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UROONCOLOGY
Systematic Review

Chemoresection by mitomycin C compared to transurethral resection of bladder tumor in patients with recurrent nonmuscle-invasive bladder cancer: A systematic review and meta-analysis

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ABSTRACT

Some studies suggest that chemoresection with mitomycin C (MMC) is comparable to transurethral resection of bladder tumor (TURBT) in the management of recurrent nonmuscle-invasive bladder cancer (NMIBC). In this meta-analysis, we compared the efficacy and safety of MMC and TURBT in recurrent NMIBC. A search was conducted for studies published in English in the electronic databases of MEDLINE/PubMed, the Cochrane Library, Scopus, Web of Science, Google Scholar, ProQuest, System for information on Grey Literature, and ClinicalTrials.gov, with no publication date restrictions. Risk of bias was assessed using the Risk of bias 2 tool for randomized controlled trials and Risk of Bias in Non-Randomized Studies of Interventions-I tool for observational studies. Data analysis was performed using the RevMan 5.4 software. Three studies were included in this systematic review (total participants is 291); two studies were included in the meta-analysis. The rate of complete response was significantly lower in MMC group compared with TURBT (relative risk [RR]: 0.55, 95% confidence interval (CI): 0.45-0.67, $P < .001$). The rates of local adverse events were lower in MMC, with a statistical significance for dysuria (RR: 0.55, 95% CI: 0.36-0.84, $P = .006$), urinary frequency (RR: 0.60, 95% CI: 0.43-0.84, $P = .003$), cystitis (RR: 0.22, 95% CI: 0.06-0.81, $P = .02$), and incontinence (RR: 0.48, 95% CI: 0.24-0.96, $P = .04$). In terms of complete response, TURBT is superior to chemoresection with MMC. Currently, chemoresection with MMC should be restricted to patients unfit for surgery and in clinical trials. Future randomized controlled trials are recommended to confirm or refute the use of MMC in treating recurrent NMIBC.

Keywords: Meta-analysis; mitomycin; urinary bladder neoplasms.

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Introduction

Globally, cancer in the urinary bladder (commonly referred to as bladder cancer) ranks the 10th most common cancer, with an estimated 549,000 new cases and 200,000 deaths in 2018.[1] Approximately 75-85% of bladder cancer patients present with nonmuscle invasive bladder cancer (NMIBC).[2] The prognosis of NMIBC is usually good. However, the rate of recurrence of NMIBC is considered high, as recurrence is diagnosed in 30-80% of patients.[3]

The European Organization for Research and Treatment of Cancer (EORTC) stratifies the risk of recurrence in patients with NMIBC into three categories (low, intermediate, and high), according to the tumor multiplicity, size, staging, presence of carcinoma in situ, and grade. The recurrence rates are 30%, 46-63%, and 78% for low-, intermediate-, and high-risk patients, respectively. This high recurrence rate has warranted strict follow-up of NMIBC patients after the treatment of the primary tumor, in order to identify recurrences early and initiate treatment before the progression of cancer.[4]

Management of recurrent NMIBC is usually achieved with transurethral resection of the bladder tumor (TURBT) followed by adjuvant intracavitary instillation of mitomycin C (MMC) or Bacille Calmette-Guérin (BCG).[4]

Another promising approach for the treatment of recurrences is the administration of short-term, intensive intracavitary chemotherapy (known as chemoresection or chemoablation). Chemoresection can avoid exposing the patients to complications of surgery, which is particularly valuable in elderly patients with comorbidities and those who are unfit for surgery. Few studies have described the efficacy and safety of chemoresection in recurrent NMIBC.[5-10]

The aim of this systematic review and meta-analysis was to assess the efficacy and safety of chemoresection using MMC compared with TURBT in patients with recurrent NMIBC.

Methods

Ethical Considerations

The ethical approval and informed consents were waived since the primary studies we are reporting herein had already obtained such approvals and consents.

Criteria for Considering Studies for this Review

Types of Studies

Both observational (cohort and case control) studies and clinical trials were included in this systematic review and meta-analysis. The search was limited to studies published in English, but no filter was used regarding the publication date.

Types of Participants

Eligible studies included adult patients previously diagnosed with NMIBC who had recurrence.

Types of Interventions

The experimental intervention was considered as chemoresection with an MMC administration compared with TURBT (with or without adjuvant chemotherapy).

Types of Outcome Measures

Primary outcome: The primary outcome was the rate of response to chemoresection. It was defined as the absence of bladder tumor by visual assessment, biopsy, or both at the first follow-up examination within 3 months after the completion of the planned neoadjuvant MMC regimen.

Secondary outcomes: Secondary outcomes included the time to recurrence, the rate of subsequent TURBT, and locoregional adverse effects. The adverse effects included dysuria, urinary frequency, cystitis, hematuria, and incontinence.

Main Points

- Efficacy of chemoresection with mitomycin C (MMC) in patients with recurrent nonmuscle-invasive bladder cancer (NMIBC) is inferior to transurethral resection of bladder tumor (TURBT).
- Chemoresection with MMC has lower rates of adverse effects than TURBT, but the evidence for its safety is inconclusive.
- Chemoresection with MMC in patients with recurrent NMIBC should be restricted to those who are unfit to undergo TURBT until further evidence is produced.

Exclusion Criteria

The publications excluded from the systematic review and meta-analysis were studies available only as abstracts or conference posters, duplicate reports, review articles, editorials, and clinical guidelines.

Search Methods for the Identification of Studies

Electronic Searches

This systematic review as well as meta-analysis was conducted according to the principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions, version 6. This review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[11]

The included studies were identified by searching the electronic databases of MEDLINE/PubMed, Cochrane library, Scopus, Web of Science, Google Scholar, ProQuest, System for information on Grey Literature, and ClinicalTrials.gov. No filters were used regarding the publication date of the studies. The search was conducted for articles published in English language. The literature search of the electronic databases was conducted during the period from the September 8, 2020 to October 8, 2020.

A search strategy was developed with the following search terms: {Chemoresection} AND {Mitomycin C} AND {NMIBC} or {Chemoablation} AND {Mitomycin C} AND {NMIBC}. The results of the search are summarized in Appendix 1.

Searching Other Resources

The reference lists of the identified studies and relevant systematic reviews were manually searched for potentially relevant eligible studies.

Data Collection and Analysis

The outcomes of the studied interventions were compared with each other. Some data were not available for comparisons.

Selection of Studies

Two independent reviewers have conducted the research and screened titles and abstracts. The abstracts that were considered

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by one or both reviewers to be potentially relevant were selected for the retrieval of their full text articles. All retrieved full articles were independently reviewed by both reviewers for the assessment of their relevance and conformance to eligibility criteria.

Data Extraction and Management

Relevant data were extracted from the included studies by two independent reviewers. A standardized excel sheet was developed to extract the data independently. The data extraction sheet included: (a) the study characteristics (the country, institution, study design, dates of patient recruitment start and end, and the sample size); (b) patients' characteristics (age, stage of cancer, and follow-up duration); (c) the intervention (MMC dose and duration of treatment); and (d) the outcomes (response to chemoresection, time to recurrence {disease-free-survival}, the rate of subsequent TURBT, and adverse effects). The collected data were revised to ensure consistency and clarity. Disagreements between the two reviewers were resolved by discussion or by consulting the third reviewer.

Assessment of Risk of Bias in Included Studies

The risk of bias was assessed for each included study by two independent reviewers using the Risk of bias 2 tool for randomized controlled trials and the Risk of Bias in Non-Randomized Studies of Interventions tool for observational cohort studies.

Statistical Analysis

Statistical analysis was conducted using the Review Manager (RevMan Version 5.4. The Cochrane Collaboration, 2020). All categorical dichotomous outcomes (including response to treatment, recurrence, and adverse effects) for each included study were summarized as relative risk (RR) along with their corresponding 95% confidence interval (CI). The data from all included studies were tested for heterogeneity using the Cochran chi square heterogeneity test and I^2 index. A Cochran chi square test with a P value of $<.1$ and an I^2 index $\geq 50\%$ were considered significant and indicated heterogeneity across the studies. We planned to explore reasons for heterogeneity across studies by subgroup analysis. The extracted data were then pooled using the fixed-effect model as heterogeneity was found to be nonsignificant.[12] A P value of $<.05$ was adopted for interpreting statistical significance of outcome comparisons.

Results

Results of the Search

The literature search yielded a total of 221 articles. The titles and abstracts of 158 articles were screened after the removal of duplicates, with subsequent exclusion of 180 articles, which were not relevant to the research question of the systematic review. The full text of the remaining eight articles was retrieved and assessed for eligibility. Out of the examined eight full-text articles, three studies (including 291 patients) were eligible for inclusion (Figure 1).[8-10]

Assessment of Risk of Bias in the Included Studies

The three included studies were assessed for the risk of bias (Figure 2). Selection bias was low in two studies,[8,9] which reported the use of random sequence generation. The risk of allocation concealment was low in the study by Lindgren et al.[8] but high in the study by Mostafid et al.[9] The blinding of participants was performed in the studies by Lindgren et al.[8] and Mostafid et al.,[9] but blinding of the staff taking part in the studies or outcome assessors was not reported. Hence, the risk of performance bias was high. The risk of incomplete reporting of outcomes (particularly recurrence and adverse events) and selective reporting was high in the study by Lindgren et al.[8] Overall, the included studies showed a high risk of bias in the domains of allocation concealment and blinding (Figure 3).

Basic Characteristics of the Included Studies

The basic characteristics of the included studies are summarized in Tables 1 and 2. The three studies included patients with NMIBC from 2007 to 2019. Two studies were randomized controlled in design,[8,9] and one study was a prospective non-randomized study.[10] The first study was carried out in a single-center in Italy[10]; the second study was conducted in two centers in Denmark[8]; and the last study was a multicenter in the United Kingdom.[9] The inclusion and exclusion criteria varied slightly among the studies as well as the duration of follow-up after the interventions. The dose and schedule of MMC was the same in the studies by Lindgren et al.[8] and Racioppi et al.[10] The frequency and duration of MMC administration in the intervention group were different in the study by Mostafid et al.[9] Male patients constituted a higher percentage than females in the three studies. The stage and grade of bladder cancer varied, where Racioppi et al.[10] included stages Ta and T1 with a low-grade NIMBIC, Lindgren et al.[8] included only Ta NIMBIC patients with low or high grade, and Mostafid et al.[9] included patients with low-grade Ta stage.

Results of Effectiveness of the Included Studies

Complete Response to Treatment

The three included studies reported the rates of complete response to treatment. Racioppi et al.[10] reported a slightly lower rate of complete response in the MMC group compared with TURBT group (72.3% vs 78.7%; $P = .47$). Lindgreen et al.[8] and Mostafid et al.[9] found a much lower rate of complete

response in MMC (56.9% vs 100% and 37% vs 75%, respectively).

Mata-analysis was performed for the studies of Lindgreen et al.[8] and Mostafid et al.[9] The study of Racioppi et al.[10] was not included in all statistical analyses due to the different study design, which may introduce heterogeneity into the results. There was mild heterogeneity among the results of the studies ($P = .53$, $I^2 = 0\%$), so the fixed effects model was used for pooling of estimates. The rate of complete response was significantly lower in the MMC group compared with the control group (RR: 0.55, 95% CI: 0.45-0.67, $P < .001$), as shown in Figure 4.

Local Recurrence

Local recurrence was reported only by two studies.[9,10] Racioppi et al.[10] reported a rate of local recurrence at 27 months post-treatment of approximately 10.6% in MMC group and 8.5% in TURBT group, with the Kaplan–Mayer survival analysis showing no significant difference in the overall cancer-free survival between the two groups ($P > .05$). On the other hand, Mostafid et al.[9] found a lower rate of local recurrence in MMC compared with TURBT group, with 16 patients (30%) in the MMC group and 11 (39%) patients in the TURBT group having at least one NMIBC recurrence. They reported that this difference did not reach statistical significance. No meta-analysis was done for local recurrence.

Results of Safety of the Included Studies

Racioppi et al.[10] reported that local toxicities were observed in 27.6% in the MMC group and 21.3% in the TURBT group ($P = .32$) and resolved upon treatment of symptoms. On the other hand, Lindgreen et al.[8] reported the absence of The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) grade 4 adverse events, while two

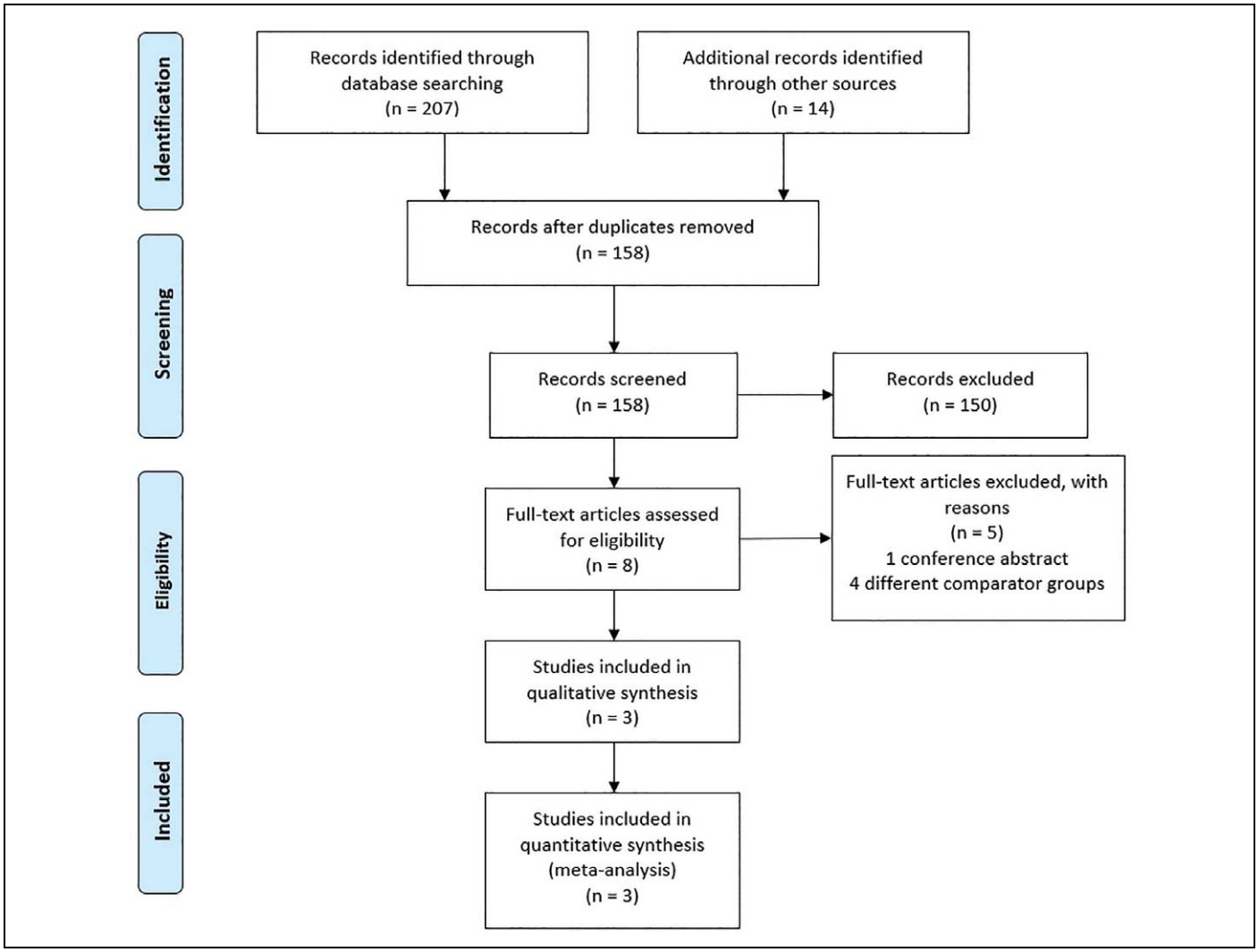

Figure 1. PRISMA flow diagram

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patients had grade 3 cystitis. They found significantly higher CTCAE scores in the TURBT group compared with the MMC group regarding dysuria ($P = .03$), frequency ($P = .01$), and incontinence ($P = .046$). Mostafid et al.[9] reported the absence of CTCAE grade 3-4 adverse events, while grade 2 adverse events were reported in 14/81 patients (17%) and a worst grade of 1 in 29/81 patients (36%). There were no significant differences between the two groups.

Mata-analysis was performed for the studies of Lindgreen et al.[8] and Mostafid et al.[9] Analysis of the point estimates for the reported adverse effects on the urinary tract showed mild heterogeneity ($P > .1$ and $I^2 = 0\text{-}11\%$). Consequently, the fixed-effect model was used for analysis of the pooled estimates for these adverse events. In all adverse events, the rates in MMC group were lower than those in the TURBT group, as indicated by overall RR less than 1 (Figure 5). These differences were statistically significant for dysuria (RR: 0.55, 95% CI: 0.36-0.84, $P = .006$), urinary frequency (RR: 0.60, 95% CI: 0.43-0.84, $P = .003$), cystitis (RR: 0.22, 95% CI: 0.06-0.81, $P = .02$), and incontinence (RR: 0.48, 95% CI: 0.24-0.96, $P = .04$). However, these results were not statistically significant in the case of hematuria (RR: 0.52, 95% CI: 0.25-1.05, $P = .07$).

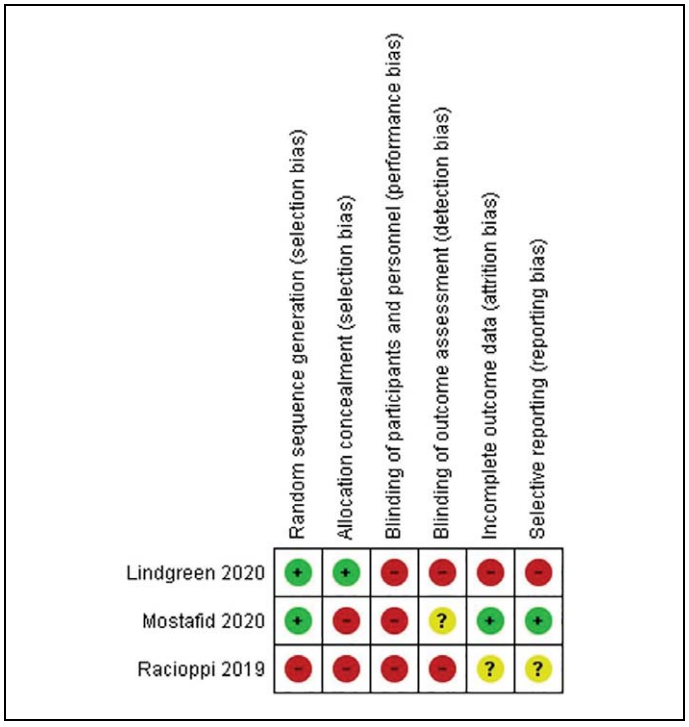

Figure 2. Risk of bias summary of the included studies

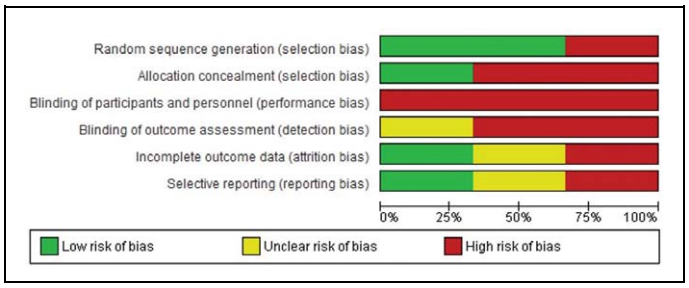

Figure 3. Risk of bias graph of the included studies

Discussion

Summary of Main Results

This meta-analysis was conducted to synthesize the existing evidence considering the management of recurrent NMIBC using either chemoresection by MMC or surgical treatment by TURBT.

After literature searching, we identified three studies that fulfilled the inclusion criteria of this meta-analysis.[8-10] Other studies have assessed the use of MMC for chemoresection, but they did not include a comparative group for patients who underwent TURBT.

There were some variations in the inclusion criteria of the studies included in this meta-analysis, particularly as regards the grading or risk category of patients. Racioppi et al.[10] studied patients with low-grade recurrences only following the management of primary NMIBC of Ta or T1 stage. Lindgren et al.[8] included patients having primary NMIBC of Ta stage with low or high grade. Mostafid et al.[9] assessed patients with low grade, stage Ta NIMBIC. Moreover, there were some variations in the TURBT groups across the studies as regards the use and duration of adjuvant chemotherapy or BCG. The studies by Racioppi et al.[10] and Lindgren et al.[8] utilized the same dose and duration of neoadjuvant MMC (40 mg three-times-a-week for 2 weeks), while Mostafid et al.[9] administered neoadjuvant MMC for a longer duration (40 mg for 4 weeks). These variations are expected to contribute to the heterogeneity of results across the studies, particularly those of complete response.

The basis for choosing the regimen of MMC in these studies was not explained. However, it is known that the cytotoxic effect of alkylating agents is enhanced in cells undergoing mitosis. Therefore, the cytotoxic effect of these agents is expected to maximize if repeated doses are scheduled close to the duplication time for tumor cells. Rapidly proliferating tumor cells—such as the case in transitional cell tumors—are more prone to the cell-killing effects of alkylating agents. in vitro studies showed that RT4 and RT112 transitional cell lines that simulate human NMIBC had a duplication time of 56

Table 1. Basic Characteristics of the Included Studies

Study	Year of publication	Study type	Times of patient recruitment	Country in which the study was conducted	Centers	Inclusion criteria	Exclusion criteria	Follow-up (months)
Racioppi et al.[10]	2019	Prospective nonrandomized study	March 2007 to January 2013	Italy	Single center	Age: 18-80 years, history of low- to intermediate-risk NMIBC, long recurrence-free intervals, endoscopic evidence of recurrence, and Eastern Cooperative Oncology Group performance status of 0–1	Known allergy to MMC, history of HG NMBIC, lower UT strictures with urodynamic alterations, residual urine volume >100 mL, bladder capacity <150 mL, urothelial bladder carcinoma involving urethra or upper UT, urinary incontinence, previous pelvic RT or systemic CT, known immunodeficiency, active or uncontrolled UT infections, kidney, liver or hematological disorders, coexistence of another 1 year malignant tumor, patients who could not be followed up properly or were unable to collaborate, pregnant or lactating women, and intravesical chemoimmunotherapy during the previous 12 months	39
Lindgren et al.[8]	2020	RCT	January 2018 to June 2019	Denmark	Two centers	History of stage Ta LG or Hg NMIBC, recurrence with >1 tumor. Papillary tumors with a diameter of up to 2 cm were included	BCG treatment within the past 24 months, previous treatment with MMC (except single shot), suspicion of CIS or invasive/solid tumor, incontinence, acute cystitis, pregnancy, or breast feeding	3
Mostafid et al.[9]	2020	RCT	February 2015 to August 2017	United Kingdom	Multicentre	Patients > 16 years, history of low-risk NMIBC with recurrence, with an EORTC risk of recurrence score ≤ 6, with no history of HG/≥T1 or nonurothelial bladder cancer	Patients with prior treatment of the recurrence or contraindication to trial treatment	Median (IQR) = 24 (15-29)

RCT, randomized controlled trial; NMIBC, nonmuscle invasive bladder cancer; MMC, mitomycin C; CIS, carcinoma in situ; CT, chemotherapy; HG, high grade; LG, low grade; RT, radiotherapy; UT, urinary tract; IQR, interquartile range.

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± 3 hours and 59 ± 2 hours.[13,14] Consequently, a regimen of repeated MMC instillations every 48-72 hours seems optimal for inhibiting the duplication of cancer cells. The manufacturer's label recommends intravesical infusion at a dose of 40 mg. According to the European Urological Association guidelines, MMC is administered in a dose of 20-40 mg.[15] The most common reported dose is 40 mg in 40 mL sterile water instilled intravesical with a dwelling time of 1-2 hours.[16]

Another potentially important factor that was not reported in the included studies is the dwell time after the instillation of

Table 2. Characteristics of the Patients and Interventions in the Included Studies

Study	Groups	N	Treatment	Age of patients (years)	Male	Stage	Grade
Racioppi et al.[10]	TURB	47	TURB and early instillation and a weekly schedule of intravesical MMC	Median (range): 64.9 (42-81)	39/47	Ta (32/47) T1 (15/47)	LG
	MMC	47	Three-times-a-week intravesical MMC (40 mg/40 mL) for 2 weeks	Median (range): 65.2 (40-80)	41/47	Ta (37/47) T1 (10/47)	LG
Lindgren et al.[8]	TURB	57	TURBT or biopsy and tumor fulguration followed by adjuvant MMC or BCG once a week for 6 weeks	Median (IQR)= 70 (65-76)	46/61	Ta	LG (43/61) HG (18/61)
	MMC	58	Three-times-a-week intravesical MMC (40 mg/40 mL) for 2 weeks	Median (IQR)= 72 (66-77)	40/59	Ta	LG (42/59) HG (17/59)
Mostafid et al.[9]	TURB	28	TURB + a single instillation of 40 mg MMC within 24 hours post-operatively	Median (IQR)= 70.7 (61.1-77.1)	23/28	Ta	G1 (15/28) G2 (13/28)
	MMC	54	Once-weekly MMC 40-mg intravesical instillations for 4 weeks	Median (IQR)= 72.5 (68.8-78.3)	40/54	Ta	G1 (22/54) G2 (32/54)

TURB, transurethral resection of the bladder; MMC, mitomycin C; HG, high grade; IQR, interquartile range; LG, low grade.

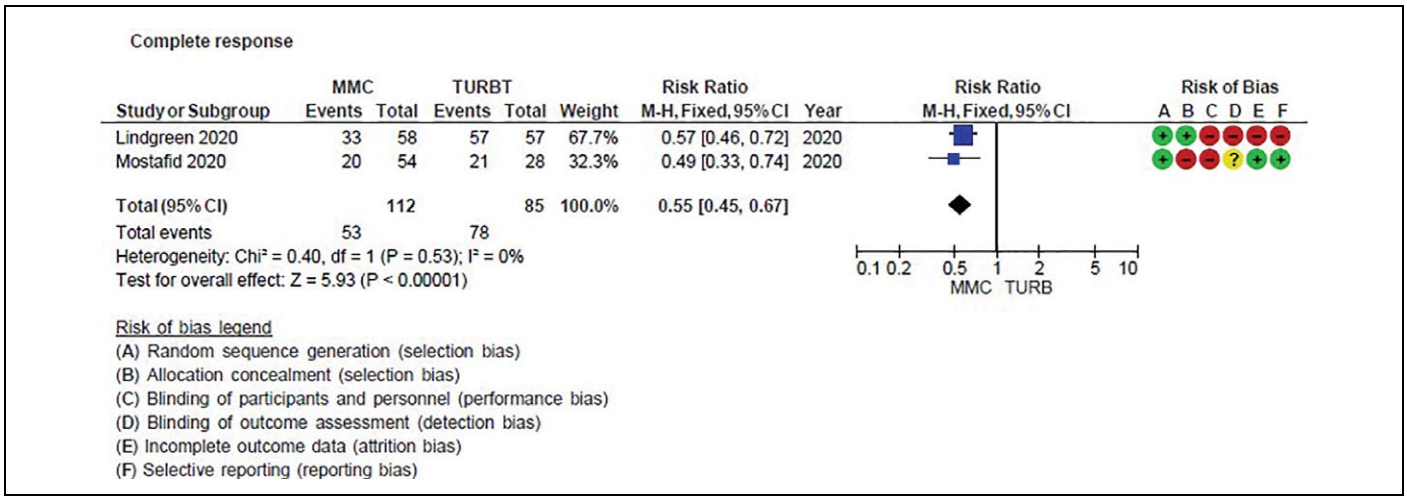

Figure 4. Forest plot of comparison of complete response to treatment

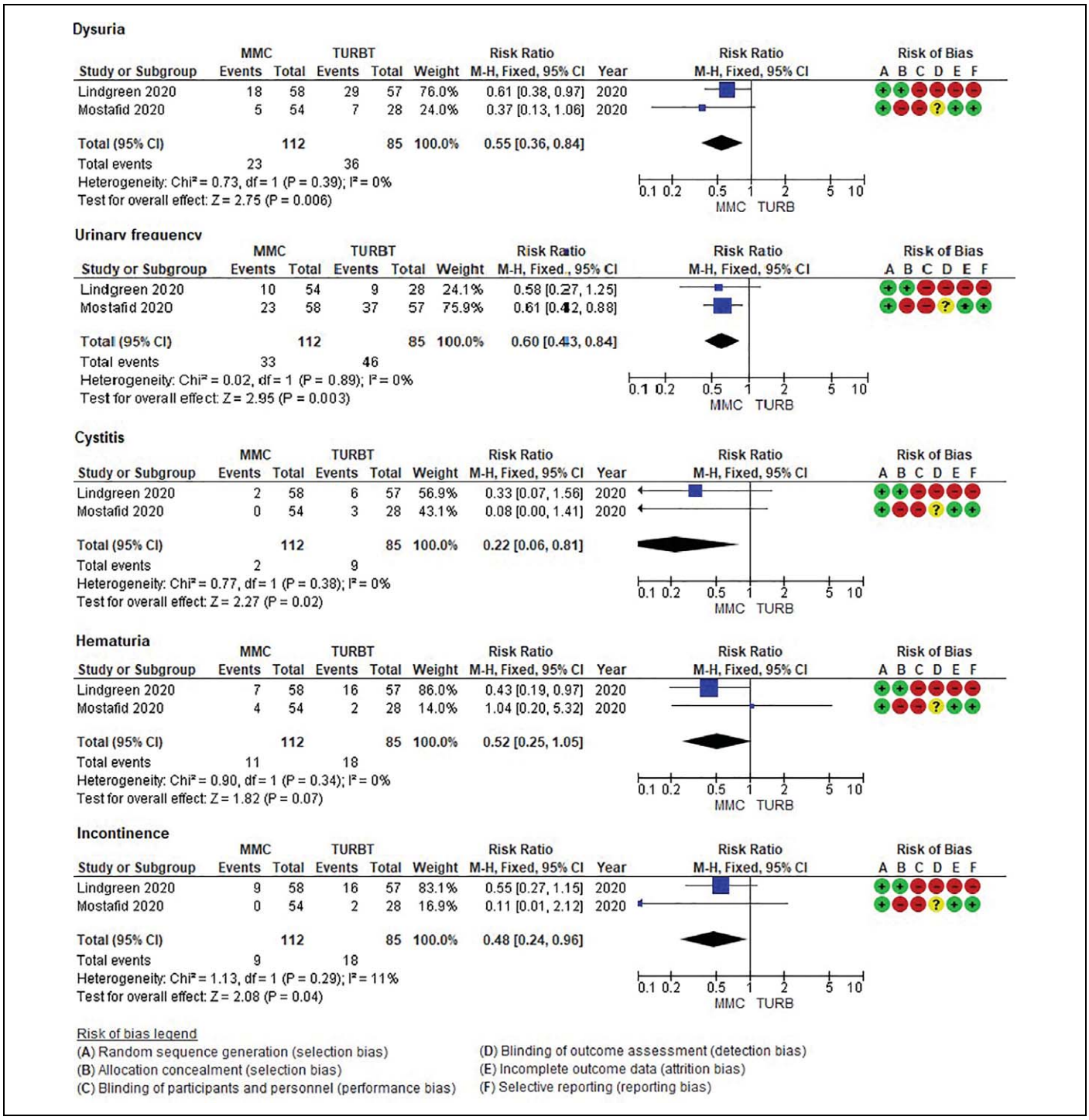

Figure 5. Forest plot for adverse events in the urinary tract

MMC into the bladder. The dwell time is estimated from the time of intracavitary instillation of MMC into the bladder until the uncapping of the urinary catheter or urine voiding by the patient. Longer dwell time allows for better penetration of the bladder wall by MMC. This helps avoid the reported disadvantages of intracavitary chemoablative agents including rapid wash-out and poor penetration of the bladder wall.[17] Some new delivery modalities have been developed to enhance better penetration of MMC to the targeted tissues. These novel systems include biodegradable gels that enhance adhesion to the

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bladder wall,[17] a sustained release thermosensitive hydrogel (UGN-102),[18] and intravesical electromotive drug administration.[19,20] Although these delivery systems were reported to provide better efficacy and same safety as the traditional intracavitary instillation, no study has compared the neoadjuvant use of MMC delivered in this method to TURBT. It is recommended that future clinical trials should compare neoadjuvant MMC delivered using these systems with traditional intracavitary MMC and TURBT to elucidate if they may incur better response.

The use of chemoresection for the treatment of NMIBC carries several potential advantages compared to the current practice, which relies usually on TURBT with or without adjuvant chemotherapy or BCG. Chemoresection by MMC or similar chemoablative agents seems more plausible to patients based on reports from Decaestecker et al.[6] Moreover, patients who are frail and unfit for anesthesia and surgery can benefit from even a partial response by MMC chemoresection. Another advantage is reducing the economic burden of the management of recurrent NMIBC in terms of costs of using the operating room, working medical staff, endoscopy utilization, duration of hospitalization, and costs for managing complications such as urinary tract infections and bleeding. Using MMC can markedly reduce all these expenses as the drug is considered inexpensive medication.[10] Moreover, cystoscopic interventions and TURBT were reported to miss some subtle clinically significant malignant lesions in the bladder.[21,22]

Overall, the results of the included studies showed that the rate of complete response was significantly lower with the use of neoadjuvant MMC chemoresection compared with TURBT. Meanwhile, the risk of local recurrence did not differ significantly between the two groups, with the results of Mostafid et al.,[9] suggesting a slightly lower local recurrence rate with MMC chemoresection than with TURBT.

The efficacy of chemoresection with MMC is thus inconclusive, owing to the low number of included studies and incomplete reporting of outcomes. In addition, the quality of evidence derived from these studies is low as the overall risk of bias was high regarding the allocation concealment as well as blinding of participants and outcome assessors.

As regards the safety of the compared interventions, the calculated pooled estimates for the rates of adverse effects were lower in MMC chemoresection than following TURBT. These differences were statistically significant in the case of dysuria, urinary frequency, cystitis, and incontinence. Here again existed wide variations across the results of the three included studies as Racioppi et al.[10] reported a higher rate of adverse effects in the MMC chemoresection group in contrast of the other two studies. However, the study by Racioppi et al.[10] is nonrandomized in design, and thus the higher rate of adverse effects may be attributed to other confounding factors in the baseline characteristics of the participants.

We planned to make a subgroup analysis for randomized and observational studies as well as for different stages and grades of tumor. However, the limited retrieved number of studies that included the two comparative groups rendered subgroup analysis nonapplicable. Theoretically, the efficacy of MMC chemoresection compared to TURBT can be affected by the tumor stage and grade.

Overall Completeness, Applicability, and of Quality of the Evidence

The results of this meta-analysis show that the current evidence on the role of chemoresection with MMC in recurrent NMIBC—as opposed to surgical treatment with TURBT—is limited. Furthermore, the quality of evidence is downgraded by the nonrandomized design in one study and the high risk of bias as regards the blinding of participants and outcome assessors. In addition, there was some variations in the inclusion criteria of these studies, notably the stage and grade of NMIBC, which resulted in variable heterogeneity across their results and resulted in relatively wide CIs of the calculated estimates of outcomes in this meta-analysis.

Agreements and Disagreements with other Studies or Reviews

Up to the best of the authors' knowledge, this is the first meta-analysis to compare the efficacy and safety of chemoresection with MMC and TURBT in patients with recurrent NMIBC. A systematic review by Alsyouf et al.[23] addressed the potential efficacy of several chemoablative agents including MMC. However, they did not critically appraise the included studies or conducted a quantitative analysis and synthesis of results. A recent meta-analysis by Li et al.[24] has compared the efficacy and safety of intravesical MMC and gemcitabine following TURBT to prevent recurrences. They reported that gemcitabine was superior to MMC in terms of reduction of the recurrence rate and local adverse effects.

Conclusions: Implications for Practice, Policy, and Future Research

Based on the results of this meta-analysis, the efficacy of chemoresection with MMC in patients with recurrent NMIBC is considered inferior to TURBT as regards the rates of complete response. Chemoresection with MMC had apparently lower

rates of adverse effects than TURBT, but wide heterogeneity across the studies rendered the evidence for the safety of MMC chemoresection inconclusive. Based on all these considerations, chemoresection with MMC in patients with recurrent NMIBC should be restricted to those who are unfit to undergo TURBT and for the settings of randomized controlled clinical trials until further evidence is produced to support or refute its regular use. The launching of randomized controlled studies to assess the efficacy and safety of chemoresection with MMC in recurrent TURBT is recommended, as potential benefits of this line of therapy are promising and have implications both on the patients' quality of life and reducing the burden of health costs.

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.A.D., A.A., H.S.; Design - A.A.D., A.A., N.N., R.K., H.S.; Supervision - A.A.D.; Data Collection and/or Processing - A.A.D., A.A., N.N., R.K., H.S.; Analysis and/or Interpretation - A.A.D., A.A., N.N., R.K., H.S.; Literature Search - A.A.D., A.A., N.N., R.K., H.S.; Writing Manuscript - A.A., N.N., R.K.; Critical Review - A.A.D., H.S.

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Appendix 1

Search Strategy and Retrieved Articles		
	"Chemoablation" AND "Mitomycin" AND "Non-muscle-invasive bladder cancer"	**"Chemoresection" AND "Mitomycin" AND "Non-muscle-invasive bladder cancer"**
Google Scholar	51	86
PubMed	5	2
Scopus	12	3
Cochrane library	0	0
Web of Science (ISI)	5	0
Medline WOS	5	0
Proquest	0	3
System for Information on Grey Literature in Europe (SIGLE)	0	0
ClinicalTrials.gov	34	1
Total from databases	207	