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REVIEW

Meta-analysis of efficacy and safety of continuous saline bladder irrigation compared with intravesical chemotherapy after transurethral resection of bladder tumors

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Abstract

Purpose We performed a meta-analysis to confirm the efficacy and safety of continuous saline bladder irrigation compared with intravesical chemotherapy after transurethral resection for the treatment of non-muscle invasive bladder cancer.

Methods Randomized controlled trials of continuous saline bladder irrigation compared with intravesical chemotherapy were searched using MEDLINE, EMBASE, and the Cochrane Controlled Trials Register. The data were evaluated and statistically analyzed using RevMan version 5.3.0.

Results Four studies including 861 participants which compared continuous saline bladder irrigation with intravesical chemotherapy were considered. One-year recurrence-free survival [odds ratio (OR) = 0.76, 95% CI = 0.55–1.05, $p = 0.09$]; 2-year recurrence-free survival (OR = 0.94, 95% CI = 0.71–1.25, $p = 0.68$); the median period to first recurrence (OR = − 1.01, 95% CI = − 2.96 to 0.94, $p = 0.31$); the number of tumor progression (OR = 0.80, 95% CI = 0.54–1.17, $p = 0.25$); and the number of recurrence during follow-up (OR = 1.12, 95% CI = 0.84–1.50, $p = 0.43$) suggested that two methods of postoperative perfusion had no significant differences. In terms of safety, including macrohematuria, frequency of urination and bladder irritation symptoms, continuous saline bladder irrigation showed better tolerance than intravesical chemotherapy.

Conclusion Continuous saline bladder irrigation seems to provide a better balance between prevention of recurrence and local toxicities than intravesical chemotherapy after transurethral resection of bladder tumors.

Keywords Non-muscle invasive bladder cancer · Meta-analysis · Randomized controlled trials · Continuous saline bladder irrigation · Transurethral resection of bladder tumors

Introduction

Bladder cancer is one of the most common clinical tumors in urology and it is the disease that can directly threaten the survival of patients [1]. Statistically, bladder cancer has 81,000 new cases each year in the US, which is estimated to result in 17,000 deaths per year [1]. In western countries, about 70% of patients diagnosed with bladder cancer show non-muscle invasive bladder cancer (NMIBC) [2]. The initial clinical manifestation of most bladder cancer is hematuria, usually manifested as painless, intermittent, gross macroscopic hematuria [3].

In terms of treatment, transurethral resection of bladder tumors (TURBT) is considered as the preferred method for the treatment of NMIBC, and postoperative bladder irrigation is routinely used to prevent the recurrence and progression of tumor [4]. Clinically, intravesical chemotherapy has been frequently used as a postoperative auxiliary treatment

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and showed good therapeutic effect [5]. However, there is still controversy about the role of the therapy. According to some reports, adverse events after intravesical chemotherapy occurred from time to time and was even a great risk to the patient's life [6]. Therefore, intravesical chemotherapy after surgery has some problems to maintain sharp vigilance as an adjuvant therapy.

Recent studies have shown that continuous saline bladder irrigation (CSBI) after TURBT would wash away floating cancer cells and prevent cancer cells from adhering to the bladder wall, and then reduce tumor recurrence [7]. Also, CSBI in many countries has a major role in the control of hematuria overnight and preventing the formation of urethral blood clots [8]. These views have posed a challenge to the therapeutic status of conventional postoperative intravesical chemotherapy. But there is no evidence-based medicine (EBM) to identify their merits and demerits.

To confirm the efficacy and safety, we performed a meta-analysis to compare CSBI with intravesical chemotherapy as adjuvant treatment for patients with NMIBC.

Materials and methods

Study design

Systematic review of Randomized Controlled Trials (RCTs) was carried out using the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist [9].

Search strategy

Our study searched MEDLINE (1970 to Aug 2018), EMBASE (1993 to Aug 2018) and the Cochrane Controlled Trials Register to screen studies investigating CSBI and intravesical chemotherapy after TURBT. The analysis used the search formula: "[continuous AND ("saline solution" OR ("saline" AND "solution") OR "saline solution" OR "saline") AND ("urinary bladder" OR ("urinary" AND "bladder") OR "urinary bladder" OR "bladder") AND ("therapeutic irrigation" OR ("therapeutic" AND "irrigation") OR "therapeutic irrigation" OR "irrigation")] AND [intravesical AND ("drug therapy" OR ("drug" AND "therapy") OR "drug therapy" OR "chemotherapy" OR "drug therapy" OR ("drug" AND "therapy") OR "chemotherapy")]". The study was limited to published research on humans, with no restrictions on language. Furthermore, we have also browsed references of related articles. The authors were contacted to offer further information from their research if necessary.

Inclusion criteria

If study met the following criteria, it would be included: (1) CSBI and intravesical chemotherapy after TURBT was investigated in the article, (2) the article was a randomized controlled study, (3) full-text content and related data can be obtained, (4) the data provided by the article are valid and worthy of study, mainly including the total number of subjects and the valuable results of each indicator. If the same experimental results were published in different journals or at different times, the latest finding would be included in the meta-analysis. However, if a group of subjects participated in multiple studies, each study may be included in the analysis. The flowchart (Fig. 1) details the process of selection and elimination.

Quality assessment

The study used the Jadad scale to evaluate the quality of RCTs retrieved [10]. Additionally, relevant research methods, including allocation method of participants, hiding allocation process, double-blinded and termination of results in data loss, were used to analyze the quality of individual studies. Afterwards, individual studies were assessed in line with the guidelines provided with the *Cochrane handbook for systematic reviews of interventions v5.30* [11]. Every article was evaluated and allotted in accordance with three quality classification standards: (A) when the study fulfilled all quality criteria, the study would be considered to have a low risk of bias; (B) when one or more of the quality criteria was just partially met or was fuzzy, the study was considered to have a secondary risk of bias; or (C) when one or more of the criteria were barely met or not included, the study was considered to have a high risk of bias. All authors participated in the quality assessment of RCTs retrieved. Differences regarding this quality assessment were resolved by discussion among the researchers.

Data extraction

The following details were collected for individual studies: (1) name of the first author; (2) time of publication; (3) sample size; (4) methods of treatment; (5) median follow-up time; (6) loss to follow-up; (7) instillation protocol; (8) data on 1-year recurrence-free survival; 2-year recurrence-free survival; the median period to first recurrence; the number of tumor progression; the number of recurrence during follow-up; macrohematuria; frequency of urination; bladder irritation symptoms.

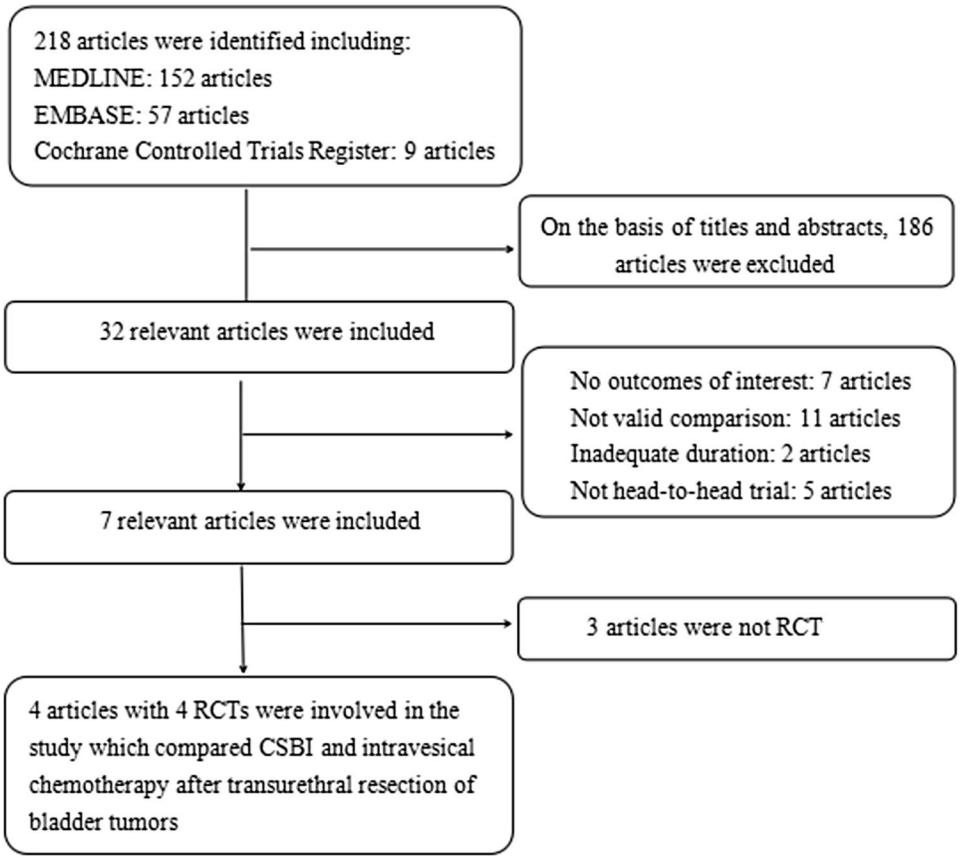


Fig. 1 The flowchart details the selection and elimination process. *RCT* randomized controlled trials, *CSBI* continuous saline bladder irrigation, *NMIBC* non-muscle invasive bladder cancer

Statistical analysis and meta-analysis

The analysis of the data was done using RevMan version 5.3.0 (Cochrane Collaboration, Oxford, UK) [11]. The number of patient would be evaluated and statistically analyzed during follow-up in the 1-year recurrence-free survival, 2-year recurrence-free survival, the median period to first recurrence, tumor progression, recurrence during follow-up, macrohematuria, frequency of urination and bladder irritation symptoms. Fixed-effects and random-effects models were used to evaluate the mean difference (MD) for continuous data and the odds ratio (OR) for dichotomous results with the corresponding 95% confidence interval (CI) [12]. When the result of analysis showed $p > 0.05$, we would consider the study to be homogeneous and fixed-effect model was used to the analysis. Otherwise, random-effect model would be chosen. We analyzed inconsistency using the I^2 statistic, which reflected the proportion of heterogeneity across trails.

Results

Characteristics of individual studies

Two-hundred and eighteen articles were found by retrieval in each database. After screening the titles and abstracts, 186 articles were excluded on the basis of the inclusion criteria. Of the remaining 32 articles, 28 articles were excluded due to lack of available data. Four articles containing 4RCTs [7, 13–15] which compared CSBI and intravesical chemotherapy after TURBT were eventually absorbed into our analysis (Fig. 1). The characteristics of the studies are summarized in Table 1.

Quality of individual studies

All four articles complied with the criteria of randomized controlled study and each study indicated the randomization processes. A potent calculation in three RCTs [7, 14, 15] was applied to determine the sample size and the standard of character of these article was A. One RCT [13] without a calculation of sample size was classified as B (Table 2). All studies were included in the analysis regardless of the grade of quality. The funnel plot showed a qualitative estimation of publication bias of the study, the plot was highly

Table 1 Study and patient characteristics

Study	Therapy in experimental group	Therapy in control group	Sample size		Administration method	Median follow-up time (year)	Inclusion population	Instillation protocol
			Experimental	Control				
[13]	CSBI	Intravesical chemotherapy	24	21	Irrigation	3	Patients with superficial bladder tumor were assigned to two groups before transurethral resection of bladder tumor	Epirubicin solution of 40 ug/ml for 20 h immediately after surgery; continuous irrigation with saline in the same manner
[14]	CSBI	Intravesical chemotherapy	162	166	Irrigation	4	Patients with clinical evidence of primary or recurrent NMIBC (Ta/T1, G1–3)	Gemcitabine (2000 mg/100 ml of saline) or placebo (100 ml of saline) followed by continuous bladder irrigation for ≥ 20 h
[15]	CSBI	Intravesical chemotherapy	123	115	Irrigation	5	Patients with intermediate risk NMIBC were treated by TUR followed by either CSBI or intravesical instillation of mitomycin C	Mitomycin C (4 weekly instillations starting 1 week after TUR followed by 11 monthly instillations to month 12); CSBI (2000 ml/h for first 1 h, then 1000 ml/h for 3 h, and then 250 ml/h for 14–18 h)
[7]	CSBI	Intravesical chemotherapy	124	126	Irrigation	5	Patients with primary low-to intermediate-risk tumors were enrolled	Single immediate instillation of 30 mg mitomycin C in 30 ml of saline; CSBI (2000 ml/h for first 1 h, then 1000 ml/h for 2 h, and then 500 ml/h for 15 h)

CSBI continuous saline bladder irrigation, *NMIBC* non-muscle invasive bladder cancer, *TUR* transurethral resection

Table 2 Quality assessment of individual study

Study	Allocation concealment	Allocation sequence generation	Blinding	Calculation of sample size	Loss to follow-up	Statistical analysis	Level of quality	ITT analysis
[13]	A	A	A	No	0	Kaplan–Meier method; log-rank test	B	No
[14]	A	A	A	Yes	44	Kaplan–Meier method; log-rank test	A	Yes
[15]	A	A	A	Yes	2	Kaplan–Meier method; log-rank test	A	No
[7]	A	A	A	Yes	0	Kaplan–Meier method; log-rank test; *T* test;	A	No

A the study has a low risk of bias, *B* the study has a secondary risk of bias, *C* the study has a high risk of bias, *ITT* intention-to-treat

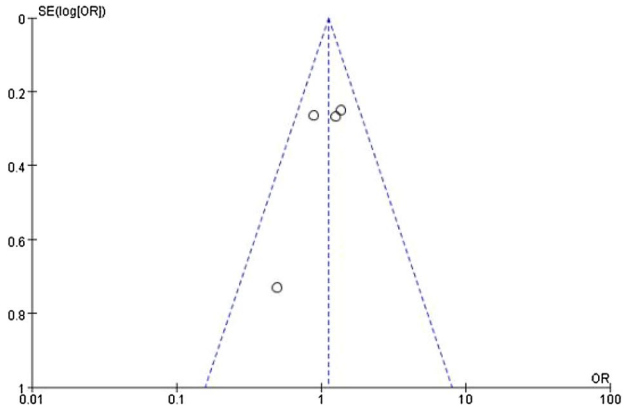


Fig. 2 Funnel plot of the studies presented in our study. *SE* standard error, *OR* odds ratio

symmetrical and four squares were contained in the large triangle, and no evidence of bias was found (Fig. 2).

Efficacy

One-year recurrence-free survival

Four RCTs, with an amount of 861 participants (433 in the saline irrigation group and 428 in the chemotherapy group), were analyzed in terms of 1-year recurrence-free survival. The fixed-effects estimate of OR was 0.76, and the 95% CI was 0.55–1.05 ($p=0.09$) (Fig. 3a). This result indicated that the saline irrigation group experienced similar efficacy compared with the chemotherapy group in the 1-year recurrence-free survival.

Two-year recurrence-free survival

Four RCTs gathering an amount of 861 participants (433 in the saline irrigation group and 428 in the chemotherapy group) included data on the 2-year recurrence-free survival. The forest plots showed an OR of 0.94 and 95% CI of 0.71–1.25 ($p=0.68$) (Fig. 3b). We found little difference between the saline irrigation group and the chemotherapy group for the 2-year recurrence-free survival.

The median period to first recurrence

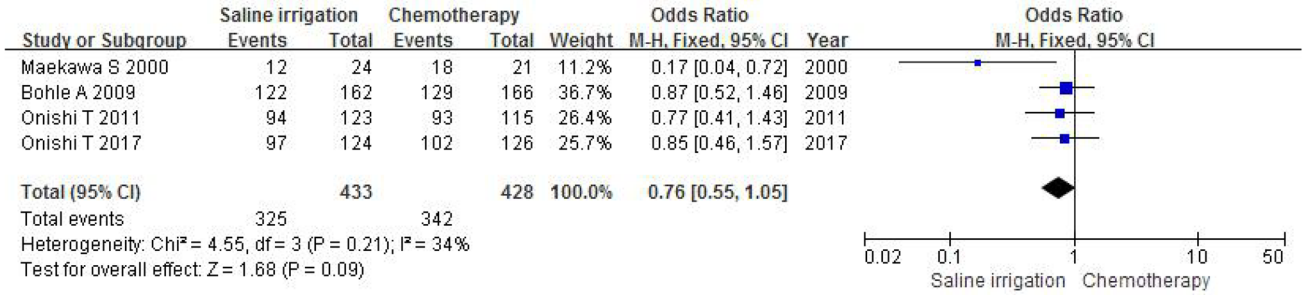
Four RCTs included data on the median period to first recurrence, gathering 861 participants (433 in the saline irrigation group and 428 in the chemotherapy group). The forest plots showed the OR of −1.01 and 95% CI of −2.96 to 0.94 ($p=0.31$) (Fig. 3c). We found no apparent difference between the saline irrigation group and the chemotherapy group for the median period to first recurrence.

The number of tumor progression

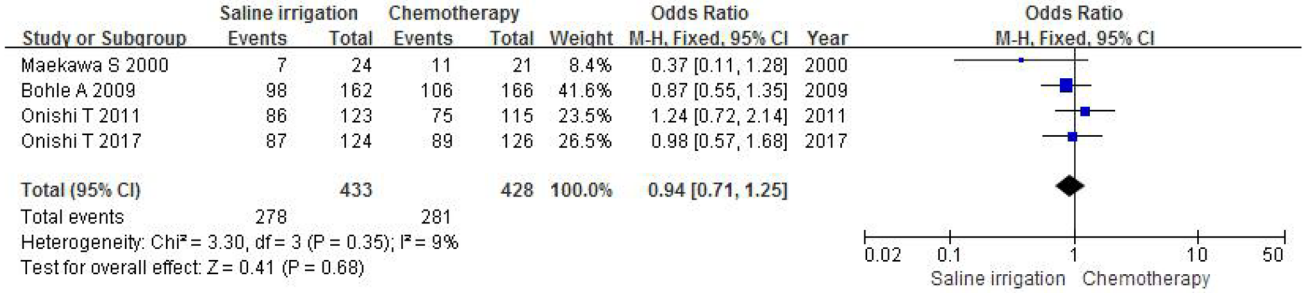
Three RCTs, with an amount of 816 participants (409 in the saline irrigation group and 407 in the chemotherapy group), were analyzed in terms of the number of tumor progression. The fixed-effects estimate of OR was 0.80 and the 95% CI was 0.54–1.17 ($p=0.25$) (Fig. 4a). This result indicated that the saline irrigation group had no statistical difference compared with the chemotherapy group in the number of tumor progression.

The number of recurrence during follow-up

Four RCTs gathering 861 participants (433 in the saline irrigation group and 428 in the chemotherapy group) involved



(A)



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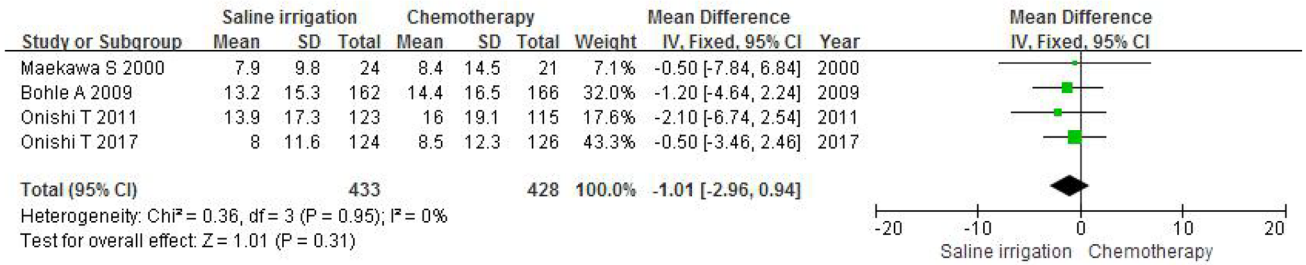


(C)

Fig. 3 Forest plots showing **a** 1-year recurrence-free survival; **b** 2-year recurrence-free survival; **c** the median period to first recurrence. *M–H* Mantel–Haenszel, *CI* confidence interval, *df* degrees of freedom

data on the number of recurrence during follow-up. A fixed-effects model showed an OR of 1.12 and 95% CI of 0.84–1.50 ($p = 0.43$) (Fig. 4b). The result demonstrated that both treatment groups had no statistical difference in terms of the number of recurrence during follow-up.

Safety

Macrohematuria

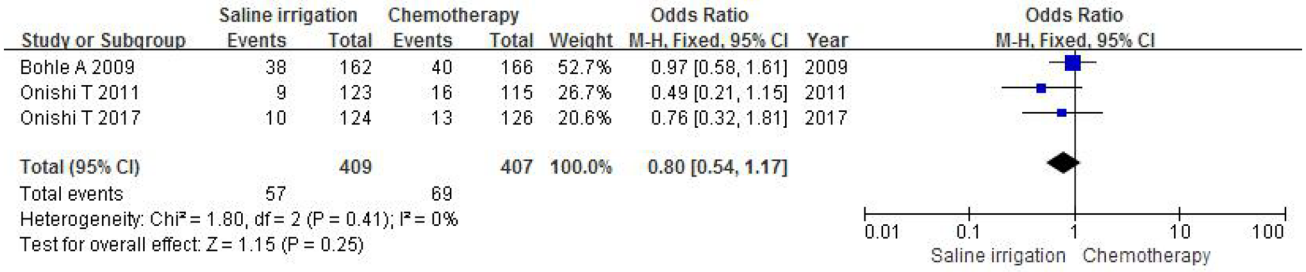
Two RCTs with an amount of 488 participants (247 in the saline irrigation group and 241 in the chemotherapy group) were involved. The OR was 0.28 and the 95% CI was 0.15–0.54 ($p = 0.002$) (Fig. 5a). This result suggested that the chemotherapy group had relatively large numbers with respect to macrohematuria.

Frequency of urination

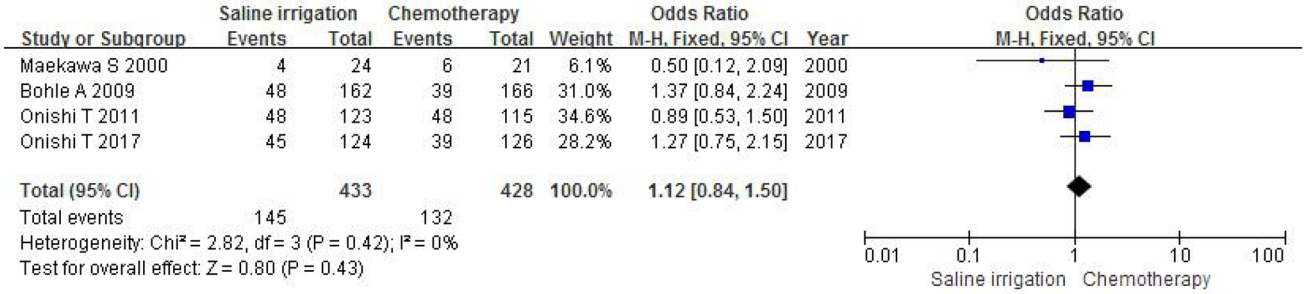
Three RCTs, with an amount of 533 participants (271 in the saline irrigation group and 262 in the chemotherapy group), were involved in the analysis for frequency of urination. The forest plots showed an OR of 0.22 and 95% CI of 0.12–0.40 ($p < 0.00001$) (Fig. 5b). The saline irrigation group showed the smaller incidence of frequency of urination relative to the chemotherapy group.

Bladder irritation symptoms

Three RCTs with an amount of 861 participants (433 in the saline irrigation group and 428 in the chemotherapy group) were involved for bladder irritation symptoms. The OR was 0.30 and 95% CI was 0.19–0.49 ($p < 0.00001$) (Fig. 5c). This result suggested that the saline irrigation group showed,



(A)



(B)

Fig. 4 Forest plots showing **a** the number of tumor progression; **b** the number of recurrence during follow-up. *M–H* Mantel–Haenszel, *CI* confidence interval, *df* degrees of freedom

respectively, smaller incidence in terms of bladder irritation symptoms.

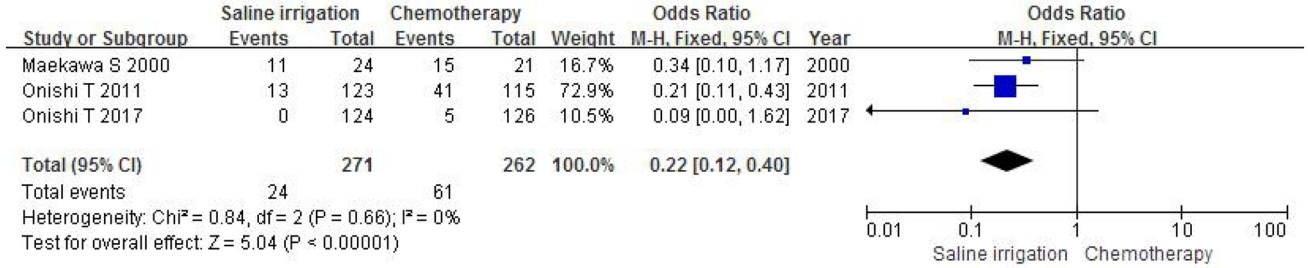
Discussion

TURBT is a vital diagnostic method of NMIBC and is also the main therapeutic method, which has two main objectives: the one is to remove all the tumor tissue visible to the naked eye and the second is to perform pathological classification and stage based on the tissue excised [16]. Theoretically, bladder tumor should be completely removed to reach the normal muscle of bladder wall, but some research shows that a considerable number of recurrences are caused by residual tumors, especially in intermediate and advanced stage T1 bladder cancer [17, 18]. Statistically, the residual rate of bladder tumor after the first resection can be as high as 33.8–36%, leading to a high ratio of postoperative recurrence and a small proportion of patients will even progress to muscle invasive bladder cancer (MIBC) [19]. It is necessary for postoperative adjuvant therapy to reduce these possibilities.

Intravesical chemotherapy after TURBT, recommended by mostly all urology association including European Association of Urology (EAU) and American Urological Association (AUA), is commonly used to lower the recurrence rate of bladder cancer after operation [5]. A meta-analysis found that single immediate instillation of chemotherapy after TUR decreased the probability of recurrence by 39% after a median follow-up of 3.4 years [20]. However, severe adverse events (mainly including chemical cystitis, hematuria, bladder irritation symptoms, bladder perforation and even death) after intravesical chemotherapy have been reported in some studies recently, suggesting that intravesical chemotherapy was not a completely harmless treatment [21]. CSBI, as a novel-innovative perfusion protocol, is rarely applied with full awareness of its oncologic benefit but is very frequently adopted as a safety maneuver after surgery to prevent catheter obstruction by clots [8]. Usually, CSBI (common perfusion scheme: 2000 ml/h for 1 h, then 1000 ml/h for 3 h, and then 250 ml/h for 14–18 h) was started immediately after TURBT [7]. Do et al. found that participants with postoperative saline irrigation were significant increase than those without perfusion in recurrence-free rate at 1, 2, and 3 years [22].

The objective of this meta-analysis was to explore the efficacy and safety of CSBI compared with intravesical chemotherapy after TURBT for patients who were suffering from primary to intermediate risk NMIBC. Our study revealed that either CSBI or intravesical chemotherapy could improve the prognosis of patients and reduce the chances of recurrence and progression. The result demonstrated that two methods of postoperative perfusion had no significant difference in 1-year recurrence-free survival, 2-year recurrence-free survival, the median period to first recurrence, the number of tumor progression and number of recurrence

(A)



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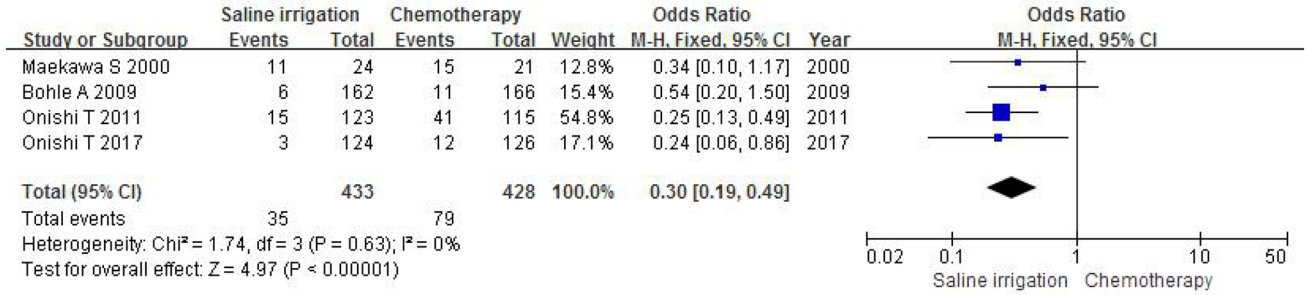

(C)

Fig. 5 Forest plots showing **a** macrohematuria; **b** frequency of urination; **c** bladder irritation symptoms. *M–H* Mantel–Haenszel, *CI* confidence interval, *df* degrees of freedom

during follow-up. One RCT [7] showed that subgroup analysis did not reveal significant difference in patients with low or intermediate risk bladder tumors. Insufficiently, we could not infer the long-term efficacy of CSBI compared with intravesical chemotherapy; more long-term clinical trials were needed to confirm the result.

The mechanism of efficacy of each chemotherapeutic agent is not the same, provided with different molecular pathways. Mytomicin C, a frequently used instillation of drugs for mild-to-moderate bladder cancer, can produce response rates ranging among 40–50% by inhibiting DNA synthesis and destroying a single strand of DNA [23, 24]. Mechanically, the chemotherapeutic drug epidoxorubicin induces GRO-α expression in primary bladder cancer cells at G1/S phase via p38-dependent activation of NF-κB. GRO-α phosphorylation of Snail on Ser246 supports Snail's accumulation in the nucleus, and thereby promotes transcription repression activity of Snail from E-cadherin promoters. In accordance, disrupting the GRO-α-Snail axis in NMIBC represents a promising alternative to prevent post-therapeutic tumor progression and recurrence [25]. Relatively, CSBI can remove floating bladder cancer cells and prevent the adhesion and plant of cancer cells from the bladder wall, thus reducing the recurrence of tumors [26]. But CSBI has no action on the removal of residual cancer cells at the resected site; whole tumor resection is required at sufficient depth around the tumor including muscle tissue. A retrospective study found that CSBI could reduce early recurrence of NMIBC after surgery and was expected to be more widely used because it was an economical, safe, and easy-to-perform technique [22]. But Lenis et al. [27] concluded that the disease-free survival (DFS) benefit seen with CSBI in other studies may be limited to patients receiving prolonged irrigation, and new intravesical agents being evaluated may

consider saline as a control given our data demonstrating that short-term CSBI is not superior to TURBT alone.

To the safety, four studies have found that serious systemic toxicities were not counted in either CSBI or intravesical chemotherapy. However, in the area of limited toxicity, CSBI showed greater superiority than intravesical chemotherapy. Our meta-analysis found that CSBI had less incidence in the macrohematuria, frequency of urination and bladder irritation symptoms compared with intravesical chemotherapy. One RCT [14] demonstrated that the dysuria and retention had a higher incidence in intravesical chemotherapy group. Onishi et al. [7] found that CSBI after TURBT had a prophylactic effect on the recurrence in patients with low to intermediate risk NMIBC and was conducive to management with a little risk of adverse events, and urologist might consider CSBI as an option instead of the single instillation of chemotherapy.

Besides, CSBI has no contraindication differently to postoperative intravesical chemotherapy which is generally not performed in cases of bladder perforation or gross hematuria [28, 29]. Clinical experience finds that bladder irrigation with saline after intravesical chemotherapy seems to significantly reduce the complications and adverse events of patients after chemotherapy, but this has not yet been confirmed by specific experiments. And long-term single intravesical chemotherapy has some limitations such as its complications, problems of handling agents, costs. Relatively speaking, CSBI has the advantages of easy management, low toxicity and cost saving.

Therefore, CSBI provides a better balance between prevention of recurrence and local toxicities in our analysis. Clinically, CSBI seems to be recommended as an alternative treatment to prevent the recurrence of NMIBC after TURBT.

Studies designed to follow the randomized controlled trials were involved in the meta-analysis. The quality of every RCTs in the meta-analysis was highly conforming the quality assessment method above. Our study could only obtain the parameter of the short term of efficacy, safety and tolerance of CSBI and intravesical chemotherapy. Also, the diagnostic methods and transurethral resection techniques have developed recently, especially in universal use of photodynamic diagnosis (PDD) and Re-TURBT [30, 31], which may lead to decrease of incomplete resections, possibly explaining the lower recurrence rates in our studies. So it still needs a lot of substitution of head-to-head comparison to confirm our findings. Moreover, the study does not include data acquired from unpublished studies. More high-quality controlled trials with suitable data should have been further studied for the purpose of investigating the efficacy and tolerance of CSBI and intravesical chemotherapy for NMIBC after TURBT.

Conclusion

This meta-analysis shows that CSBI seems to provide a better balance between prevention of recurrence and local toxicities than intravesical chemotherapy after transurethral resection of bladder tumors.

Author contributions DY and YC participated in the design of this study. JW performed the statistical analysis. YL and YL collected important background information. ZZ and SZ drafted the manuscript. ZG conceived this study, participated in the design and helped to draft the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval and consent to participate The authors have no ethical conflicts to disclose.

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