

Hyperthermic Intravesical Chemotherapy Shed New Light on Therapy for NMIBC: A Meta-Analysis

Gang Zhao *

Nanjing Medical University

* Corresponding Author Email: zhao_gang2001@163.com

Abstract. Background: Non-muscle-invasive bladder cancer accounts for the 75% of bladder cancers but with limited kinds of therapies, especially in the situation that the shortage and high failure rate of intravesical bacillus Calmette-Guérin. There is some evidence that hyperthermic intravesical chemotherapy could enhance the effect of normal intravesical chemotherapy and may be the alternative. **Method:** To verify the effect of hyperthermic intravesical chemotherapy, we searched three databases including PubMed (Medline), Embase, and Cochrane Library for related studies. The main outcome were the OR (odds ratio) and the survival data. The quality of studies was evaluated by two authors independently using Jadad Scale for prospective studies and Newcastle-Ottawa Scale (NOS) for retrospective studies. **Result:** In total, 1,900 patients were included in the quantitative evaluation. The meta-analysis demonstrated significant difference in recurrence rate (OR = 0.42, 95%CI = 0.25-0.72, p=0.0015) and RFS (HR = 0.69, 95%CI = 0.54-0.88, p=0.0029) between hyperthermic intravesical chemotherapy with control groups (intravesical bacillus Calmette-Guérin and normal intravesical chemotherapy) but no obvious advantage in OS (HR = 0.84, 95%CI = 0.59-1.19, p=0.7805) and PFS (HR = 0.51, 95%CI = 0.06-4.08, p=0.5285). We separately use way of heat, control therapy, solvent, country and study type to conduct the subgroup analysis for recurrence rate and RFS. **Conclusion:** Hyperthermic intravesical chemotherapy can enhance the effect of normal intravesical chemotherapy and act as the alternative for intravesical bacillus Calmette-Guérin, and more studies are needed for further analyses.

Keywords: NMIBC; Bladder Cancer; BCG; Hyperthermic Intravesical Chemotherapy, Chemotherapy.

1. Introduction

Bladder cancer is the seventh most commonly diagnosed cancer in the men and the tenth when both genders considered. The worldwide age-standardised incidence rate (per 100,000 person/years) is 9.5 in men and 2.4 in women (1). Bladder cancer is categorized as Non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC), and NMIBC accounts for the 75% of bladder cancers and the proportion in younger patients (< 40 of age) is even higher (2).

The main therapy of NMIBC is Transurethral Resection of Bladder Tumor (TURBT) with adjuvant therapies, but up to 52% of patients with high risks NMIBC will have disease recurrence and up to 20% will process to muscle-invasive bladder cancer (3). Intravesical bacillus Calmette-Guérin (BCG) immunotherapy is a common adjuvant therapies which is considered more effective than intravesical chemotherapy and also in general more toxic (4). Chemotherapy installation is another important therapy and the efficacy of it may be enhanced by hyperthermia therapy (5) which use intravesical device-assisted technology to deliver hyperthermia to the bladder wall. As for BCG-failure patients who are BCG unresponsive and unwilling to undergo cystectomy, hyperthermic intravesical chemotherapy may be an option.

In 1972, Lunglmayr et al. (6) first applied hyperthermic therapy to the treatment of bladder tumors. Subsequently, Colombo et al. (7) used microwave equipment to locally heat the bladder for intravesical hyperthermic chemotherapy means the advent of this new therapy. Henceforth Gofrit et al. (8) and many other pioneers examine the possibilities of intravesical hyperthermic chemotherapy.

Nowadays, there is much literature published on the efficacy of hyperthermic intravesical chemotherapy, but different cohort studies differ in results, so we made the meta-analysis.

2. Methods

2.1. Search Strategy

The database search was completed on April 15 2023. Three databases were searched including PubMed (Medline), Embase, and Cochrane Library.

Also, we used American Society of Clinical Oncology (ASCO) conference abstract, the European Association of Urology (EAU) conference abstract, the American Urology Association (AUA) conference abstract, and pre-print databases to search the Grey literature. The detailed search strategies were described in Supplementary File S1. All abstracts and review articles about the subject and references in related meta-analyses were reviewed. We noticed that there are similar meta-analyses published recent years. We had read relevant meta-analyses before and updated new studies after comparison.

2.2. Inclusion Criteria

All the studies included must meet the following PICOS (patients, interventions, comparison, outcomes, and study design) criteria:

- Patients: Diagnosed as non-muscle-invasive or superficial or Ta/T1 with/without Tis bladder cancer. All patients had undergone TURBT before formal therapy are selected.
- Interventions: Hyperthermic intravesical chemotherapy.
- Comparison: BCG or normal intravesical chemotherapy.
- Outcomes: Odds ratio (OR), overall survival (OS), recurrence-free survival (RFS), progression-free survival (PFS).
- Study design: Cohort studies with a controlled group or single arm trials.

2.3. Exclusion Criteria

Animal experiments, cell research, review, meta-analysis, case report or letter.

2.4. Data Extraction and Quality Assessment

Data and information were extracted from final studies, such as the first author, year of publication, country of study, study type, clinical treatment, characteristics of patients, tumor stage, age, survival analysis and side effects. The quality of studies was evaluated by using Jadad Scale for prospective studies and Newcastle-Ottawa Scale (NOS) (Supplementary File S2) for retrospective studies. Among prospective studies using Jadad Scale, score of 4-7 was defined as high-quality, and <4 was defined as low-quality. Among retrospective studies using NOS, score of 7-9 was defined as high-quality, and <7 was defined as low-quality.

2.5. Statistical Analysis

The meta-analysis was made with “meta” package in R v4.0.0 (9). We manifested effect size by hazard ratio (HR) with 95% Cis (10). We extracted them directly when the HRs and their 95% CIs were available in the original articles, or we estimated them based on the Kaplan-Meier survival curves or the related data by the method described by Tierney et al. (10). Studies included in the meta-analysis were tested the heterogeneity with standard Cochrane’s Q test and I^2 statistics. The value of I^2 statistics >50% and $p < 0.1$ indicated significant heterogeneity and when there existed the significant heterogeneity, we then conducted the subgroup, sensitive and accumulative analysis. Besides, due to the small number of studies, we could not evaluate the publication bias by Egger test

or Begg funnel plot (11, 12), but we could apply sensitive and accumulative analysis to estimate the stability of our meta-analysis and the funnel plot to test the bias.

3. Results

3.1. Eligibility Criteria and Characteristics for Studies

As is shown in the flow chart, initially 1050 records were obtained from three databases with 363 duplicate records on April 15, 2023. Then 55 papers were removed as they are marked as ineligible by automation tools. After reading titles and abstracts of the left 632 papers, 500 of them were removed as they are irrelevant to the meta-analysis. Finally, 13 papers that were eligible from the 68 accessed papers were included in the meta. In total, 1,900 patients were included in the quantitative evaluation. These papers were published between 2003 and 2023, 13 studies with 8 prospective and 5 retrospective studies. There are 7 studies and 6 separately using normal intravesical chemotherapy and BCG as control groups. All of the studies had enrolled patients with NMIBC and had undergone complete transurethral resection of all tumors. Other characteristics were summarized in the Table 1.

Table 1. Other characteristics of patients

Study	Year	Country/ multicenter	Study Type	treatment vs. control	number	Tevent	Ttotal	Cevent	Ctotal	Age	Male (%)	solvent
Renzo Colombo et al.	2003	America	prospective	RITE + MMC vs. MMC	42 vs.41	14	35	32	40	NA	83	bidistilled water
Ming Chen Ba et al.	2017	China	prospective	CHT + MMC vs. MMC	28 vs.25	3	28	7	25	50.7(mean)	93	saline
Wei Shen Tan et al.	2019	multicenter	prospective	RITE + MMC vs. BCG	48 vs. 56	NA	48	NA	56	77(median)	71	sterile water
Jun Zhou et al.	2019	China	retrospective	CHT + THP vs. THP	76 vs. 85	NA	76	NA	85	63(median)	84	saline
Fedir Kostyev et al.	2021	Ukraine	retrospective	CHT + MMC vs. BCG	53 vs. 54	9	53	21	54	65.26(mean)	76	bidistilled water
Qiang Ruan et al.	2021	multicenter	retrospective	CHT + MMC/THP vs. MMC/THP	182 VS.182	NA	182	NA	182	NA	79	sterile water
Yuvaraja B. Thyavihally et al.	2021	India	prospective	CHT + MMC vs. BCG	22 vs. 29	1	22	6	29	62(median)	91	saline
Yu-Ching Wen et al.	2021	China	retrospective	RITE + MMC vs. MMC	18 vs. 25	2	18	12	25	66.5(median)	72	saline
Javier C. Angulo et al.	2022	multicenter	prospective	CHT + MMC vs. MMC	213 vs.106	NA	213	NA	106	NA	NA	saline
Félix Guerrero- Ramos et al.	2022	Spain	prospective	CHT + MMC vs. BCG	25 vs. 25	4	24	7	24	74.1(mean)	84	bidistilled water
Wei Shen Tan et al.	2022	multicenter	prospective	CHT + vs. MMC	127 vs. 125	42	127	49	125	70(median)	76	sterile water
Shuo Wang et al.	2023	China	retrospective	CHT + THP vs. BCG	72 vs. 117	10	72	34	117	60.88(mean)	82	5% glucose soluti
Miguel Ángel Arrabal Polo et al.	2023	German	prospective	CHT + MMC vs. BCG	61 vs. 63	15	61	11	63	74(median)	77	bidistilled water

3.2. Recurrence Rate

There are 9 studies contain 942 patients included in the OR of recurrence analysis. The heterogeneity was high ($p=0.02$, $I^2=56\%$), then we used random-effects model for analysis and conducted subgroup analysis. The meta-analysis demonstrated a significant difference (OR = 0.42, 95%CI = 0.25-0.72, $p=0.0015$, Figure 1a) in recurrence rate between hyperthermic intravesical chemotherapy and control groups. Accumulative analysis and sensitive analysis shows the result was relatively stable (Figure 1b,c). We separately used way of heat, control therapy, solvent, country and study type to conduct subgroup analyses. Both ways of heat of hyperthermic intravesical chemotherapy have lower recurrence rate than control groups (OR = 0.16, 95%CI = 0.07-0.38, Figure 2a; OR = 0.55, 95%CI = 0.33–0.90, Figure 2a). And hyperthermic intravesical chemotherapy have an advantage over normal intravesical chemotherapy (OR = 0.32, 95%CI = 0.13-0.78, Figure 2b) but no significant difference over BCG therapy (OR = 0.51, 95%CI = 0.25-1.03, Figure 2b). Concerning kinds of solvent, group of saline (OR = 0.21, 95%CI = 0.08-0.56, Figure 3a) is statistically significant comparing to group of sterile-water (OR = 0.52, 95%CI = 0.25-1.10, Figure 3a). Considering the

country as subgroup, both group of China (OR = 0.32, 95%CI = 0.17-0.61, Figure 3b) and group of others (OR = 0.41, 95%CI = 0.17-1.00, Figure 3b) have lower recurrence rate but group of multicenter have no statistical significance (OR = 0.77, 95%CI = 0.46-1.28, Figure 3b).

The funnel plot indicates that there exists bias and heterogeneity (Supplement1b), then we use trim and fill method for the forest plot (Supplement1a) and funnel plot (Supplement1c), but there was no significant difference (OR = 0.62, 95%CI = 0.36 - 1.08, Supplement1a).

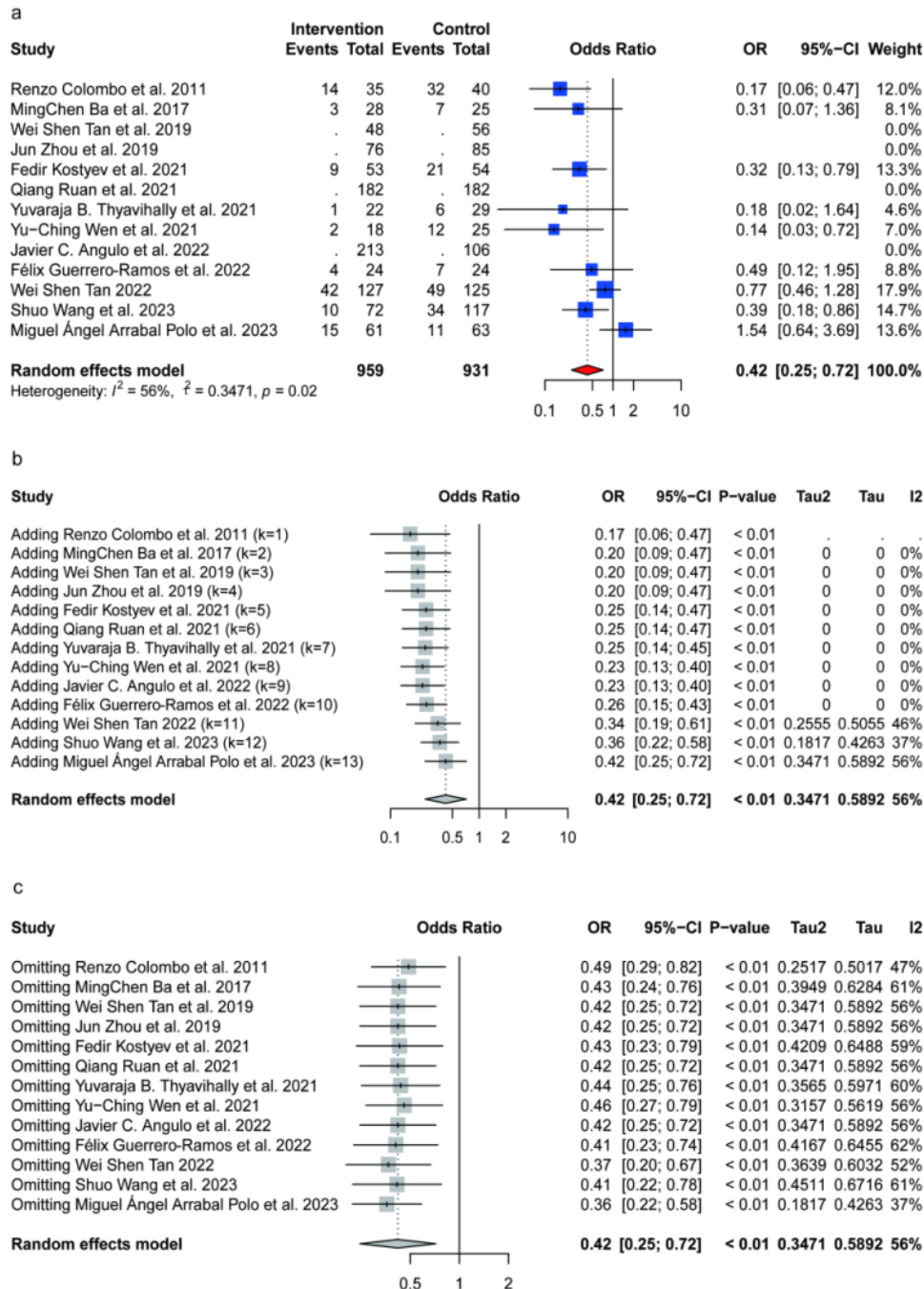


Figure 1. Forrest plots of recurrence rate comparing hyperthermic intravesical chemotherapy and control groups

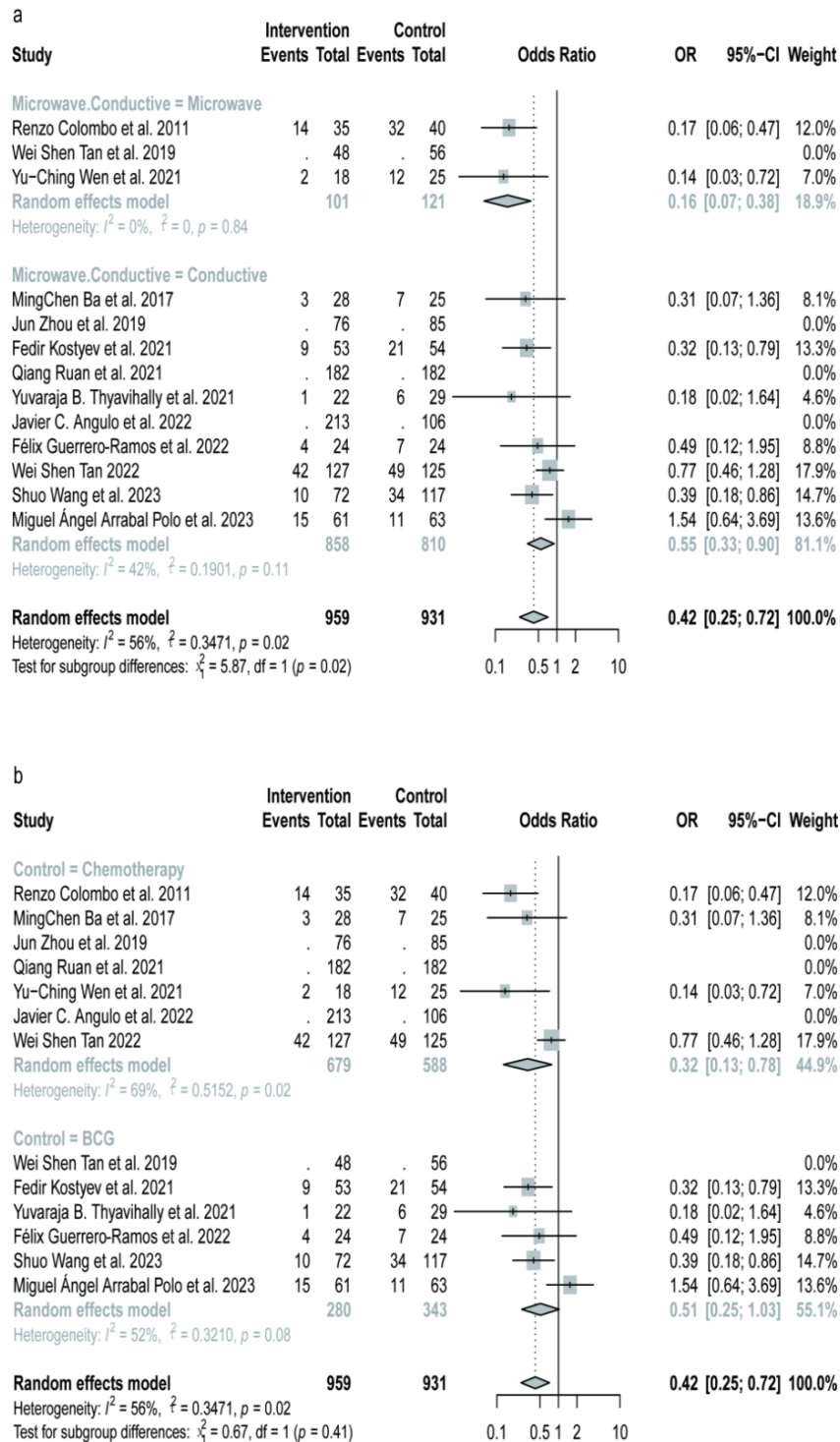


Figure 2. Forrest plots for the meta-analysis of the recurrence rate by different subgroups

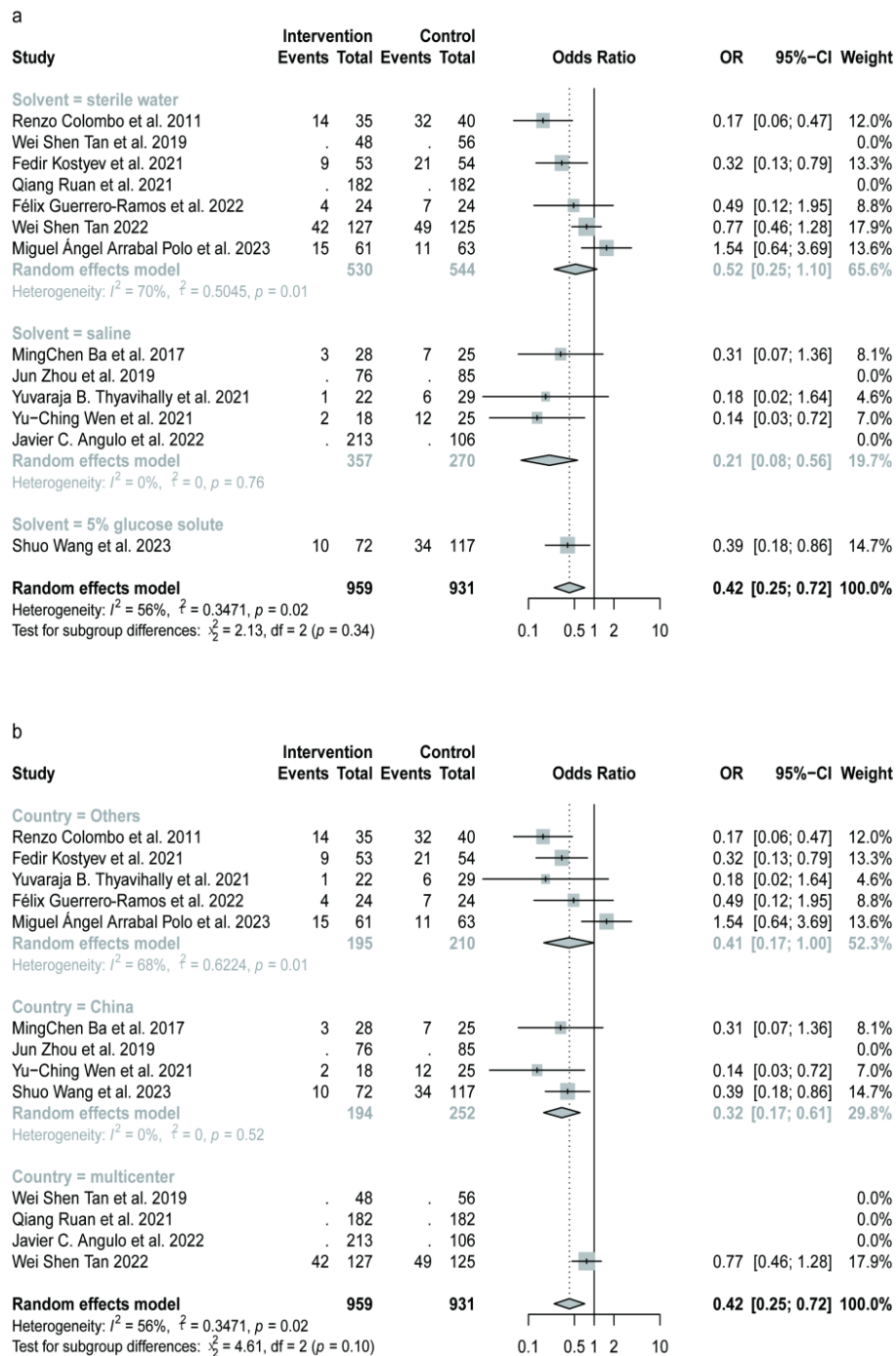


Figure 3. Forrest plots for the meta-analysis of the recurrence rate by different subgroups

3.3. Survival Data

3.3.1. OS

There are 4 studies containing 739 patients included in the hazard ratio (HR) of OS analysis. We used fix-effects model for analysis considering the heterogeneity was low ($P=0.29, I^2=20\%$). Although the OS of the hyperthermic intravesical chemotherapy is better than control group but with no statistical significance ($HR = 0.84$, $95\%CI = 0.59-1.19$, $p=0.7805$, Figure 4a) and so do the forest plot using trim and fill method ($HR = 0.77$, $95\%CI = 0.39-1.52$, Figure 4d). Accumulative analysis and sensitive analysis reveal the results are not stable (Figure 4b,c).

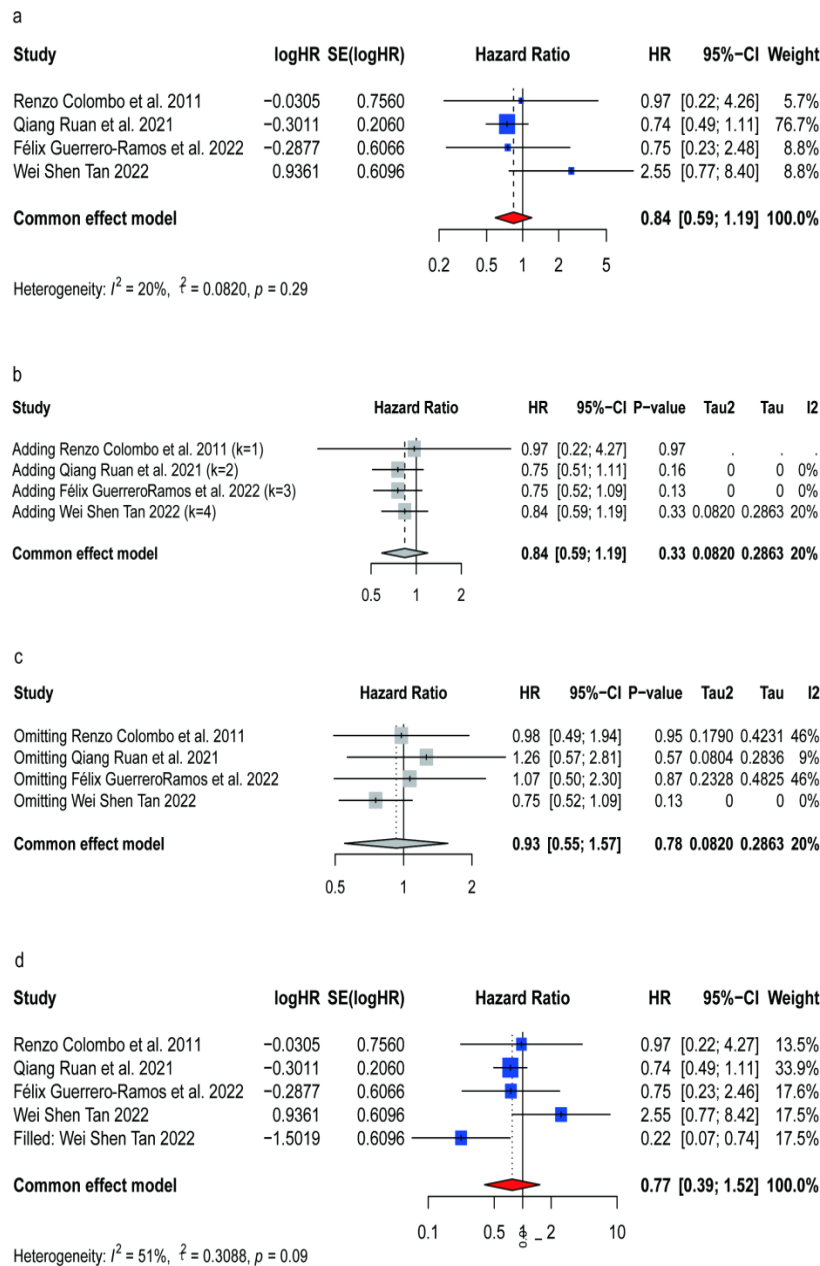


Figure 4. Forrest plots of overall survival comparing hyperthermic intravesical chemotherapy and control groups

3.3.2. PFS

There are 3 studies containing 461 patients included in the HR of progress free survival (PFS) analysis. We used random-effects model for analysis considering the heterogeneity was high ($P=0.01$, $I^2=78\%$). The result is not statistically significant ($HR = 0.51$, $95\%CI = 0.06-4.08$, $p=0.5285$, Supplement2a), and so do the forest plot using trim and fill method ($HR = 2.87$, $95\%CI = 0.24-34.02$, Supplement2d). Accumulative analysis and sensitive analysis reveal the results are not stable (Supplement2b,c).

3.3.3. RFS

Totally 9 studies contain 1214 patients were included in the HR of recurrence free survival (RFS) analysis. The heterogeneity is low ($P=0.40$, $I^2=4\%$) so we used random-effects model for analysis and conducted subgroup analysis. The meta-analysis demonstrated a significant difference ($HR = 0.69$, $95\%CI = 0.54-0.88$, $p=0.0029$, Figure 5a) in RFS between hyperthermic intravesical chemotherapy with control groups. Accumulative analysis and sensitive analysis shows the result is stable (Figure 5b,c). The funnel figure reveals that bias and heterogeneity is unobvious

(Supplement3c), and we use trim and fill method for the forest plot (Supplement3a) and funnel plot (Supplement3b), which may present a better result (HR = 0.65, 95%CI = 0.51-0.82, Supplement3a).

We separately use way of heat, control therapy, solvent, country and study type to conduct the subgroup analysis. Conductive hyperthermic intravesical chemotherapy has better RFS than control groups (HR = 0.67, 95%CI = 0.48-0.93, Figure 6a) but microwave hyperthermic intravesical chemotherapy is not statistical better than control group (HR = 0.77, 95%CI = 0.49-1.20, Figure 6a). And hyperthermic intravesical chemotherapy have an advantage over normal intravesical chemotherapy (HR = 0.62, 95%CI = 0.45-0.84, Figure 6b) but no significant difference over BCG therapy (HR = 0.82, 95%CI = 0.56-1.21, Figure 6b). Concerning kinds of solvent, group of sterile-water (HR = 0.72, 95%CI = 0.54-0.96, Figure 7a) is statistically significant comparing to group of saline (HR = 0.68, 95%CI = 0.37-1.25, Figure 7a). Considering the country as subgroup, group of multicenter have better RFS (HR = 0.71, 95%CI = 0.53-0.94, Figure 7b) but both group of China (HR = 0.49, 95%CI = 0.21-1.13, Figure 7b) and group of others (HR = 1.04, 95%CI = 0.41-2.65, Figure 7b) have no statistical significance.

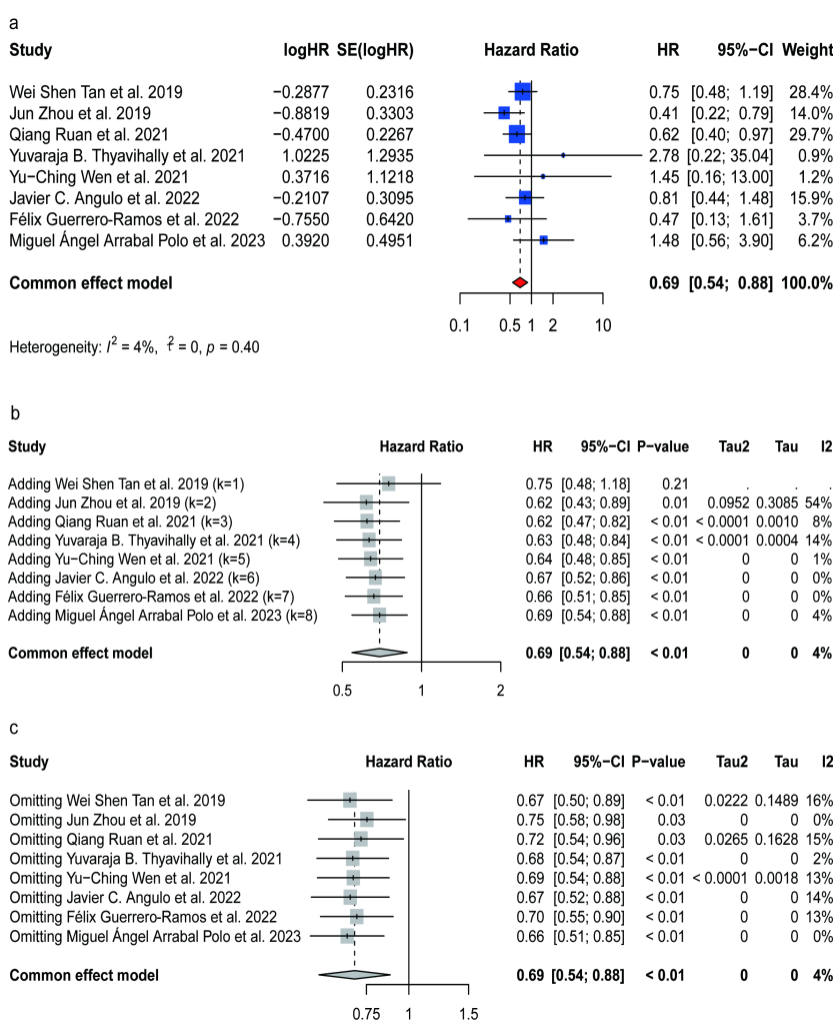


Figure 5. Forrest plots of recurrence free survival comparing hyperthermic intravesical chemotherapy and control groups

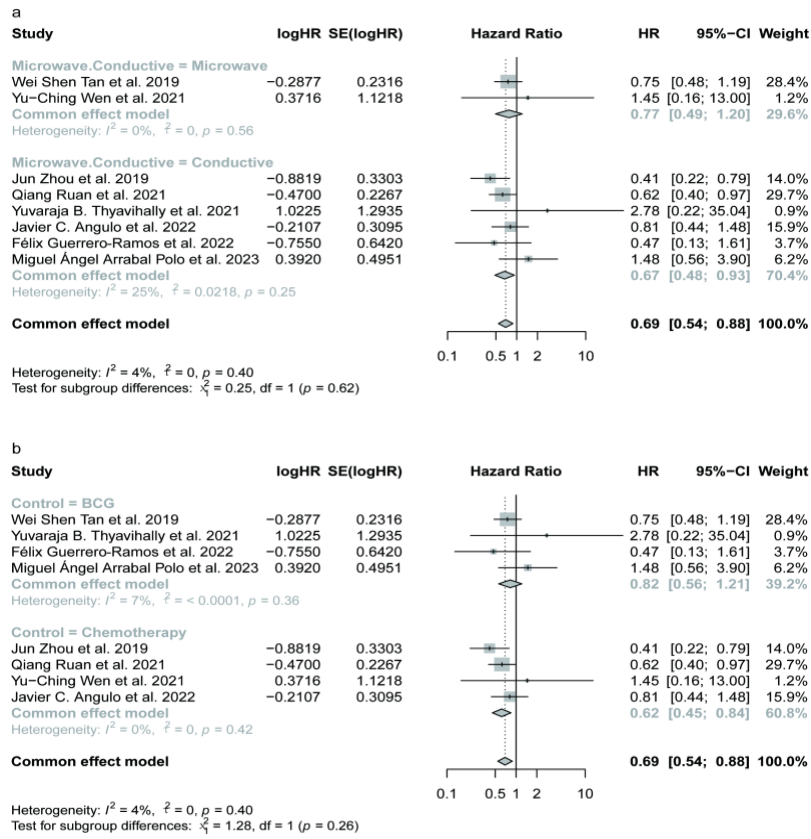


Figure 6. Forrest plots for the meta-analysis of recurrence free survival by different subgroups

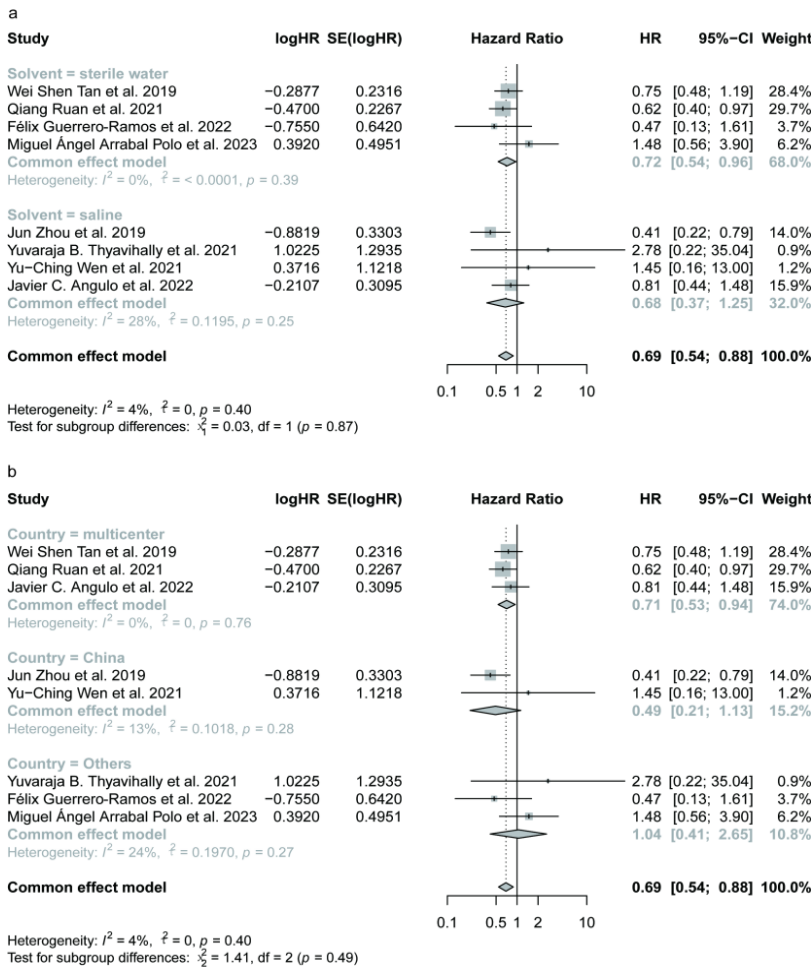


Figure 7. Forrest plots for the meta-analysis of recurrence free survival by different subgroups

4. Discussion

After the diagnosis of NMIBC, TURBT is the essential therapy but there still be a high probability of residual tumors and progression to MIBC even with detrusor muscle in the sample (13). Patients who diagnosed with non-muscle-invasive bladder cancer account for the 75% of all bladder cancer patients, and radical cystectomy is inevitable once they progress as muscle-invasive bladder cancer (14), so the suspension of the recurrence and progress is the key. BCG (bacillus Calmette-Guérin) is the most verified therapy but with shortage and high rate of failure (1). Among those BCG-failure NMIBC patients, radical cystectomy seems to be the best option (1) although it impairs the quality of life of patients. Besides, between 13% and 19% of patients discontinue therapy because of side effects like hematuria, dysuria, and urinary tract infections (UTI) (15). Compared with BCG, normal intravesical chemotherapy such as Mitomycin C(MMC) couldn't reach a satisfying result in recurrence (16) or progression (17) so it can hardly serve as an independent therapy. Therefore, as a therapy that has aroused discussion in recent years, hyperthermic intravesical chemotherapy may act as an alternative to BCG. This article compared the efficacy and side effects of intravesical hyperthermic chemotherapy with other commonly used treatments to examine whether hyperthermic intravesical chemotherapy can be the new trend.

In this meta-analysis, both Intravesical bacillus Calmette-Guérin and normal intravesical chemotherapy are control groups. The results show that hyperthermic intravesical chemotherapy is better in recurrence rate (OR = 0.42) and recurrence free survival (HR = 0.69) which proves hyperthermic intravesical chemotherapy is a potential choice. There is no statistical difference in OS (HR=0.84) and DFS (HR = 0.51), we deduce that limited number of studies may be the reason.

Microwave hyperthermia and conductive hyperthermia are two common ways of hyperthermia. A study demonstrate that Hyperthermia could improve cell membrane permeability and increase drug absorption (18, 19). It also makes the issue release the heat shock proteins (HSPs) which activate the immune system to kill cancer cells (20, 21). Microwave hyperthermia deliver energy to the entire bladder at a frequency of 915 MHz by microwave radiation which can penetrate low-conductive tissues (22) while conductive hyperthermia is the process of heating chemotherapy (23) to conduct heat which requires less care and monitoring than microwave hyperthermia (24). We took hyperthermia as a subgroup, both ways of hyperthermia can reduce the recurrence rate (microwave hyperthermia OR = 0.16, conductive hyperthermia OR = 0.55), and microwave hyperthermia has more obvious effect. We speculated that microwave hyperthermia has stronger penetration rate and even can work on the full bladder wall thickness (24) while the actual temperature of conductive hyperthermia is more difficult to control (25). When it comes to RFS, conductive thermochemotherapy (HR = 0.67) was still a protective factor compared with the control group, but there was no statistical difference between microwave hyperthermic intravesical chemotherapy (HR = 0.67) and the control group, which possibly because only two articles were included in the analysis.

Due to the difference between BCG and normal intravesical chemotherapy, separating the control group may produce more precise results, so we performed the subgroup analysis by treatment of the control group. Hyperthermic intravesical chemotherapy is superior to normal intravesical chemotherapy in both recurrence rate (OR = 0.32) and RFS (HR = 0.62). In summary, it can be explained that hyperthermic intravesical chemotherapy can greatly improve the effectiveness of chemotherapy (18-21). At the same time, hyperthermic intravesical chemotherapy has no statistically advantage over BCG. More data are needed to ensure whether hyperthermic intravesical chemotherapy can be a substitute.

Since all these studies mainly use saline and sterile water as solvents, so drug solvents were used for the subgroup analysis. The results showed that in terms of recurrence rate, the saline as a solvent for chemotherapy drugs has statistically difference, while in terms of RFS (HR=0.72), sterile water (distilled water) as a solvent for chemotherapy drugs has statistically effect. So, we couldn't make a decision whether saline was the better choice.

Considering the influence of different regions, we divide the articles into China, multicenter and others. The results of OR and RFS are not consistent, so it is hard to draw the conclusion.

The effect of bladder hyperthermia on cancer cells is of great value to NMIBC patients. Although the advantage of hyperthermia is not statistically significant compared with BCG, it provides an additional treatment method for patients who have failed BCG treatment. Moreover, compared with BCG's high cost and shortage crisis, hyperthermia is undoubtedly the preferred choice in poor regions.

The experimental group in this paper included MMC and pirarubicin (THP), but the subgroup analysis was not conducted in this respect due to the lack of studies on the THP treatment group. Meanwhile, drugs like epirubicin, doxorubicin and gemcitabine are all potential choices for thermochemotherapy (26-28). So, if there will be more studies added, it may be possible to select the best thermochemotherapy drug by the subgroup analysis.

The temperature of hyperthermic intravesical chemotherapy may have an impact on treatment, because increasing temperature can lead to exponential growth of cell death (29), and cancer cells are more sensitive to temperature than common cells (30). In the studies included in this meta, the devices used in hyperthermia chemotherapy were different, and the temperature could only be controlled between 41-45°C, so it was difficult to analyze by subgroup. Time also has an effect on thermochemotherapy, and the study have shown that the concentration of drugs rises rapidly within 15 minutes, and the concentration peaks in 45-60 minutes (31). However, the time control of the included articles is limited to a certain range, so more articles are expected to appear to find the most appropriate time for hyperthermia chemotherapy.

The meta-analysis exists some limitations. First, some HR values were extracted through the survival curve so some errors may exist. Hence, we repeat it three times and take the average to reduce the influence. And we only included English language studies, which would lead to publication bias, while due to the small number of included studies, we could not evaluate publication bias. Last, considering the difficulty of obtaining articles, we did not retrieve unpublished studies. So, we expect more clinical studies so we could get a more convincing result.

5. Conclusion

This meta-analysis demonstrated that hyperthermic intravesical chemotherapy could reduce the recurrence rate and improve the RFS of bladder cancer patients with NMIBC. Although no statistical difference between the OS, PFS and bladder cancer, some clinical studies still showed a positive attitude. Thus, further analyses await the publication of more studies.

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