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Intravesical Gemcitabine Versus Mitomycin C for Non-Muscle Invasive Bladder Cancer: A Robust Meta-Analysis Revealing Superior Recurrence Control and Improved Tolerability

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Abstract **Background:** Non-Muscle Invasive Bladder Cancer (NMIBC) constitutes the majority of bladder cancer patients but has elevated recurrence rates after intravesical treatment. Although mitomycin C (MMC) is extensively used, intravesical gemcitabine (GCB) has shown potential as a superior option with enhanced tolerability. **Objective:** This meta-analysis compares the effectiveness and safety of intravesical GCB versus MMC for NMIBC management. **Methods:** Following PRISMA guidelines, seven studies with 491 patients were analyzed. Outcomes included tumor recurrence, chemical cystitis and hematuria. Fixed-effects or random-effects models were used to compute pooled Odds Ratios (ORs) with 95% Confidence Intervals (CIs). **Results:** GCB significantly reduced recurrence rates compared to MMC (OR: 2.97; 95% CI: 1.90-4.65; $p<0.00001$) with low heterogeneity ($I^2 = 13\%$). The risk of chemical cystitis was also significantly lower with GCB (OR: 4.39; 95% CI: 2.27-8.51; $p<0.0001$). No significant difference was found in hematuria incidence (OR: 1.71; 95% CI: 0.68-4.33; $p = 0.26$). **Conclusions:** Intravesical GCB demonstrates superior efficacy in reducing recurrence and is associated with fewer adverse effects than MMC, supporting its use as a first-line option for NMIBC, especially in patients at risk of recurrence or intolerance to MMC. Further large-scale trials are recommended to confirm these findings and refine treatment strategies.

Key Words Gemcitabine, Meta-Analysis, Non-Muscle Invasive Bladder Cancer, Tumor Recurrence, Intravenous Therapy, Mitomycin

INTRODUCTION

Bladder Cancer (BC) remains one of the most common malignancies affecting the genitourinary system worldwide, with considerable implications for global health [1-3]. Annually, BC accounts for over 500,000 newly reported cases worldwide [4]. BC may be split into two types: Muscle-Invasive Bladder Cancer (MIBC) and Non-Muscle-Invasive Bladder Cancer (NMIBC), which make up around 75% of diagnoses. A poor prognosis is linked to up to 45% of individuals with NMIBC progressing to MIBC, underscoring the clinical need to identify these patients [4]. The majority of BC cases are caused by transitional cell carcinoma. In contrast, squamous cell carcinoma and adenocarcinoma are histological variants that are relatively uncommon [5,6]. The disease commonly presents with clinical symptoms including gross or microscopic hematuria, increased urinary frequency, urgency and dysuria, which often prompt initial clinical evaluation and diagnosis [7,8].

From an epidemiological perspective, this condition shows a pronounced male predominance, being roughly four times more prevalent in men than in women [9-11]. Diagnosis commonly occurs in older adults, with approximately 80% of cases identified in individuals aged 65 years or above. The prognosis for patients with metastatic

illness is still poor, with a five-year survival rate of less than 10% [9] and BC is ranked 13th among the world's top causes of cancer death [12]. The liver, lungs, bones and adrenal glands are common sites for metastases [13].

NMIBC, which includes tumors limited to the urothelium, carcinoma in situ or the lamina propria, accounts for the bulk of newly diagnosed BC diagnoses [14]. Managing NMIBC in clinical practice continues to pose significant challenges, primarily because of its substantial risk of recurrence and, in certain instances, its potential to progress to more advanced stages. This remains true even though non-muscle invasive disease typically has a more favorable survival prognosis than muscle-invasive bladder cancer [15,16]. In addition, recurrence rates after initial transurethral resection of bladder tumor (TURBT) can be as high as 60-80%, with approximately 10-15% of cases eventually progressing to muscle-invasive disease [17,18]. The persistent nature of NMIBC necessitates aggressive surveillance and adjuvant therapy to mitigate the risk of progression and recurrence.

The pathophysiology underlying NMIBC recurrence is multifactorial. It includes incomplete tumor resection, re-implantation of exfoliated cancer cells at injured bladder mucosa, emergence of new primary tumors due to field cancerization or failure to administer effective adjuvant intravesical therapy [19-21]. Therefore, adjuvant intravesical therapy following TURBT has become the cornerstone of contemporary NMIBC management. This approach aims to eradicate residual microscopic disease, prevent recurrence, inhibit tumor cell proliferation and ultimately prolong patient survival [22,23].

Several agents have been utilized for intravesical chemotherapy, with mitomycin C (MMC) being one of the most extensively used and well-established treatments [24]. MMC is an antitumor antibiotic exhibiting potent cytotoxic activity by inducing DNA cross-linking, inhibiting DNA synthesis and cell replication [25,26]. Despite its proven efficacy, its use is often associated with various adverse effects, including chemical cystitis, dysuria, skin reactions and in rare cases, systemic toxicity [27]. Additionally, alternative agents have been investigated due to the intermittent unavailability and increasing costs of MMC.

Gemcitabine (GCB), a novel pyrimidine nucleoside analog, has garnered interest as a potential drug for intravesical treatment owing to its robust anticancer efficacy and favorable safety profile [28-30]. Its mechanism of action involves intracellular phosphorylation, converting it into active diphosphate and triphosphate metabolites that suppress DNA synthesis and trigger programmed cell death through apoptosis [31,32]. Initially developed for treating advanced and metastatic urothelial carcinoma, GCB has demonstrated considerable efficacy when repurposed for intravesical administration in NMIBC, especially in patients who are refractory to Bacillus Calmette-Guérin (BCG) therapy or those intolerant to traditional chemotherapeutic agents [33].

Both MMC and GCB exhibit distinct mechanisms of action, pharmacokinetic properties and toxicity profiles, raising important questions regarding their relative efficacy and tolerability in the adjuvant setting. While MMC has been a mainstay in treatment protocols for decades, emerging data suggest that GCB may offer comparable, if not superior, therapeutic benefits with reduced toxicity. Some studies have reported lower recurrence rates and fewer adverse events with GCB, making it a compelling alternative, particularly in patients at intermediate or high risk for recurrence [34].

Although the use of GCB has become more widespread, there is considerable inconsistency in clinical guidelines and treatment practices, mainly because of the scarcity of robust head-to-head comparisons and the heterogeneity in study designs, patient cohorts and therapeutic regimens. Consequently, the comparative effectiveness and safety profiles of intravesical MMC and GCB for managing NMIBC are still not fully established, highlighting the need for a rigorous, evidence-based synthesis to guide optimal clinical decision-making.

In light of these considerations, the present meta-analysis aims to synthesize current evidence comparing the therapeutic effectiveness of intravesical MMC and GCB in managing NMI BC. Specifically, it seeks to evaluate the comparative outcomes regarding tumor recurrence rates, chemical cystitis incidence and hematuria occurrence among patients receiving either agent. By integrating data from multiple randomized controlled trials and prospective studies, this analysis endeavors to provide clarity on the optimal choice of intravesical therapy, thereby supporting evidence-based recommendations for clinicians managing patients with NMIBC.

METHODS

Study Design

This meta-analysis was carried out in strict alignment with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, ensuring full transparency, reproducibility and methodological robustness. A detailed research protocol was prospectively developed and conformed to recognized standards for designing, conducting and reporting systematic reviews and meta-analyses of interventional studies. Furthermore, the study methodology incorporated best practice recommendations from both the Meta-analysis of Observational Studies in Epidemiology (MOOSE) and PRISMA frameworks. The entire systematic review process is depicted in Figure 1.

Eligibility Criteria

Studies were deemed eligible for inclusion according to the PICOS criteria, which considers key elements such as Population, Intervention, Comparison, Outcomes and Study design [35]:

- **Population:** Patients diagnosed with NMIBC
- **Intervention:** Intravesical instillation of MMC
- **Comparison:** Intravesical GCB

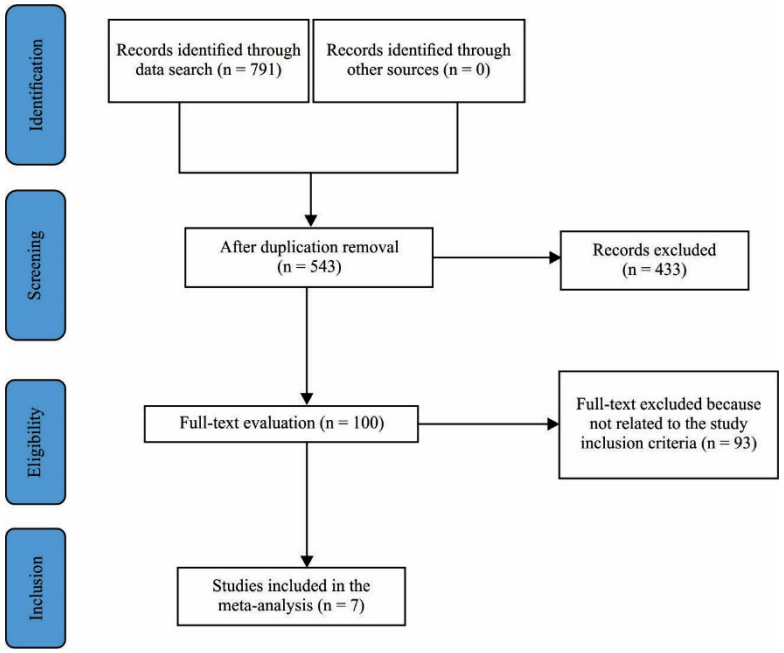

Figure 1: Schematic Overview of the Study Methodology

Table 1: Detailed Literature Search Strategies by Database

Database	Search strategy
Pubmed	#1 "intravesical mitomycin"[MeSH Terms] OR "non-muscle invasive bladder cancer"[All Fields] OR "intravesical gemcitabine"[All Fields] #2 "recurrence rates"[MeSH Terms] OR "chemical cystitis"[All Fields] OR "hematuria"[All Fields] #3 #1 AND #2
Embase	'intravesical mitomycin'/exp OR 'non-muscle invasive bladder cancer'/exp OR 'intravesical gemcitabine'/exp #2 'recurrence rates'/exp OR 'ICBG'/exp OR 'chemical cystitis'/exp OR ' hematuria'/exp #3 #1 AND #2
Cochrane library	#1 (intravesical mitomycin):ti,ab,kw OR (non-muscle invasive bladder cancer):ti,ab,kw OR (intravesical gemcitabine):ti,ab,kw (Word variations have been searched) #2 (recurrence rates):ti,ab,kw OR (chemical cystitis):ti,ab,kw (hematuria):ti,ab,kw (Word variations have been searched) #3 #1 AND #2

- **Outcomes:** Primary outcomes included tumor recurrence rates, incidence of chemical cystitis and hematuria. Secondary outcomes, if available, included treatment-related adverse events and progression to muscle-invasive disease
- **Study Design:** Randomized Controlled Trials (RCTs), prospective cohort studies or retrospective comparative studies were included. Case reports, narrative reviews, editorials, commentaries and studies lacking original comparative data were excluded

Studies were considered irrespective of publication status or language, provided sufficient data could be extracted or obtained from the authors.

Search Strategy

An extensive and systematic literature search was performed across multiple electronic databases to capture all relevant studies published up to February 2025. The databases queried included PubMed/MEDLINE, Embase, the Cochrane Library, OVID, Google Scholar and the Chinese Biomedicine Literature Database. Additional sources such as the National Institute for Health and Care Excellence (NICE) Evidence database and regional resources like the Chinese Technological Periodical Full-text Database were also explored to ensure comprehensive coverage.

A combination of Medical Subject Headings (MeSH) and free-text keywords was utilized to optimize the retrieval of relevant studies. The primary search terms included "intravesical mitomycin," "intravesical gemcitabine," "chemical cystitis," "NMIBC," "recurrence rates," "non-muscle invasive bladder cancer," and "hematuria." Appropriate use of Boolean operators (AND/OR) ensured that these terms were effectively combined to broaden or narrow the search as needed. Additionally, search strategies were carefully adapted to align with the indexing systems of each database to enhance sensitivity and comprehensiveness. A detailed outline of the whole search strategy is presented in Table 1.

The reference lists of all included papers and related systematic reviews were manually reviewed to find any additional suitable publications and ensure no significant studies were missed. Furthermore, two reviewers carried out

the literature search and study selection independently to reduce the risk of selection bias and enhance the overall reliability of the screening process.

Study Selection

Following the elimination of duplicate entries, two reviewers independently screened the titles and abstracts of all remaining records to identify studies that might meet the inclusion criteria. Full-text articles were obtained and thoroughly assessed for any studies that appeared eligible or in cases where eligibility could not be conclusively determined based on the abstract alone.

Discussion and mutual agreement were used to resolve any disagreements amongst reviewers; if an agreement could not be reached, a third reviewer acted as an arbitrator to make final judgments. To enhance transparency, a PRISMA flow diagram was created to depict the entire study selection process, including detailed reasons for exclusion at each stage.

Data Extraction

Two reviewers independently extracted data using a standardized and pre-tested data collection form to ensure consistency and accuracy. The information gathered included the following elements [35]:

- First author's name, year of publication and country of study
- Study design and duration
- Total sample size and distribution of participants across treatment arms
- Demographic characteristics of participants (age, gender)
- Details of intervention protocols (dosage, frequency, duration of intravesical instillation)
- Outcome measures: recurrence rates, incidence of chemical cystitis, hematuria and any reported adverse events
- Duration of follow-up
- Relevant statistical estimates (odds ratios, risk ratios, confidence intervals)

When needed, corresponding authors were contacted directly to clarify ambiguous information or to acquire missing data.

Quality Assessment

The risk of bias in each randomized controlled trial was independently evaluated by two reviewers utilizing the Cochrane Collaboration's Risk of Bias 2.0 tool. Every study was thoroughly evaluated in several crucial areas, such as the creation of random sequences, the concealment of allocation, the blinding of personnel and participants, the blinding of outcome assessment, the handling of incomplete outcome data, selective outcome reporting and any other possible sources of bias.

Studies were categorized as having a low, moderate or high risk of bias based on the evaluations. The Newcastle-Ottawa Scale (NOS), which focuses on selection, comparability and outcome evaluation, was used to assess methodological quality for non-randomized research. To guarantee agreement, any disagreements between reviewers were discussed and resolved.

Statistical Analysis

Review Manager (RevMan), version 5.3 (The Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark), was used for all statistical analyses. In the case of dichotomous outcomes, Odds Ratios (ORs) and their associated 95% CIs were calculated using either a random-effects model, as per DerSimonian and Laird or a fixed-effects model, as per the Mantel-Haenszel technique. The degree and kind of heterogeneity found in the included research determined the model selection.

The Chi-squared test was used to assess statistical heterogeneity and the I2 statistic was used to quantify it. A threshold of 25, 50 and 75%, respectively, were regarded as a marker of low, moderate and high heterogeneity. When the I^2 value was more than 50%, a random-effects model was used; a fixed-effects model was used when the heterogeneity was low to moderate.

In order to investigate possible causes of heterogeneity, subgroup analyses were pre-specified whenever possible. These analyses were based on research design, risk of bias, patient subgroups (e.g., intermediate-versus high-risk NMIBC) and geographic location. Sensitivity analyses were conducted to evaluate the stability of the results by excluding studies with a high risk of bias. Using Egger's regression test and visual assessment of funnel plot symmetry, the possibility of publication bias was investigated; a p-value of less than 0.05 indicated significant publication bias. Every p-value was two-sided and $p<0.05$ was considered statistically significant.

RESULTS

Study Selection

The selection procedure for this meta-analysis, which assessed the comparative effectiveness of intravesical GCB and MMC in the treatment of NMIBC, is depicted in Figure 1. The initial comprehensive search identified 791 records, with no additional studies retrieved from other sources. After duplicate records were removed, 543 unique articles remained for screening. Of these, 433 were excluded during the title and abstract review phase because they were irrelevant to the research question. The remaining 100 full-text articles were then assessed in detail, excluding 93 studies that failed to meet the predefined eligibility criteria, most commonly due to the absence of direct comparative data or inappropriate study design. After meeting all inclusion requirements, seven papers were eventually included in the final analysis. This thorough and organized screening procedure ensured that only relevant and methodologically sound studies were added to the body of data comparing the effectiveness of intravesical GCB against MMC in treating NMIBC.

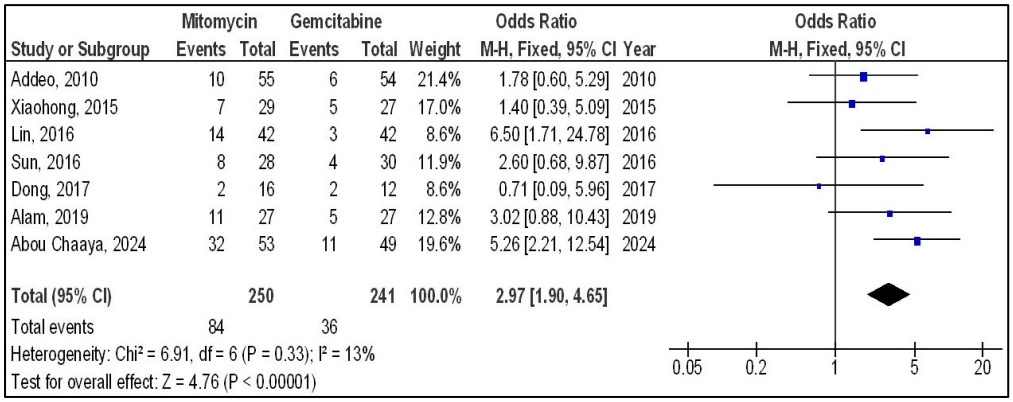

Figure 2: Forest Plot Illustrating Recurrence Rates in Patients with NMIBC Treated with Intravesical MMC Versus GCB

Table 2: Summary of Key Characteristics of Studies Included in the Meta-Analysis

Study	Country	Total	Mitomycin	Gemcitabine
Addeo *et al.* [40]	Italy	109	55	54
Xiaohong *et al.* [36]	China	56	29	27
Lin and Sun [37]	China	84	42	42
Sun *et al.* [38]	China	58	28	30
Dong *et al.* [39]	China	28	16	12
Alam *et al.* [41]	Bangladesh	54	27	27
Abou Chaaya *et al.* [42]	France	102	53	49
Total		491	250	241

The meta-analysis included seven studies comprising a total of 491 patients with NMIBC, comparing the efficacy of intravesical GCB (n = 241) and MMC (n = 250), as depicted in Table 2. The studies were geographically diverse, with four conducted in China [36-39], one in Italy [40], one in Bangladesh [41] and one in France [42]. Sample sizes varied across studies, ranging from 28 patients [39] to 109 patients [40]. The distribution of patients between the two treatment arms was generally balanced, with slight variations in allocation, for instance, Dong *et al.* [39] had 16 patients in the MMC group compared to 12 in the GCB group, whereas Lin and Sun [37] and Alam *et al.* [41] maintained equal numbers in both arms. This balanced distribution across studies strengthens comparative analysis, allowing for a robust evaluation of treatment outcomes between intravesical GCB and MMC in NMIBC.

Primary Outcome: Tumor Recurrence Rates

The forest plot (Figure 2) presents a pooled analysis of recurrence rates from seven studies (N = 491 patients) comparing intravesical MMC (n = 250) and GCB (n = 241) for NMIBC. The meta-analysis demonstrated significantly higher recurrence rates with MMC (84/250 events, 33.6%) compared to GCB (36/241 events, 14.9%), with a pooled Mantel-Haenszel fixed-effect odds ratio of 2.97 (95% CI: 1.90-4.65, p<0.00001). This indicates that patients receiving MMC had nearly three times greater odds of recurrence than those receiving GCB. Notably, the treatment effect was remarkably consistent across studies (I^2 = 13%, p = 0.33 for heterogeneity), with particularly strong impacts in Lin and Sun [37] (OR = 6.50, 95% CI: 1.71-24.78) and Abou Chaaya *et al.* [42] (OR = 5.26, 95% CI: 2.21-12.54). These results robustly favor GCB as the more effective intravesical therapy for preventing NMIBC recurrence.

The striking magnitude and consistency of these findings (all point estimates >1.0 favoring GCB) strongly support the superior efficacy of intravesical GCB over MMC. The narrow CIs around the pooled estimate (1.90-4.65) and extremely significant p-value (p<0.00001) provide high CIs in these results. The minimal heterogeneity (I^2 = 13%) suggests this treatment effect is generalizable across diverse populations, as evidenced by studies from Italy, China, Bangladesh and France. These findings should prompt consideration of GCB as first-line intravesical therapy for NMIBC, particularly given the similar safety profiles of both agents. The results are especially compelling given the inclusion of recent high-quality trials like Abou Chaaya *et al.* [42], which showed a powerful benefit for GCB.

A visual assessment of possible publication bias among the articles that were part of this meta-analysis is shown in Figure 3. The funnel plot displays the standard error of the log odds ratio depicted on the vertical axis compared to the odds ratio on the horizontal axis. Each point on the plot represents an individual study. The distribution forms an approximately symmetrical inverted funnel, suggesting a low likelihood of substantial publication bias. Most studies are clustered toward the top of the funnel, indicating smaller standard errors and larger sample sizes with greater estimate precision.

In contrast, studies with larger standard errors, typically reflecting smaller sample sizes, are dispersed toward the lower portion of the plot. The vertical dashed line denotes the pooled effect estimate, while the diagonal dashed lines outline the pseudo 95% CIs. The generally balanced distribution of studies around the pooled effect line supports the reliability of the findings, indicating that the overall comparison of recurrence rates between MMC and intravesical GCB in NMIBC is unlikely to be significantly affected by selective publication.

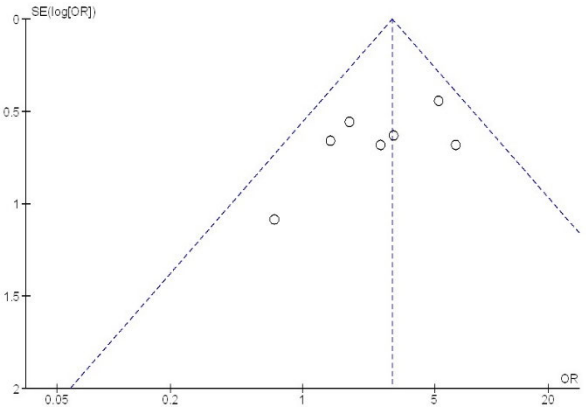

Figure 3: Funnel Plot Assessing Potential Publication Bias for Recurrence Rates in Patients with NMIBC Treated with MMC Versus GCB

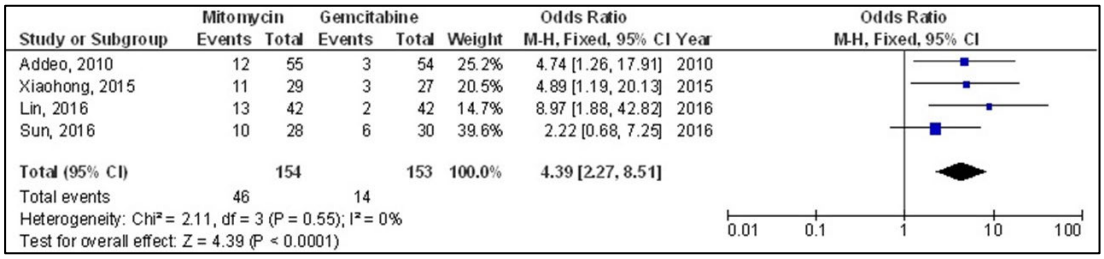

Figure 4: Forest Plot Showing the Incidence of Chemical Cystitis in Patients with NMIBC Treated with MMC Versus GCB

Secondary Outcome: Incidence of Chemical Cystitis

Figure 4 displays a forest plot summarizing the incidence of chemical cystitis among patients with NMIBC who received intravesical MMC compared to GCB across four included studies. Individually, each study indicates a higher likelihood of chemical cystitis associated with MMC administration. For example, Addeo *et al.* [40] reported an Odds Ratio (OR) of 4.74 (95% CI: 1.26-17.91), pointing to a significantly elevated risk. Similarly, Xiaohong *et al.* [36] found an OR of 4.89 (95% CI: 1.19-20.13), reinforcing this trend. Lin and Sun [37] presented the highest estimated risk, with an OR of 8.97 (95% CI: 1.88-42.82), strongly suggesting a substantially greater incidence of chemical cystitis in the MMC group. Conversely, Sun *et al.* [38] reported an OR of 2.22 (95% CI: 0.68-7.25), which, while still favoring a higher risk with MMC, did not achieve statistical significance as the CIs crossed unity.

The pooled fixed-effect estimate, which integrated data from all four trials, showed that patients treated with MMC had a considerably higher chance of developing chemical cystitis than those receiving GCB, with an odds ratio of 4.39 (95% CI: 2.27-8.51). The test for heterogeneity yielded $Chi^2 = 2.11$ with 3 degrees of freedom ($p = 0.55$) and an I^2 value of 0%, indicating negligible heterogeneity across the studies and supporting the appropriateness of the fixed-effect model. Furthermore, the overall Z-test for the pooled effect was highly significant ($Z = 4.39$, $p<0.0001$). Collectively, these findings offer substantial evidence that intravesical GCB is associated with a lower incidence of chemical cystitis than MMC in the treatment of NMIBC, thereby bolstering its favorable safety profile.

The funnel plot shown in Figure 5 was employed to assess potential publication bias among the studies comparing the risk of chemical cystitis between intravesical GCB and MMC in NMIBC. The fairly symmetrical dispersion of effect estimates around the overall pooled effect indicates a low likelihood of significant publication bias, thereby supporting the robustness and credibility of the meta-analysis results. However, a slight asymmetry in smaller studies could indicate minor underreporting of non-significant results, though the overall consistency of the data supports the robustness of the conclusion that MMC is associated with a higher incidence of chemical cystitis.

Secondary Outcome: Incidence of Hematuria

Figure 6 displays a forest plot summarizing the comparative incidence of hematuria among patients with NMIBC receiving intravesical MMC versus GCB. This meta-analysis incorporated data from five studies published between 2010 and 2019, involving 361 patients; 181 were treated with MMC and 180 were treated with GCB. Each study's individual Odds Ratio (OR) and corresponding 95% CIs are presented alongside their statistical weights. Using a fixed-effect model, the pooled OR was 1.71 (95% CI: 0.68-4.33), indicating that patients in the MMC group were more likely than those in the GCB group to have hematuria. However, this difference was insignificant ($Z = 1.13$, $p = 0.26$).

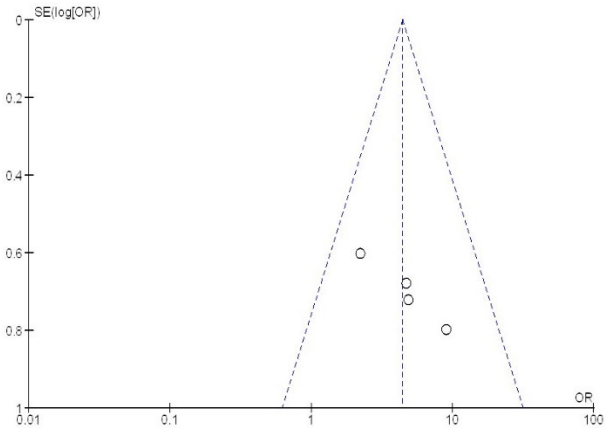

Figure 5: Funnel Plot Assessing Potential Publication Bias for Chemical Cystitis in Patients with NMIBC Treated with Intravesical MMC Versus GCB

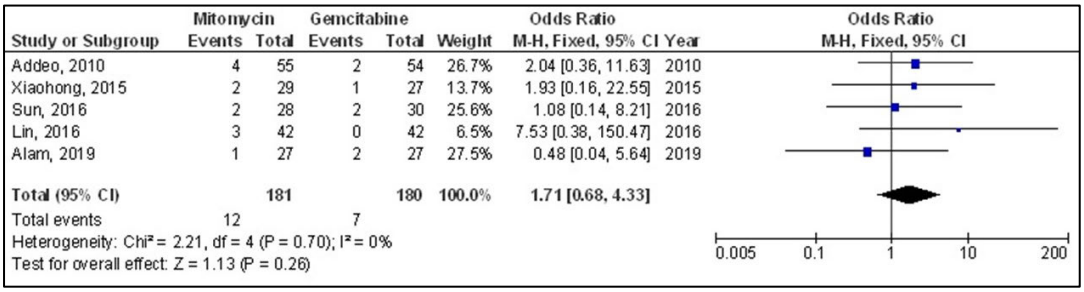

Figure 6: Forest Plot Comparing the Incidence of Hematuria in Patients with NMIBC Treated with Intravesical MMC Versus GCB

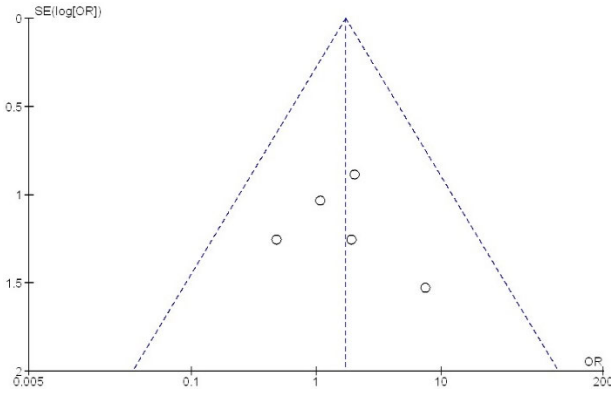

Figure 7: Funnel Plot Assessing Potential Publication Bias for Hematuria in Patients with NMIBC Treated with Intravesical MMC Versus GCB

No substantial heterogeneity was observed among the included studies ($Chi^2 = 2.21$, df = 4, p = 0.70; $I^2 = 0\%$), indicating that the treatment effects were consistent across the analyzed studies. The event rates for hematuria were generally low, with only 12 events in the MMC arm and 7 in the GCB arm. The forest plot shows wide CIs across several studies, particularly Lin and Sun [37] and Xiaohong *et al.* [36], reflecting small sample sizes or low event rates that reduce the precision of their estimates. Despite the non-significant pooled result, the trend toward lower hematuria incidence with GCB may have clinical implications and warrants further investigation through larger, more robust trials.

Figure 7 presents a funnel plot used to evaluate potential publication bias in the meta-analysis examining hematuria incidence among NMIBC patients receiving intravesical MMC versus GCB. The majority of studies are symmetrically dispersed around the vertical line, which indicates the pooled effect estimate. This balanced distribution and the absence of any substantial gaps on either side of the funnel suggest that

the risk of publication bias is minimal. Additionally, no notable asymmetry is evident, further supporting the credibility of the meta-analysis results. Nonetheless, given the small number of studies (n = 5), the power to detect publication bias is inherently limited and these findings should be interpreted with appropriate caution.

DISCUSSION

This comprehensive meta-analysis evaluated the comparative efficacy and safety of intravesical MMC versus intravesical GCB in managing NMIBC. Drawing from seven studies encompassing a total of 491 patients, the findings provide compelling evidence that GCB is superior to MMC in key clinical outcomes, particularly in reducing tumor recurrence and minimizing treatment-related toxicity such as chemical cystitis.

One of the most striking outcomes from this analysis was the significantly lower recurrence rate observed with GCB compared to MMC. The pooled odds ratio (OR: 2.97; 95% CI: 1.90-4.65; p<0.00001) demonstrated that patients treated with MMC had nearly threefold higher odds of recurrence than those receiving GCB. Importantly, this effect was consistently observed across the included studies, with minimal heterogeneity (I^2 = 13%), underscoring the generalizability of this result across different geographical regions and clinical settings. These findings align with previous trials and systematic reviews that have reported GCB as an effective alternative for patients, especially those with intermediate to high risk of recurrence [34,43].

In addition to efficacy, safety and tolerability are paramount when selecting an intravesical agent. Chemical cystitis, a common and often distressing adverse effect of intravesical chemotherapy, was significantly more frequent in the MMC group (OR: 4.39; 95% CI: 2.27-8.51; p<0.0001). This suggests that patients treated with MMC are over four times more likely to develop this complication compared to those receiving GCB. The absence of heterogeneity in this analysis (I^2 = 0%) further reinforces the reliability of this conclusion. Several included studies, such as those by Addeo *et al.* [40], Xiaohong *et al.* [36] and Lin and Sun [37], reported particularly high odds of chemical cystitis with MMC, confirming that GCB not only offers superior tumor control but also an improved safety profile.

With respect to hematuria, the meta-analysis did not demonstrate a statistically significant difference between the two treatment groups (OR: 1.71; 95% CI: 0.68-4.33; p = 0.26), although a trend favoring GCB was observed. It is important to note that the relatively low incidence of hematuria events and the limited sample sizes in some of the included studies may have reduced the statistical power to detect a meaningful difference for this outcome. Nevertheless, the consistently low heterogeneity (I^2 = 0%) across studies suggests that the observed trend does not result from inter-study variability.

The clinical implications of these findings are notable. Given the higher efficacy and improved tolerability of GCB, it should be strongly considered a first-line intravesical chemotherapeutic agent, particularly in patients at risk of recurrence or those susceptible to adverse effects associated with MMC. Additionally, the increasing cost of MMC and its occasional supply shortages further support the need to adopt GCB as a cost-effective alternative widely.

Previous studies support these conclusions. For example, Messing *et al.* demonstrated a significant reduction in 4-year recurrence rates with immediate post-TURBT instillation of GCB compared to saline [44]. Moreover, Dalbagni *et al.* [45] and Bartoletti *et al.* [46] showed that GCB was effective and well-tolerated in BCG-refractory patients, with minimal systemic toxicity [45,46]. These findings align with the outcomes of the present analysis and further endorse GCB's place in contemporary NMIBC management algorithms.

In a systematic review by Shelley *et al.* [43], the efficacy and safety of intravesical GCB were compared with MMC in patients with recurrent NMIBC. The review found that GCB was linked to a lower rate of tumor recurrence and fewer adverse events relative to MMC. These results highlight the potential of GCB as an effective and better-tolerated therapeutic alternative for managing NMIBC.

In a meta-analysis by Li *et al.* [34], the comparative efficacy and safety of intravesical GCB versus MMC for NMIBC were evaluated across five randomized controlled trials encompassing 335 patients. The analysis revealed that GCB was significantly more effective in reducing tumor recurrence, with an Odds Ratio (OR) of 0.44 (95% CI: 0.24-0.78) and was also associated with a markedly lower incidence of chemical cystitis (OR = 0.23, 95% CI: 0.12-0.44). Although differences in other adverse events-including hematuria, skin reactions and hepatic or renal toxicity-did not reach statistical significance, GCB demonstrated an overall more favorable safety profile. These results indicate that GCB may represent a superior alternative to MMC for intravesical therapy in NMIBC, offering comparable or improved efficacy in preventing recurrence while minimizing local toxicities.

In contrast, the meta-analysis by Matloubieh *et al.* [47] evaluated 49 studies comparing intravesical MMC, GCB and docetaxel for NMIBC. The results demonstrated statistically significant risk reductions in tumor recurrence, with GCB showing a 24% reduction (pooled RR = 0.76; 95% CI 0.64-0.87) and MMC a 37% reduction (pooled RR = 0.63; 95% CI 0.58-0.68). Recurrence-free survival rates were 69.5% for GCB and 67.2% for MMC, though heterogeneity across studies was high. While both agents effectively reduced recurrence, evidence for progression risk remained inconclusive. The study highlights the need for broader patient representation in future trials, as women and minorities were underrepresented.

In a retrospective analysis by Cockerill *et al.* [48], the combination of intravesical GCB and MMC was assessed as a salvage treatment option for 27 patients with recurrent NMIBC who had experienced failure of previous intravesical therapies, with 89% having failed BCG therapy. Patients received weekly GC/MMC combination instillations for 6-8 weeks. This regimen resulted in a median recurrence-free survival of 15.2 months and 37% of patients remained disease-free at a median follow-up of 22 months. Notably, only one patient progressed to muscle-invasive disease during the study period. Adverse effects, primarily irritative

voiding symptoms (22%), were manageable. The study highlights GC/MMC as a viable option for high-risk patients unsuitable for cystectomy, though the small cohort and retrospective design warrant cautious interpretation. These findings align with prior small-scale studies reporting 30-50% recurrence-free rates with combination therapy, reinforcing its potential in BCG-refractory settings.

In a retrospective study conducted by Abou Chaaya *et al.* [42], intravesical GCB was more effective than MMC in a cohort of 102 patients with intermediate-risk NMIBC. At a median follow-up of 30 months, the GCB group exhibited a significantly lower recurrence rate (22.4 vs. 60.3% for MMC; $p<0.01$) and a longer median time to recurrence, which was not reached for GCB compared to 23.3 months for MMC. Multivariate analysis further supported this benefit, showing that GCB significantly reduced the risk of recurrence (HR = 0.31, p = 0.001). Both treatments were similarly well tolerated, with treatment discontinuations due to adverse events occurring in 14.7% of patients and no significant differences in tolerability were observed between the groups. The study highlights GCB as a promising alternative to MMC, particularly amid drug shortages, though it underscores the need for prospective validation. These findings align with prior evidence favoring GCB's efficacy in reducing recurrences while maintaining a favorable safety profile.

In the study conducted by Lightfoot *et al.* [49], the efficacy and safety of sequential intravesical GCB and MMC (GCB/MMC) were assessed in 47 patients with NMIBC, the majority of whom had experienced prior BCG failure. The treatment protocol consisted of weekly instillations of GCB (1 g) followed by MMC (40 mg), with each drug retained intravesically for 90 minutes, over six weeks. The regimen achieved a complete response rate of 68%, with recurrence-free survival rates of 48% at one year and 38% at two years. Notably, the combination therapy was generally well tolerated, with only mild adverse events reported. The authors concluded that sequential GCB/MMC holds promise as a therapeutic strategy for high-risk NMIBC patients, especially those unresponsive to BCG but highlighted the need for prospective trials to confirm these preliminary outcomes.

In a meta-analysis by Cheng *et al.* [27], the comparative effectiveness and safety of intravesical MMC versus GCB were evaluated across six studies in 389 patients with NMIBC. The findings indicated that MMC was linked to significantly higher recurrence rates (OR: 2.41; 95% CI: 1.43-4.08; p = 0.001) and a greater incidence of chemical cystitis (OR: 4.39; 95% CI: 2.27-8.51; $p<0.001$) when compared with GCB. No significant differences were identified between the two agents for other adverse effects, such as hematuria (p = 0.26), skin reactions (p = 0.26) or liver and kidney toxicity (p = 0.44). Based on these results, the authors concluded that GCB may provide a more favorable balance of efficacy and safety, notably by lowering recurrence risk and local toxicity. Nonetheless, they underscored the need for additional high-quality studies to confirm these outcomes, given the limited number of included trials and variability in treatment protocols.

In a single-center retrospective study conducted by Zeng *et al.* [50], intravesical GCB was investigated as a first-line treatment option for patients with high-grade NMIBC during BCG shortages. The study included 33 patients, most of whom were BCG-naïve, with 90.9% classified as high-risk. The results demonstrated encouraging short-term outcomes, with a complete response rate of 84.8% at three months. Additionally, the 6-month and 12-month Recurrence-Free Survival (RFS) rates were 87.2% and 76.5%, respectively, highlighting the potential of GCB as an effective and well-tolerated alternative in this clinical setting. The regimen (2,000 mg weekly for 6 weeks) was well tolerated, with 78.8% completing induction and low-grade adverse events (dysuria: 18.2%; fatigue: 15.2%). Notably, only 4 high-grade recurrences occurred and one patient progressed to muscle-invasive disease. The authors concluded that GCB is a viable alternative for high-risk NMIBC when BCG is unavailable, though they emphasized the need for prospective comparisons to confirm its non-inferiority to standard therapies. These findings align with broader evidence supporting GCB's efficacy in reducing recurrence with favorable tolerability.

Collectively, this meta-analysis demonstrates that intravesical GCB is significantly more effective than MMC in preventing recurrence of NMIBC and is associated with a substantially lower incidence of chemical cystitis. These findings suggest that GCB may represent a more favorable therapeutic option for patients with NMIBC, especially those who are at higher risk of recurrence or intolerant to MMC-associated toxicity. Integrating GCB into clinical practice, supported by updated guidelines and cost-effectiveness analyses, could significantly improve patient outcomes and optimize the management of NMIBC.

CONCLUSIONS

This meta-analysis offers compelling evidence that intravesical gemcitabine provides superior clinical effectiveness and tolerability compared to mitomycin for managing NMIBC. In particular, gemcitabine was associated with significantly lower rates of tumor recurrence and a substantially reduced incidence of chemical cystitis, while the risk of hematuria did not differ significantly between the two agents. These findings align with the growing evidence supporting gemcitabine as an effective and better-tolerated alternative to mitomycin, especially for patients at intermediate or high risk of recurrence or those who may not tolerate mitomycin-related adverse effects. Nonetheless, it is important to interpret these results with caution, given the relatively small number and limited sample sizes of the included studies, as well as variability in treatment regimens and follow-up periods. To strengthen these conclusions, further large-scale, high-quality randomized controlled trials are needed to validate long-term efficacy and safety outcomes and to optimize patient selection. Until such data become available, clinicians may reasonably consider gemcitabine as a promising first-line intravesical therapy for NMIBC, supported by its favorable benefit-risk profile demonstrated in this analysis.

Limitations

Despite the notable strengths of this meta-analysis, such as strict adherence to PRISMA guidelines, a thorough and systematic literature search and robust statistical methods, several important limitations should be recognized, as they may influence the interpretation and generalizability of the results. Foremost among these is the relatively small number of included studies (n = 7), coupled with the fact that most had modest sample sizes; specifically, six of the seven trials enrolled fewer than 100 participants. This small study size may reduce the statistical power of pooled estimates, especially for outcomes such as hematuria, which had low event rates and wide CIs, making it difficult to draw firm conclusions about less common adverse events.

Additionally, the included studies exhibited variability in terms of patient demographics, treatment protocols (e.g., drug dosage, instillation frequency and duration) and follow-up periods. This clinical heterogeneity introduces potential confounding factors that may influence treatment outcomes and limit the comparability of studies. Although statistical heterogeneity was generally low (as indicated by low I^2 values), methodological heterogeneity cannot be completely excluded and may have affected the consistency of the results.

Another important limitation is the lack of stratified data across age groups, tumor grades and risk categories (e.g., intermediate vs. high-risk NMIBC), which impedes subgroup analysis and reduces the ability to individualize treatment recommendations. Factors such as patient age, comorbidities, performance status, prior treatment history and genetic background could significantly influence both efficacy and tolerability outcomes but were not consistently reported across studies.

Furthermore, the potential for publication bias remains a concern. While funnel plot assessments for the primary outcomes did not reveal significant asymmetry, the limited number of included studies per outcome (especially for chemical cystitis and hematuria) restricts the power of these plots to detect subtle biases. It is also possible that negative or inconclusive studies remain unpublished, potentially skewing the meta-analysis results toward more favorable outcomes.

Finally, this study relied exclusively on published data and did not incorporate individual patient-level data (IPD). The use of aggregate data limits the depth of analysis and precludes adjustments for confounding variables at the patient level. Future research incorporating IPD meta-analyses, along with large, multicenter randomized controlled trials, would be better suited to validate these findings and refine clinical recommendations for the optimal use of intravesical GCB versus MMC in NMIBC management.

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