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SYSTEMATIC REVIEW

A systematic review and meta-analysis of intraarterial chemotherapy for non muscle invasive bladder cancer: Promising alternative therapy in high tuberculosis burden countries

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Summary

Introduction: *Local therapies for high risk non-muscle-invasive bladder cancer (NMIBC) such as intravesical chemotherapy (IVC) have shown a high rate of progression and recurrence (1). Intravesical Bacillus Calmette-Guérin (BCG) for local therapies has been shown to reduce progression and recurrence in patient with NMIBC. However, its potential role is limited in high burden countries for tuberculosis (TB) due to its low specificity that can cause wrong diagnosis or false positive in patients with clinically diagnosed tuberculosis. BCG vaccine that has to be given for most people in tuberculosis endemic countries will induce trained immunity that could reduce the effectivity of intravesical BCG for NMIBC Moreover, intravesical BCG is contraindicated in patient with or previous tuberculosis. The potential clinical benefit of intraarterial chemotherapy (IAC) in delaying the recurrence and progression of high-risk NMIBC have been investigated with promising results (2, 3). We aimed to conduct a meta-analysis to evaluate the potential anti-tumor effect of IAC in NMIBC.*

Methods: *We conducted a comprehensive search of published articles in Cochrane Library, Pubmed, and Science-Direct to identify relevant randomized controlled trials (RCTs) and observational studies comparing IAC alone or combined with IVC versus IVC/BCG alone in NMIBC. The protocol of preferred reporting items for systematic review and meta-analysis (PRISMA) was applied to this study.*

Results: *Four RCTs and 4 cohort observational studies were eligible in this study and 5 studies were included in meta-analysis. The risk ratio of tumor recurrence was reduced by 35% (RR = 0.65; 95% CI 0.49-0.87; p = 0.004) in IAC plus IVC, while recurrence-free survival (RFS) was prolonged by 45% (HR: 0.55; 95% CI, 0.44-0.69; p < 0.001). The risk of tumor progression was reduced by 45% (RR = 0.55; 95% CI 0.41-0.75; p = 0.002) and tumor progression-free survival (PFS) was also prolonged by 53% (HR: 0.47; 95% CI, 0.34-0.65; p < 0.001). Some RCT's had high or unclear risk of bias, meanwhile 4 included cohort studies had overall low risk of bias, therefore the pooled results need to be interpreted cautiously. Subgroup analysis revealed that the heterogeneity outcome of tumour recurrence might be attributed to the difference in NMIBC stages and grades.*

Conclusions: *The IAC alone or combined with IVC following bladder tumor resection may lower the risk of tumor recurrence and progression. These findings highlight the importance of further multi institutional randomized controlled trials with bigger sample size using a standardized IAC protocol to validate the current results.*

KEY WORDS: *Intraarterial chemotherapy; Bladder cancer; NMIBC; Tumor recurrence; Tumor progression.*

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INTRODUCTION

Urothelial bladder cancer is one of the most common cancer by incidence in men and women (4). It occurs four times more frequently in men than in women worldwide with an average age of 70 years at diagnosis (5). The WHO classifies primary tumor of bladder as *non-muscle invasive bladder cancer* (NMIBC) and *muscle invasive bladder cancer* (MIBC) (6). The NMIBC accounts for 75% of all bladder cancer incidence and 20-25% of NMIBC cases presented with T1 stages (7, 8). The 5-year progression and recurrence rates in patients with T1 stage of NMIBC are 20.7% and 41.8%, respectively. Cancer specific death for high-risk NMIBC progressing to MIBC is 65.0% (8, 9).

The disease management for NMIBC should be stratified into low risk, intermediate risk, high risk and very high risk group. *Transurethral bladder tumor resection* (TURBT) followed by single instillation of *intravesical chemotherapy* (IVC) is recommended for low risk group. More advanced therapy is needed for intermediate, high risk and very high risk group. Intermediate risk group need to add intravesical BCG for 1 year or IVC for up to 1 year. For high risk group, only intravesical BCG for 1-3 years after TURBT is an alternative to radical cystectomy. IVC is not recommended by some guidelines for high risk group. Radical cystectomy is the therapy of choice for very high risk group. Intravesical therapy is one strategy for bladder preservation, although the efficacy of IVC in reducing recurrence and progression is arguable. On the other hand, early cystectomy might result in excessive treatment for some patients being associated with decreasing patient's quality of life (QoL) (4, 10).

Nowadays, transurethral tumor resection followed with *Bacillus Calmette-Guérin* (BCG) instillation has been considered the gold standard of bladder preservation treatment (7, 11). Nonetheless, 37-45% patients with NMIBC suffer recurrence within 2 years (12). A systematic review of 1.476 patients concluded that adjuvant IVC after TURBT may help to prevent recurrence but not progression (13). Furthermore, the use of BCG for IVC in tuberculosis-burden/endemic countries can be challenging, since the primary diagnostic tests for tuberculosis (acid-fast bacillus smear or culture) could not differentiate between mycobacterium bovis as the cause of BCG disease and mycobacterium tuberculosis, leading to false positive/wrong diagnosis. BCG vaccine that has to be given for most people in tuberculosis endemic countries will induce trained immunity that could reduce the effectivity of intravesical BCG for NMIBC. Some clinicians are afraid of giving this treatment due to the evidence of disseminated BCG, urinary tract tuberculosis and miliary tuberculosis, moreover, intravesical BCG is contraindicated in patient with or previous tuberculosis (14-16).

Looking to these drawbacks, a novel strategy to enhance the efficacy of IVC following TURBT in delaying the recurrence and progression of high-risk NMIBC is currently emerging. *Intra-arterial chemotherapy* (IAC), which was initially introduced by Kubota et al. (1986), could reduce disease recurrence and progression to MIBC. The injection of chemotherapeutic agents into the artery that lead to the tumor, may increase its efficacy and reduce the systemic toxicity (17, 18). Administration of chemotherapy using the IAC method increases the local peak of plasma concentration of the drug, resulting in higher tumor concentrations of the chemotherapy agent (17-19). The IAC has been shown to be an effective treatment for NMIBC patients and even MIBC. Three- and five-years overall survival in patients with MIBC that received IAC for bladder preservation therapy were 70-75% and 60-65%, respectively, whilst their five year rates of recurrence and progression were 62.2% and 76.9%, respectively. The potential toxicity of IAC is less when compared to systemic chemotherapy in patient with MIBC (17-20). To date, systematic reviews and meta-analysis supporting the use of IAC for NMIBC are scarce. The objective of this meta-analysis was to critically review and evaluate the quality of the evidence supporting the use of IAC for high-risk NMIBC.

Materials and methods

This meta-analysis followed The *Preferred Reporting Items for Systematic Reviews and Meta-analysis* (PRISMA) protocol for conducting and reporting meta-analyses (21).

This systematic review and meta-analysis was registered through the international prospective register of systematic reviews (PROSPERO) as CRD42020165004.

Systematic search

A systematic search was carried out in August 2022. *Cochrane Library*, *PubMed* and *Science-Direct* were used to identify the relevant studies. The detailed search strategy was performed using advanced search of each database (Table 1). The reference list of trials, review and clinical practice guidelines were also searched to find other relevant literatures.

Inclusion and exclusion criteria

Randomized controlled trials (RCT) and observational studies were included in this study. Only English-language publications that meet the inclusion criteria were included. The included studies must contain intra-arterial chemotherapy, and a control group that only receive *intravesical chemotherapy* (IVC) or another treatment.

The IAC group could receive instillation of intravesical chemotherapy for both induction and maintenance with subsequent intra-arterial chemotherapy or receive only IAC using *Seldinger* technique. Meanwhile the control group only received intravesical chemotherapy instillations for induction and maintenance or received another treatment such as intravesical BCG. There was no restriction of any type and dose of chemotherapy for this systematic review and meta-analysis.

The 1973 or 2004 *World Health Organization* (WHO) system of TNM classification and tumor grade was used in this study for bladder cancer staging and grading (22, 23). Patients with Ta, T1 and *carcinoma in situ* (CIS) transitional cell carcinoma of the bladder that was histologically confirmed with all tumor grades (G1, G2, G3 or LG and HG) are considered appropriate as long as meet the criteria of high risk group. Any method of bladder tumor resection was considered acceptable.

Studies without control were included in the systematic review. Review articles, editorials, commentaries, letters, animal studies, abstract only and case series or case con-

Table 1.
Search strategy including search terms and databases.

Database	Search Terms
Pubmed	(((((("intraarterial"[All Fields] OR "intraarterially"[All Fields]) AND ((((((("chemotherapy s"[All Fields] OR "drug therapy"[MeSH Terms]) OR ("drug"[All Fields] AND "therapy"[All Fields])) OR "drug therapy"[All Fields]) OR "chemotherapies"[All Fields]) OR "drug therapy"[MeSH Subheading]) OR "chemotherapy"[All Fields])) OR ("intra-arterial"[All Fields] AND ((((((("chemotherapy s"[All Fields] OR "drug therapy"[MeSH Terms]) OR ("drug"[All Fields] AND "therapy"[All Fields])) OR "drug therapy"[All Fields]) OR "chemotherapies"[All Fields]) OR "drug therapy"[MeSH Subheading]) OR "chemotherapy"[All Fields])))) AND ("nmibc"[All Fields] OR "nmibcs"[All Fields])) OR ("non"[All Fields] AND ((("muscle s"[All Fields] OR "muscles"[MeSH Terms]) OR "muscles"[All Fields]) OR "muscle"[All Fields]) AND (((((((("invasibility"[All Fields] OR "invasible"[All Fields]) OR "invasion"[All Fields]) OR "invasions"[All Fields]) OR "invasive"[All Fields]) OR "invasively"[All Fields]) OR "invasiveness"[All Fields]) OR "invasives"[All Fields]) OR "invasivity"[All Fields])))) AND ((((("urinary bladder neoplasms"[MeSH Terms] OR (("urinary"[All Fields] AND "bladder"[All Fields]) AND "neoplasms"[All Fields])) OR "urinary bladder neoplasms"[All Fields]) OR ("bladder"[All Fields] AND "cancer"[All Fields])) OR "bladder cancer"[All Fields])
	Additional Filter: Randomized controlled trial, Clinical Study, Clinical Trial, Controlled Clinical Trial, Comparative Study, Multicenter Study and Observational Study
Science-Direct	Intraarterial bladder cancer: title, abstract, keywords; Intraarterial chemotherapy bladder cancer: title, abstract, keywords
Cochrane	(intraarterial chemotherapy): ti,ab,kw AND (bladder cancer): ti,ab,kw

trol were excluded. Studies that did not measure the tumor progression or recurrence rates in IAC and control group were also excluded.

Study selection and data extraction

The first (ZRA) and second (LHA) investigator independently performed both the study selection and data extraction. Should problems or disagreements occur, they were resolved by discussion. The information retrieved from each study included: author name, year, country and type of the study, clinical follow-up protocol, intraarterial chemotherapy protocol, numbers of intervention and control group outcomes (tumor recurrence, tumor progression, toxicity, withdrawal), *Risk Ratio* (RR), *Hazard Ratio* (HR) and *confidence interval* (95% CI) of each outcome results.

Statistical analysis

The primary outcomes of this meta-analysis were tumor recurrence and tumor progression. RR with a 95% CI was used to measure the primary outcomes. *Recurrence-free survival* (RFS) and *progression-free survival* (PFS) were measured using HR with a 95% CI. In a study without published HR, we measured the HR and 95% CI using a method for estimating HR by *Tierney* (24).

Statistical heterogeneity

The Cochrane Q test and I^2 statistics were used to evaluate the heterogeneity of studies. This method would have quantified inconsistency among studies. Heterogeneity was considered significant if the I^2 was greater than 50% and P value less than 0.05 (25). Random-effects model was used should a significant heterogeneity occur; otherwise, a fixed-effects model was used (26, 27). Data analysis and synthesis were performed using Review Manager software (*version 5.3.5, The Cochrane Collaboration, Oxford, UK*).

Risk of Bias

The risk of bias for each RCT study that meet the inclusion criteria was assessed by the Cochrane tool using review manager software, which included selection bias, performance bias, detection bias, attrition bias, and reporting bias (28). We used CLARITY system tool to assess the risk of bias for cohort studies (29). In addition, the quality of the included observational studies was evaluated according to the Newcastle Ottawa quality assessment scale (30).

Sensitivity analysis

A sensitivity analysis was performed by excluding a study one by one, to validate the results consistency of this meta-analysis (31). Subgroup analyses were also performed considering the highest risk of NMIBC to analyse the sources of potential heterogeneity (32).

Results

Search results and study characteristics

We identified 436 references in our systematic literature search. Following a full text review of 152 articles, eight relevant studies consisting of 4 RCTs and 4 cohort studies were synthesized and analysed. Three studies were included only in the systematic review because of difference in the control group. The excluded studies were listed in this meta-analysis protocol (Figure 1).

A total of 846 patients were pooled from 5 eligible stud-

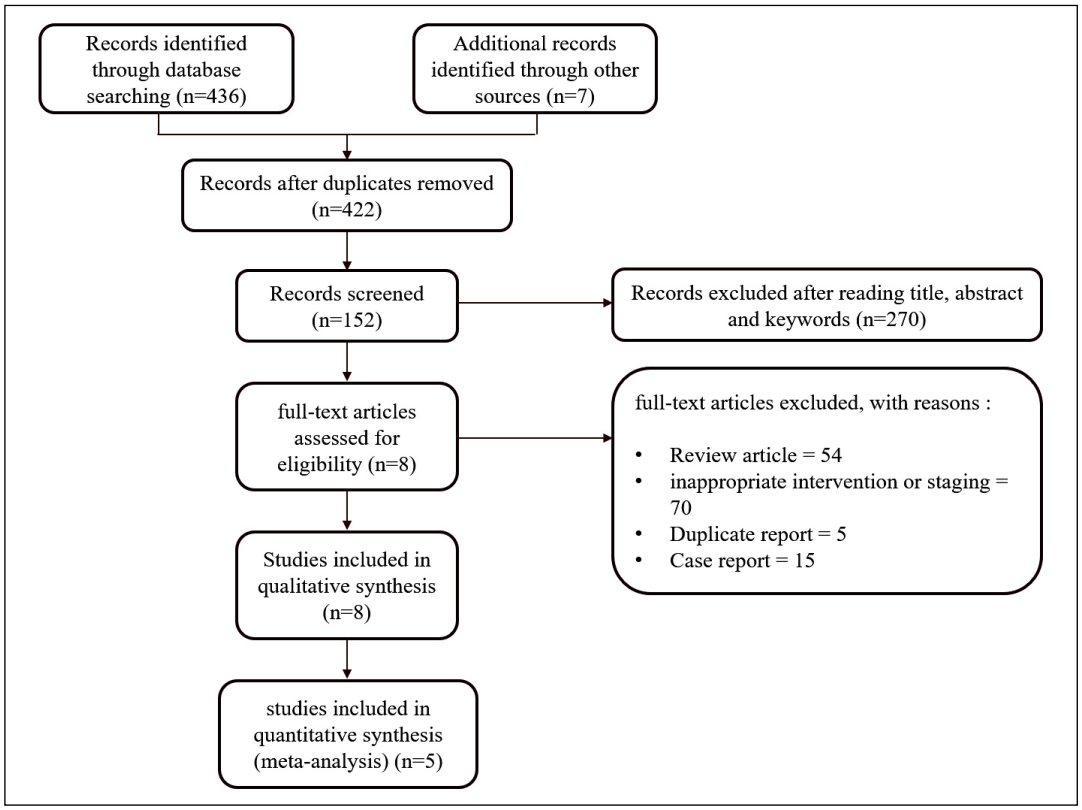


Figure 1. *PRISMA Flowchart for Systematic Search Strategy.*

Table 2.
Studies included in this meta-analysis comparing intra-arterial only or combined with intravesical chemotherapy with control groups.

Study	Country	No. of patient		Follow up (mo)		Recurrence		Progression	
		IAC	IVC	IAC	IVC	IAC	IVC	IAC	IVC
Bin Huang et al. 2018 (2)	China	53	98	79 (7-131)	59 (7-127)	19 (35.8%)	41 (41.8%)	11 (20.7%)	23 (23.5%)
Feng Sun et al. 2019 (3)	China	141	142	47.3 (16-78)	46.8 (13-76)	41 (29.1%)	61 (42.9%)	22 (15.6%)	36 (25.3%)
Junxing Chen et al. 2013 (36)	China	29	31	22 (5-58)	23 (11-58)	3 (10.3%)	14 (45.2%)	0 (0%)	7 (22.6%)
Zefu Liu et al. 2018 (35)	China	62	141	51 (21-83)	35 (23-60)	28 (45.2%)	78 (55.3%)	10 (16.1 %)	48 (34.0%)
Fan Lian et al. 2019 (34)	China	99	50	24.25 (5-50)	22.30 (10-42)	24 (24.2%)	26 (52.0%)	2 (2.0%)	4 (8.0%)
Bin Huang et al. 2021 (37)	China	43	53 BCG	28 (10-58)	25 (11-56) (BCG)	12 (27.9%)	14 (26.4%) (BCG)	4 (9.3%)	5 (9.4%) (BCG)
Eapen L et al. 2004 (20)	America	21	-	34 (2-180)	-	5 (23%)	-	n.a	-
Chen M.K et al. 2009 (40)	China	25	27	40 (6-67)	40 (6-67)	3 (12%)	14 (51.8)	0 (0%)	7 (25.9%)

Table 3.
Characteristics of all studies.

Study	Inclusion criteria	IAC protocol				Follow up protocol
		Drugs	Dose	frequency	Time	
Bin Huang et al. 2018 (2)	Primary, High grade T1 NMIBC	Cisplatin; Pirarubicin	60; 50	4 cycles with 1 month interval between each injection	4 month (4 cycles)	Cystoscopy, urine cytology and blood test every 3 months for 2 years and yearly thereafter
Feng Sun et al. 2019 (3)	Primary or recurrence NMIBC, T1G3 tumor, CIS, multiple and recurrent and large (> 3 cm) Ta, and G1 and G2 tumors (High risk NMIBC)	Cisplatin; Epirtubicin	50; 30	3 cycles with 4 weeks interval between each injection	3 months (3 cycles)	Cystoscopy, urine cytology, routine blood examination, serum biochemistry every 3 months, chest X ray, CTU, enhanced pelvic MRI every 6 months in the first 2 years, and then cystoscopy every 6 months between 3 and 5 years and annually thereafter
Junxing Chen et al. 2013 (36)	Primary or recurrence NMIBC, T1G3 tumor	Cisplatin; Epirtubicin	60; 50	4-6 weeks interval between each injection	No data	Cystoscopy and urine cytology every 3 months for the first 2 years and then cystoscopy every 6 months between 3 to 5 years and annually thereafter
Zefu Liu et al. 2018 (35)	Primary or recurrence NMIBC, T1 G1-G3 tumor	Cisplatin; Gemcitabine	25; 800	28 days interval between cycles	2 months (2 cycles)	Cystoscopy every 3 months for the first 2 years and then every 6 months for 5 year and then every year thereafter
Fan Lian et al. 2019 (34)	Primary tumor, NMIBC, Histopathological diagnosis transitional cell carcinoma	Cisplatin; Epirubicin	60; 50	4-6 weeks interval between each injection	3-4 months (3 cycles)	Cystoscopy every 3 months for the first 2 years and then every 6 months thereafter, CT urogram at 3 months postoperatively and then 6-12 months thereafter
Bin Huang et al. 2021 (37)	Primary or recurrence tumor, NMIBC, High risk features	Cisplatin; Epirubicin	60 ; 50	1 month interval between each injection	4 months (4 cycles)	Cystoscopy every 3 months for a period of 2 years and then every 6 months for the next 3 years. Bladder biopsy if there was suspicious of tumor during follow up
Eapen L et al. 2004 (20)	Primary or recurrence tumor, all stage and grade tumor	Cisplatin (with adjuvant radiotherapy to bladder 40 gy)	60-120	3 weeks interval between each injection	2 months (3 cycles)	Cystoscopy, bladder biopsies and urinary cytology 6-8 weeks after last cycles. CT scan imaging
Chen M.K et al. 2009 (40)	Primary tumor, G3 superficial without any other concomitant types of tumor, no less than three tumors, T1, no less than 3 cm in diameter	Gemcitabine; Cisplatin	900; 30	4 weeks interval	3 months (3 cycles)	Cystoscopy every 3 months in first 2 years then every 6 months for 2-5 years. Chest X ray annually.

ies. Inclusion criteria, number of patients, tumor recurrence, tumor progression, chemotherapy protocol and follow-up protocol were recorded (Tables 2, 3). One study included all the stages of bladder cancer, therefore we only included the data of NMIBC patients from that study (33). Cisplatin chemotherapy (25-120 mg) for IAC was used in all of the studies. It was combined with epirubicin (30-50 mg) in 3 studies, with pirarubicin (50 mg) in one study and with gemcitabine (800 mg) in another study. The IAC protocols varied from one instillation every 2-3 weeks to one every 4 weeks (Tables 2, 3) (2, 3, 33-38).

Figure 2.
Forrest plot of Recurrence Rates.

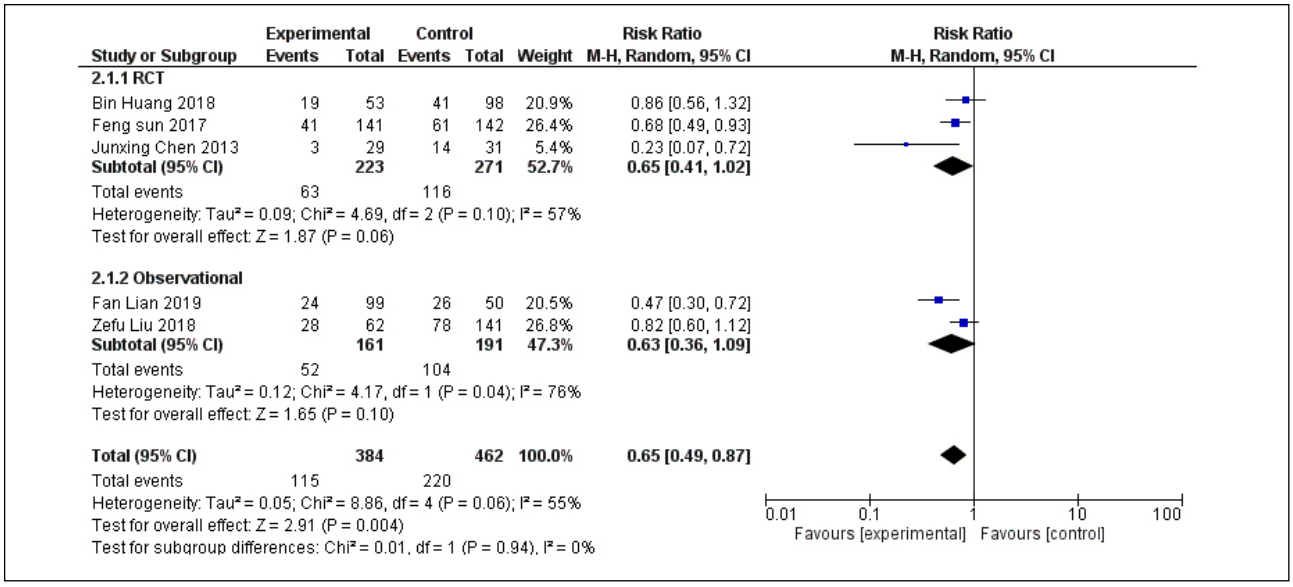
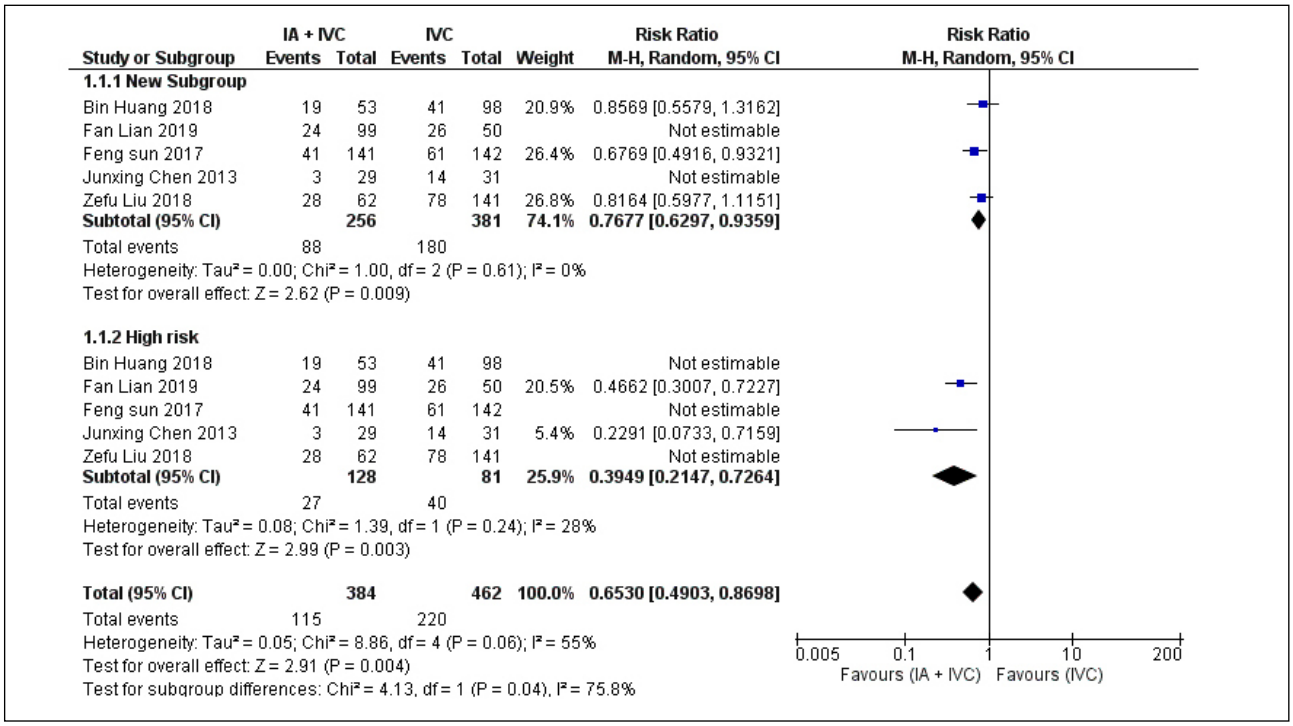


Figure 3.
Forrest plot of Recurrence Rates with subgroup of difference risk stratification of NMIBC.



Tumor recurrence

All five studies showed that the IAC group had lower tumor recurrence rate; however, 2 studies did not show a statistical significance for this outcome. The overall I^2 was 55.5% and p-value for heterogeneity was 0.06, therefore random effects model was used for this outcome. About 115 (29.94%) patients on IAC group and 220 (47.61%) on IVC group, had tumor recurrence during the follow up of each study. We observed a reduction of 35% in the recurrence's risk ratio on IAC group (RR = 0.65; 95% CI 0.49-0.87; p = 0.004), as shown in Figure 2. Pooled-effects of RCTs were similar to those of cohort studies for all outcome measurements. We further performed a subgroup analysis for this outcome that included the highest risk NMIBC. Tumor recurrence reduction in the IAC group was different for these two subgroups, suggesting that the different stage and grade of tumors might increase the heterogenity of this outcome (Figure 3). IAC only showed less recurrence if compared with IVC only and had comparable result with BCG instillation only (Table 2) (37, 38).

Figure 4.
Forrest plot of Progression Rates.

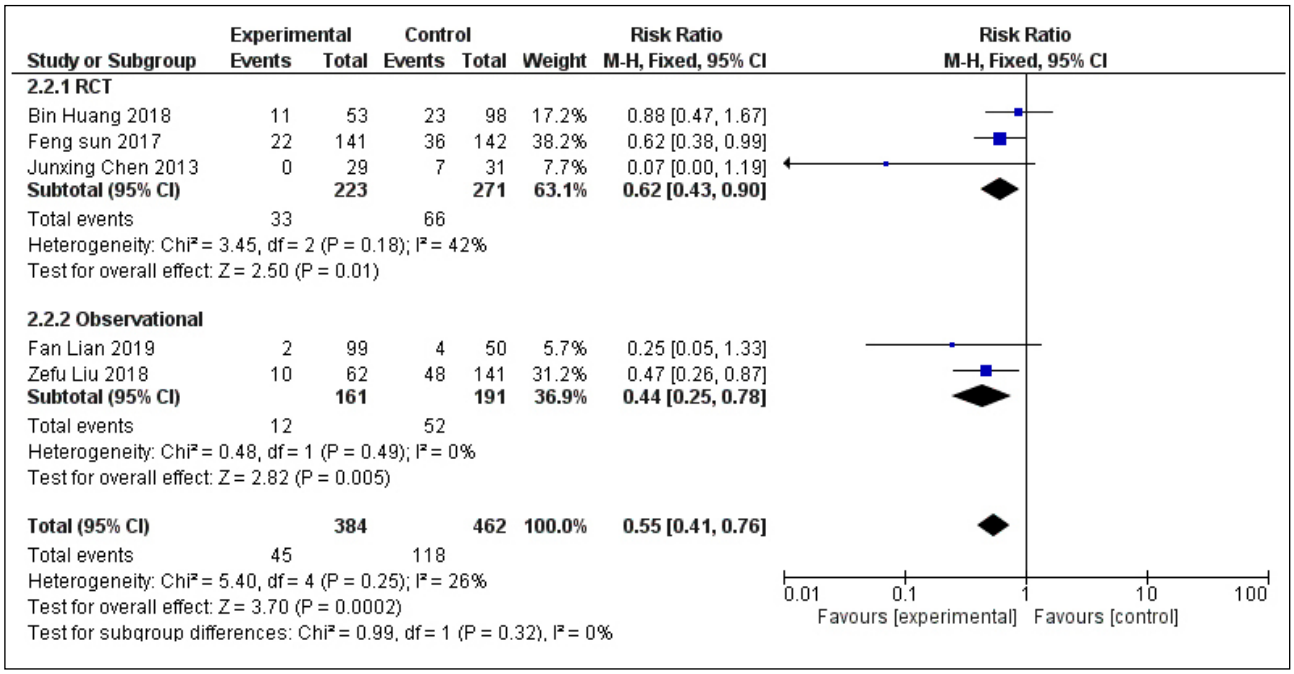
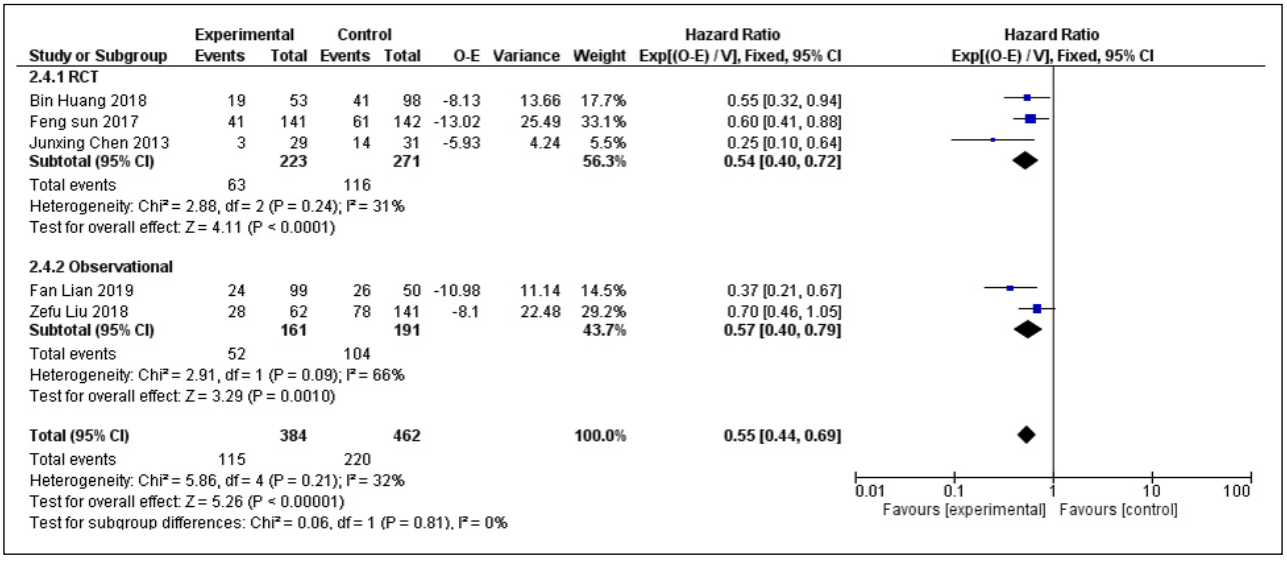


Figure 5.
Forrest plot of Reccurence Free Survival.



Tumor progression

All five included studies favoured IAC group, although 3 studies did not reach statistical significance. We used fixed-effects model for this outcome since there was low heterogeneity between all included studies (I^2 = 26%, p = 0.25). We found that 11.71% (45/384) of patients in the IAC group experienced tumor progression compared to 25.54% (118/462) in patients who received IVC only. There was 45% reduction in the RR of tumor progression on patients receiving IAC. When stratified by study design, cohort observational studies showed a lower risk of tumor progression in the IAC group compared to the IVC group (RR = 0,44; 95% CI = 0.25-0,78; p < 0,005; I^2 = 0%) (Figure 4). Moreover, in qualitative measure, IAC only showed less progression if compared with IVC only and had comparable result with BCG instillation only (Table 2) (37, 38).

Recurrence free survival and progression free survival

In this meta-analysis, we observed that the IAC group had longer RFS compared to the IVC group (HR: 0.55; 95% CI, 0.44-0.69; p < 0.001) (Figure 5).

There was a slight increase of heterogenity in all pooled-studies (I^2 =32%, p = 0.21). We used fixed effects model despite of the moderate heterogenity for this outcome.

Figure 6.
Forrest plot of Progression Free Survival.

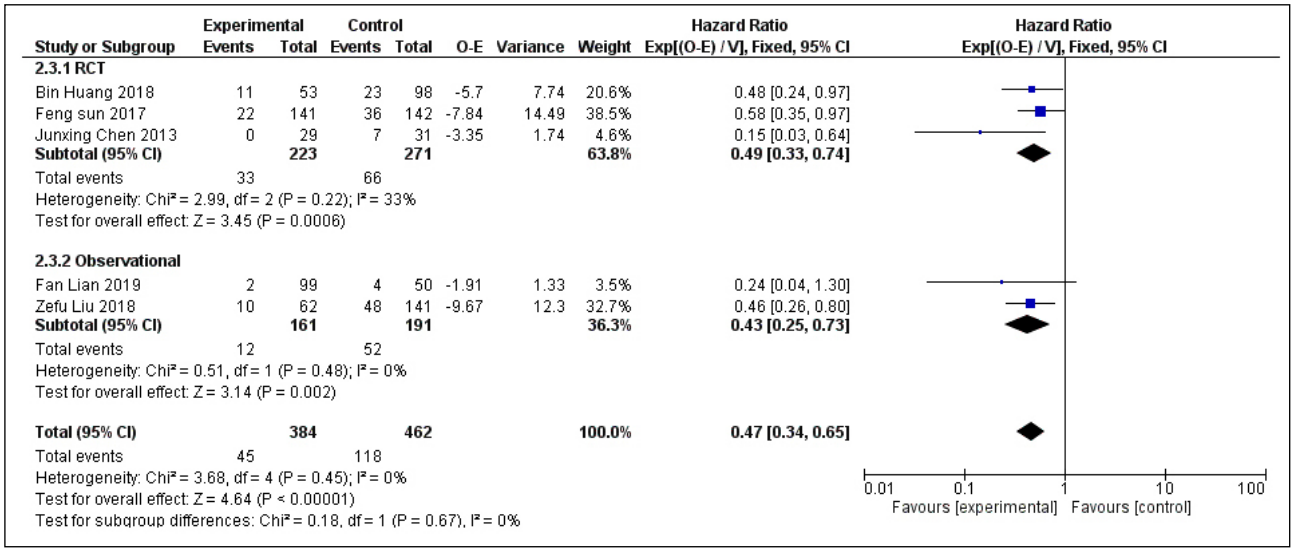


Table 4.
Side effects in maintenance group of included studies.

Study	IAC type and dose	Time	No. of total Patients	Nausea/ vomiting	Neutropenia	Increased Liver Enzyme	Increased Creatinine	Low Leukocytes Count	Anemia	Thrombocytopenia
Bin Huang et al. 2018 (2)	Cisplatin 60; Pirarubicin; 50	4 months	53	35	9	12	3	7	n.a	n.a
Feng Sun et al. 2019 (3)	Cisplatin 50; Epirubicin 30	3 months	141	53	14	n.a	n.a	n.a	21	9
Junxing Chen et al. 2013 (36)	Cisplatin 60; Epirubicin 50	n.a	29	15	3	5	2	3	n.a	n.a
Zefu Liu et al. 2018 (35)	Cisplatin 25; Gemcitabine 800	2 months	62	24	21	9	9	23	24	16
Fan Lian et al. 2019 (34)	Cisplatin 60; Epirubicin 50	3-4 months	99	8	n.a	n.a	n.a	n.a	2	2
Bin Huang et al. 2020 (37)	Cisplatin 60; Epirubicin 50	4 months	43	12	5	4	1	7	n.a	n.a
Chen M.K et al. 2009 (40)	Gemcitabine 900; cisplatin 30	3 months	25	3	n.a	n.a	2	5	2	1

n.a, data was not available.

Similarly, PFS was significantly increased in the IAC group (HR: 0.47; 95% CI, 0.34-0.65; p < 0.001) (Figure 6). Fortunately, the measured heterogeneity between all pooled- studies was very low (I^2 = 0%, p = 0.45). When stratified by study design, both RCT and cohort observational studies subgroups of RFS and PFS showed a similar and significant pooled effect.

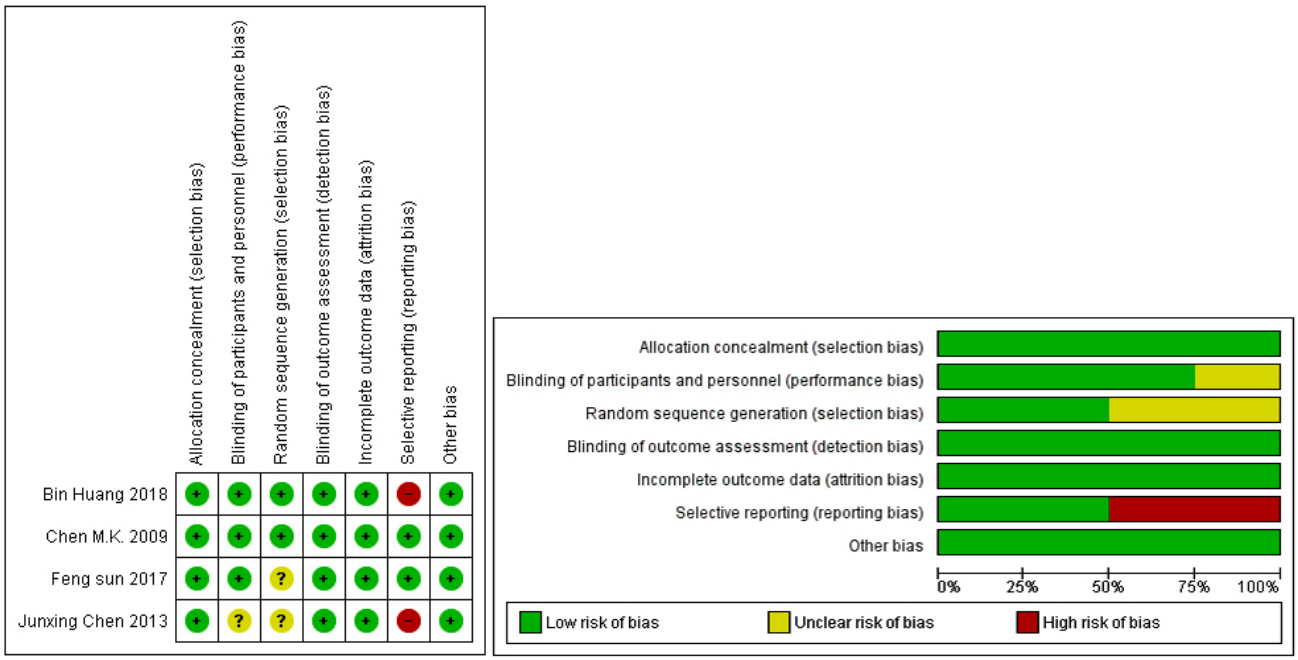
Side effects of treatment

Seven studies reported the number of patients suffered from chemotherapy side effects in group receiving IAC (Table 4). One study couldn't be extracted for side effect data because they added pelvic radiotherapy to IAC (33). The common toxicities were nausea/ vomiting, neutropenia, anemia, low leukocyte count, increased liver enzyme, increased serum creatinine and thrombocytopenia. Table 4 showed the number of patients withdrew from the intraarterial chemotherapy and their main reasons. We measured that 75% of all patients in 5-pooled studies could stand and completed the whole IAC protocol (Table 5).

Table 5.
Withdrawal in maintenance group of included studies.

Study	No. of Patients	No. of Withdrawal	Withdrawal reasons (n)
Bin Huang et al. 2018 (2)	53	19	Died caused by progressed bladder cancer (3), Tumor reccurence (16)
Feng Sun et al. 2019 (3)	141	51	Died caused by bladder tumor (9), Died caused by pneumonia (1), tumor recurrence (41)
Junxing Chen et al. 2013 (36)	29	4	Died caused by non-oncologic factor (1), Tumor recurrence (3)
Zefu Liu et al. 2018 (35)	62	20	Died caused by bladder tumor (8), Recurrence and progression (9), severe hematological toxicity (2), Personal reasons (1)
Fan Lian et al. 2019 (34)	99	2	Tumor progression (2)

Figure 7.
Risk of Bias of RCT Studies.



The causes of withdrawal were toxicity, tumor recurrence and progression. Quantitative analyses were not performed as all 5 pooled studies did not report the side effects and withdrawal patients in their control group.

Sensitivity analysis

Sensitivity analysis was performed to validate the results consistency by excluding studies one by one. We did not find any significant variation in the combined-RR for the primary outcomes (tumor recurrence and tumor progression), thus the results may be considered relatively stable and consistent among studies. However, the IAC did not significantly reduce the risk of recurrence (RR = 0.70; 95% CI 0.49-1.00; p = 0.05) after excluding *Sun et al.* and *Chen et al.* studies.

The tumor progression showed similar trend, where IAC did not significantly prevent patients from progression if we excluded *Lian et al.*, *Sun et al.* and *Liu et al.* studies (RR = 0.63; 95% CI 0.35-1.15; p = 0.13).

Risk of Bias

Cochrane tools was used to evaluate the risk of bias of randomized controlled trial study (Figure 7).

For all included RCT's study, patients were assigned randomly into IAC or control (IVC or BCG) with adequate technical description. However, there are two studies that did not describe the process of randomization (3, 36). All RCT studies have low risk of bias in allocation concealment. Only one study did not describe how the physicians were blinded to the study participants. Figure 7 shows that 50% of the studies had high risk of bias in selective reporting due to the unreported HR of progression and recurrence free survival in two of the studies (2, 36). Therefore, we had to use an indirect method of estimating HR (24). All studies had low risk of bias in attrition bias and other bias. In conclusion 2 studies has high risk of bias, 1 study has unclear risk bias and another one has low risk of bias.

For non-randomised studies, the risk of bias was assessed using CLARITY tools for cohort studies. Fortunately, all included cohort studies had low risk of bias in all 7 points of CLARITY tools (Table 6).

In Addition, the quality of included observational studies was evaluated according to the Newcastle Ottawa quality assessment scale (30).

Table 7 summarized the total score acquired for each quality domain. Based on the selection domain, three studies scored four out of four points. In the comparability domain, 2 studies scored one over two points and another 2 studies scored a full point of two. In the exposure domain, all four cohort studies scored three out of four quality score points.

Four cohort studies were considered to have good quality of study design (20, 34, 35, 37).

Table 6.
CLARITY tool for assessing quality of observational studies.

Study	Study year	CLARITY tools						
		1	2	3	4	5	6	7
Zefu Liu et al.	2018	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Fan Lian et al.	2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Bin Huang et al.	2021	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Eapen L et al.	2004	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Table 7.
Newcastle Ottawa Scale (NOS) tool for assessing quality of observational studies.

Study	Study year	Quality Score Point			
		Selection	Comparability	Exposure	Total
Zefu Liu et al.	2018	4	1	3	8
Fan Lian et al.	2019	4	2	3	9
Bin Huang et al.	2021	4	2	3	9
Eapen L et al.	2004	3	1	3	7

Selection: maximum 4 points.
Comparability: maximum 2 points.
Exposure: maximum 3 points.
≥ 7 points were considered as "good", 2 to 6 points were considered as "fair", and ≤ 1 point was considered as "poor" quality.

Discussion

The present study was based on RCTs and cohort observational study that explored the effect of IAC on the risk of recurrence, progression, RFS and PFS when treating NMIBC. This study was restricted to the trials comparing intraarterial only or combined with *intravesical chemotherapy* (IAC) *versus intravesical chemotherapy* (IVC) or BCG directly, to avoid trials with major differences in treatment regimens (28). Low heterogeneity between included studies was detected by the Cochrane Q test and I2 statistics and RR was used to compare the treatment effect in groups of patients categorized by several confounders. However, our study was not without limitations. We have included 4 non RCTs which may involve eliminating selection, recall, and confounder biases. Moreover, we have also included one pilot RCT which only enrolled few subjects for its trial. Potential clinical heterogeneity might results by inclusion of studies, in which patients with NMIBC of different tumor stages,grades and risk were considered and treatment protocols were performed with different chemotherapy agents, doses and schedules. However, previous studies suggested that the optimal number of induction instillations and optimal frequency and duration of IAC was not fully known, and there was no large differences in efficacy between various drugs and different dose of intraarterial chemotherapy (13, 35, 39). Interestingly, with the exception of tumor recurrence, low heterogeneity between included studies was detected by the Cochrane Q test and I^2 statistics in our study. So the potential clinical heterogeneity of included studies might not significantly interfere with the pooled results of our study and we considered it appropriate to perform a meta-analysis. Different follow-up protocols among the included studies could also affect the outcomes as patients less frequently monitored would appear to have a recurrence at later time frames compared to those that were more closely monitored. Our study could not perform quantitative analyses of side effects and withdrawal since they were not reported in the control groups (IVC only).

Several weaknesses affected the quality of the data provided. Four of 8 studies included in this meta-analysis were cohort studies. It is undeniable that these cohort studies had good study designs and robust data collection and each study had appropriate sample size and clear comparison. However, the evidence from cohort studies have to be considered as level 2, thus they had lower hierarchy of evidence than RCTs. To evaluate the efficacy of IAC in NMIBC more accurately, more RCTs with good study design and large sample sizes are necessary.

Additionally, we also observed some drawbacks in the RCTs that were included in this review. Despite the importance for assessing quality of a study, we found that most of the included RCTs did not describe the details of allocation concealment and blinding, therefore the potential biases-involved were unclear (Figure 7). If bias existed, it would have a great impact on the interpretation of the meta-analysis.

The pooled results in our study showed that for intermediate or high-risk NMIBC, induction IVC followed by IAC instillation after bladder tumor resection, compared with IVC only, could reduce the risk ratios of tumor recurrence and tumor progression, and prolong RFS by 45% and PFS by 63%. All studies demonstrated prolonged-PFS with IAC, but progression was defined as a broad, composite end point: worsening-free survival, which was created by the authors. Studies that couldn't be measured in meta-analysis also showed that IAC only is superior than IVC and has comparable result with BCG only in terms of reducing recurrence and progression. There was some confusion in treating patients with NMIBC in high tuberculosis burden country. Most guidelines suggested BCG instillation in intermediate, high and very high risk of NMIBC, although there is a risk of tuberculosis seeding, mislead diagnosis and reduced treatment efficacy in tuberculosis endemic area, where IAC could be a promising therapy.

To explore the sources of potential clinical heterogeneity of included studies, a subgroup analysis for tumor recurrence was performed by different risk criteria of NMIBC in our study (21). The reduction in tumor recurrence with IAC differed from those with highest risk NMIBC and those who are not. This result implied that the stage, grade and risk of NMIBC might be one of the sources of potential clinical heterogeneity of included studies. However, since the subgroup analysis might be underpowered, the conclusions should be drawn cautiously. The optimal duration and schedule of IAC protocol is not fully defined yet. Previous studies recommended at least 3-4 cycles (with 2-4 weeks interval between each instillation) of IAC that are required in order to obtain superiority of IAC over IVC for prevention of recurrence or progression. The IAC is associated with more systemic side effects compared to control group, but all of these were minor. Finally, the benefit of IAC should be weighed against its added cost, side effects and inconvenience.

Conclusions

It may be concluded from this meta-analysis that IAC injections only or combined with IVC instillation preceded by bladder tumor resection could reduce the risk of tumor recurrence and progression, and extend the recurrence free survival and progression free survival in intermediate, high-risk or even the highest risk of NMIBC, compared to the IVC or BCG instillation only. IAC could be a promising treatment option for NMIBC in high tuberculosis burden country. However, a standardized-IAC protocol has not been definitely determined, therefore further RCTs with

larger number of NMIBC patients in a multi-institutional scheme are emerging to reach this aim.

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