effects (%) |
|                                  |           |                                 |                    |                               |                       |                          |                          |                              |                               |                          |                              |                              |
| **Sequential instillation with MMC and BCG** |           |                                 |                    |                               |                       |                          |                          |                              |                               |                          |                              |                              |
| Di Stasi et al.15                 | 107       | 66                              | 91                 | 45 (42.1)                     | 62 (57.9)             | 10 (9.3)                  | 23 (21.5)                   | 6 (5.6)                      | —                              | 3 (2.8)                      | —                            |                              |
| Oosterlinck et al.16              | 41        | 68                              | 56.4               | 23 (56.1)                     | 25 (61)               | 3 (7.3)                   | 7 (17.1)                   | 0                             | 51.4%                          | 5 (12.2)                     | —                            |                              |
| He et al.17                      | 40        | 61.2                            | 21.2               | 5 (12.5)                      | —                     | —                         | 0                          | 0                            | 0                              | 0                            | —                            |                              |
| Liu et al.18                     | 59        | 55                              | 35                 | 9 (15.3)                      | 3 (5.1)               | —                         | 0                          | 0                            | 0                              | 0                            | —                            |                              |
| Ma et al.19                      | 29        | 52                              | 37.9               | 3 (10.3)                      | —                     | —                         | —                          | —                            | —                              | —                            | —                            |                              |
| Kaasinen et al.20 and Jarvinen et al.21 | 102     | 68                              | 30.7               | 14 (13.7)                     | 73 (71.6)             | 3 (2.9)                   | 4 (3.9)                    | 0                             | 67%                            | 2 (2)                        | —                            |                              |
|                                  |           |                                 |                    |                               |                       |                          |                          |                              |                               | —                            | —                            |                              |
| **Alternating instillation with MMC and BCG** |           |                                 |                    |                               |                       |                          |                          |                              |                               |                              |                              |                              |
| Rintala et al.22 and Jarvinen et al.21 | 28        | 66                              | 33                 | 6 (21.4)                      | 14 (50)               | 2 (7.1)                   | 0                          | 0                            | —                              | 0                            | —                            |                              |
|                                  |           |                                 |                    |                               |                       |                          |                          |                              |                               |                              |                              |                              |
|                                  |           |                                 |                    |                               |                       |                          |                          |                              |                               |                              |                              |                              |
| Kaasinen et al.24                | 159       | 71                              | 56.3               | 71 (44.7)                     | 72 (45.3)             | 34 (21.4)                 | —                          | 13 (8.2)                    | 40.7%                          | 10 (6.3)                     | —                            |                              |
| Zhang et al.26 and Sun et al.23   | 32        | 62.5                            | 28                 | 2 (6.3)                       | 30 (93.7)             | 0                         | 0                          | 0                            | 0                              | —                            | 0                            | —                            |
| Bao et al.27                     | 20        | 70                              | 24                 | 0                             | —                     | 0                         | 0                          | 0                            | 0                              | —                            | 0                            | —                            |
| Rintala et al.23                 | 95        | 68.5                            | 54                 | 57 (60)                       | 38 (40)               | 3 (3.2)                   | 2 (2.1)                    | 0                            | 6 (6.3)                        | —                            | —                            | —                            |
| **Mixed instillation with MMC plus BCG** |           |                                 |                    |                               |                       |                          |                          |                              |                               |                              |                              |                              |
| Solsona et al.13                 | 211       | 65                              | 85.2               | 44 (20.9)                     | 26 (12.3)             | 51 (24.2)                 | 10 (4.7)                   | —                            | 20 (9.5)                       | —                            | —                            | —                            |
| Fang et al.24                    | 21        | 67.5                            | 23.4               | 1 (4.8)                       | —                     | —                         | 0                          | 0                            | —                              | —                            | —                            | —                            |

Table 2. Detailed outcomes of patients receiving combination therapy. BCG = bacillus Calmette-Guerin; MMC = mitomycin C.

So far, several studies8–13 have investigated the antitumor effect of combined intravesical MMC plus BCG instillation. Lan et al.31 recently conducted a meta-analysis including only RCTs, having compared the efficacy of combined BCG and MMC therapy with each monotherapy on NMIBC patients. Results from 8 RCTs in their study showed a significant decreased recurrence rate in patients receiving combination therapy compared with monotherapy. However, since a lot of comparative and cohort studies were not included, their conclusions appeared to be rigorous to some extent. Some animal experiments also drew a similar conclusion with us22, 42. Matsushima et al.45 found MMC plus BCG treatment could inhibit tumor growth and cellular proliferation, and prolong the survival period compared to the BCG-alone therapy through an orthotopic bladder cancer model. Moreover, Svatek et al.22 identified macrophages were polarized toward a beneficial M1 phenotype after MMC plus BCG instillation in a murine model of bladder cancer, which indicated the antitumor effect of combination instillation could be improved by increased number of beneficial cells.

In this systematic review, we recognized that different combination regimens were carried out in these studies, which might have caused varied effects. Table 3 showed that combination regimen 4 could reduce recurrence but lead to more severe side-effects than others. While considering delaying tumor progression and reducing cancer-specific mortality in long-term follow-up, combination regimen 2 might be a better choice. Several courses of MMC before sequential BCG instillation could not only improve the antitumor function, but also promote the activation and production of immune effector cells8–13. Nevertheless, since these findings were not obtained by statistical comparisons and cumulative analyses of different combination regimens, they should only represent our own opinions and could not be regarded as evidential results.

Solsona et al.13 conducted a RCT demonstrating that combined MMC plus BCG therapy was more toxic than BCG alone with severe side-effects rate of 9.5%. However, our analysis indicated that taking all clinical trials into...
consideration, combination therapy did not cause more toxicities than BCG or MMC monotherapy. Therefore, combination of MMC plus BCG treatment seems to be safe, while more clinical studies are still needed for further evaluation.

Several potential limitations should be addressed about this analysis. First, included studies lasted a time span as long as 21 years, during which the living environment and quality of life might change. Second, data of some studies was incomplete even by contacting authors. Third, most high-quality trials were conducted in Europeans

Table 3. Patients’ prognoses with different combination regimen and follow-up time. Combination regimen 1: a single dose of perioperative MMC prior to BCG; Combination regimen 2: sequential instillation with MMC and BCG; Combination regimen 3: alternating instillation with MMC and BCG; Combination regimen 4: mixed instillation with MMC plus BCG.

Figure 3. Forest plot of tumor recurrence rate comparing combination therapy with BCG monotherapy.

| Combination regimen | Follow-up time | No. of included study | No. recurrence/total (%) | No. disease-free case/total (%) | No. progression/total (%) | No. death from any causes/total (%) | No. death from bladder cancer/total (%) | No. severe side-effects/total (%) |
|---------------------|---------------|-----------------------|-------------------------|-----------------------------|-------------------------|----------------------------------|----------------------------------|-------------------------------|
| Combination regimen 1 | Medium-term (2–5 yrs) | 4 | 43/146 (29.5) | 53/96 (55.2) | 1/75 (1.3) | 3/23 (13) | 0/50 | 0/75 |
| Combination regimen 2 | Short-term (≤2 yrs) | 5 | 49/221 (22.2) | 103/146 (70.5) | 6/181 (3.3) | 1/181 (0.6) | 0/221 | 3/221 (1.4) |
| | Medium-term (2–5 yrs) | 5 | 84/321 (26.2) | 145/233 (62.2) | 14/292 (4.8) | 32/233 (13.7) | 5/292 (1.7) | 23/321 (7.2) |
| | Long-term (≥5 yrs) | 2 | 89/209 (42.6) | 94/209 (45) | 16/209 (7.7) | 79/209 (37.8) | 9/209 (4.3) | 5/209 (2.4) |
| Combination regimen 3 | Short-term (≤2 yrs) | 1 | 0/20 | — | 0/20 | — | 0/20 | 0/20 |
| | Medium-term (2–5 yrs) | 5 | 136/314 (43.3) | 154/314 (49) | 39/314 (12.4) | 2/155 (1.3) | 13/314 (4.1) | 16/314 (5.1) |
| | Long-term (≥5 yrs) | 1 | 19/28 (67.9) | — | 8/28 (28.6) | 20/28 (71.4) | 8/28 (28.6) | — |
| Combination regimen 4 | Short-term (≤2 yrs) | 1 | 1/21 (4.8) | — | — | 0/21 | 0/21 |
| | Long-term (≥5 yrs) | 1 | 44/211 (20.9) | — | 26/211 (12.3) | 51/211 (24.2) | 10/211 (4.7) | 20/211 (9.5) |

Table 3. Patients’ prognoses with different combination regimen and follow-up time. Combination regimen 1: a single dose of perioperative MMC prior to BCG; Combination regimen 2: sequential instillation with MMC and BCG; Combination regimen 3: alternating instillation with MMC and BCG; Combination regimen 4: mixed instillation with MMC plus BCG.

Figure 3. Forest plot of tumor recurrence rate comparing combination therapy with BCG monotherapy.
and Asians, which might restrict the application of our results on other populations. At last, insufficient numbers of related studies might bring some potential bias to our results.

Conclusion
Our study concluded that combination of MMC plus BCG intravesical instillation was an effective and safe adjuvant treatment for NMIBC patients after TUR. This therapy could significantly reduce the tumor recurrence rate and would not bring more toxicities than BCG or MMC monotherapy. However, further high-quality clinical trials are still needed to verify conclusions of our study.
Materials and Methods

Search strategy. A systematic literature search using Pubmed, Embase, Medline, Cochrane Library, CBM, CNKI and VIP databases was performed to identify studies exploring the efficacy of intravesical MMC plus BCG therapy for NMIBC patients up to June 2016. Search terms were “mitomycin C” or ‘MMC” and ‘bacillus Calmette-Guerin’ or ‘BCG' in combination with “‘non-muscle-invasive bladder cancer’ or ‘NMIBC’ or ‘superficial bladder cancer’ or ‘orthotopic bladder cancer’ or ‘bladder carcinoma in situ’”. The study language was restricted to English and Chinese. Reference lists of relevant studies were also checked.

Inclusion and exclusion criteria. Studies applying intravesical MMC plus BCG therapy on NMIBC patients and providing detailed information were included in this systematic review, and data comparing the efficacy of combination therapy with MMC or BCG monotherapy was pooled in cumulative analysis. Accordingly, we excluded studies involving congress abstracts, conference proceedings, editorials, reviews, animal experiments and repeated publications. Two authors (T.D. and B.L.) independently assessed relevant records, evaluated the quality of included studies and extracted studies' data. Discrepancies were resolved via open discussion.

Study quality assessment and data extraction. GRADE approach was used to assess the LOE of all eligible studies. Furthermore, the Cochrane Collaboration Risk of Bias Tool was applied to evaluate the quality of RCTs. Data was attentively extracted including research methodology, participants' information, tumor stage, surgical procedure, therapeutic regimens of MMC plus BCG (instillation schedule, dose and retaining time), course of treatment, and disease-related outcomes (recurrence, progression, disease-free survival, disease-free interval, cancer-specific survival, overall survival and severe side-effect). In comparative studies, HRs and 95% CIs were also extracted to predict the recurrence-free survival between combined MMC plus BCG and MMC or BCG alone.

Statistics analysis. In the cumulative analysis, summarized unadjusted ORs and 95% CIs were calculated to assess the efficacy of combined MMC and BCG instillation compared with MMC or BCG alone. Available multivariable adjusted HRs were also pooled as references. Subgroup analyses were conducted according to type of combination regimen, study design, patient ethnicity, number of instillation, therapeutic course, and follow-up time. Statistical heterogeneity among included studies was tested through chi-square test. If no heterogeneity existed with p value > 0.10, the fixed-effect model was used. Otherwise, the random-effect model was applied. A two-sided p value < 0.05 was considered significant for all results in cumulative analysis. Publication bias was assessed by inverted funnel plot and Egger's test. All statistical analyses were conducted by RevMan (version 5.3; Cochrane Collaboration, Oxford, UK) and STATA (version 13.0; StataCorp, College Station, Texas, USA) software.

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**Author Contributions**

All authors contributed significantly to this work. G.Z. and T.D. designed this study; T.D., B.L. and X.D. performed the research study, collected and analyzed the data; T.D., B.L. and X.D. wrote the manuscript; T.Z. and C.C. resolved discrepancies and provide significant advices for this research. All authors reviewed, edited and approved the manuscript.

**Additional Information**

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