

Evaluating the efficacy and safety of intravesical chemotherapies for non-muscle invasive bladder cancer: a network meta-analysis

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ABSTRACT

Various intravesical therapies have been introduced into clinical practices for controlling non-muscle invasive bladder cancer (NMIBC). However, evidence with respect to the efficacy and safety of those intravesical therapies is very limited. Hence, we present a network meta-analysis in order to address this limitation in the current literature. The primary outcomes were the risk of tumor recurrence (TR), tumor progression (TP) and disease-specific mortality (DM). Secondary outcomes included the risk of fever, cystitis and haematuria. Conventional pair-wise and network meta-analysis were both performed for each endpoint. The surface under the cumulative ranking curve (SUCRA) was incorporated in our analysis for ranking the corresponding intravesical instillation interventions. In total, 23 randomized clinical trials (RCTs) were finally included in our study after irrelevant papers were screened out. Results of network meta-analysis suggested that Epirubicin (EPI) was less preferable than Bacille Calmette Guerin (BCG), BCG+EPI, BCG+ Isoniazid (INH), BCG+ Mytomicin C (MMC), Gemcitabine (GEM) and MMC with respect to TR. As suggested by the corresponding ranking probabilities and SUCRA, incorporating EPI or MMC into BCG may enhance the efficacy of BCG monotherapy.

INTRODUCTION

A large number of populations suffer from bladder cancer which resulted in 380,000 cases and 150,000 deaths over the world in 2008 [1]. Bladder cancer is classified as either muscle-invasive bladder cancer (MIBC) or non-muscle-invasive bladder cancer (NMIBC) according to disease severity (high or low) and the extent of permeation [2]. Approximately 70% of bladder cancers are NMIBC

which can be further classified into carcinoma-in-situ (CIS), papillary tumor (Ta) and those that are able to invade the lamina propria rather than the detrusor muscle (T1) [3]. Transurethral resection (TUR) is a standard treatment for NMIBC [4]. However, patients treated with TUR are often accompanied with a high tumor recurrence (TR) rate ranging from 50% to 70% as well as a high tumor progression (TP) rate between 10% and 20% over a period of 2–5 years [5, 6]. Hence, a few intravesical

therapies which instill chemotherapeutic agents into bladder have been developed to supplement TUR.

Bacille Calmette-Guerin (BCG) is one of the most popular chemotherapeutic agents that have been incorporated into intravesical therapies. Adjuvant treatments such as intravesical instillations of BCG are appropriate for those NMIBC patients with a high risk of recurrence [4, 7]. Unfortunately, about one third of NMIBC patients eventually experience side effects resulted from BCG, including mild dysuria [8]. Recently, mytomicin C (MMC) is introduced into intravesical therapies in order to overcome the corresponding side effects [9]. MMC is effective for non-severe bladder cancer and it is usually administered by using multiple infusions which is able to produce response rates ranging between 40% and 50% [6].

Apart from the above mentioned chemotherapeutic agents, epirubicin (EPI) is another one which is applied in conjunction with intravesical therapies and the popularity of EPI has been increased in the Europe and Japan [10]. EPI belongs to the anthracyclines family and it was developed to reduce adverse effects resulted from chemotherapeutic agents without significant compensation of antitumor effects [11]. Antitumor effects are triggered by EPI which is able to interfere with DNA synthesis and EPI is associated with a relatively low risk of side effects particularly in patients with Ta or T1 bladder cancer [12].

On the other hand, new agents such as gemcitabine (GEM) are well adapted for intravesical instillation treatment and they are usually incorporated into systemic therapies for advanced invasive bladder cancer [13]. GEM is an antimetabolite pyrimidine base analogue and it has been widely used as a chemotherapeutic agent for pancreatic and lung cancer [14, 15]. Various experimental studies *in vitro* and *in vivo* have been conducted to verify the effects of GEM on bladder cancer and its efficacy has been validated in an *in vitro* model [16].

As suggested by published data, intravesical chemotherapies (both monotherapy and polytherapy), namely BCG, EPI, MMC and GEM, are effective for preventing TR and TP [9, 17–19]. However, a comprehensive analysis of both efficacy and safety of these therapies has not been disclosed by the current literature due to the lack of evidence. For this purpose, we designed this network meta-analysis in order to determine the relative efficacy and safety of several intravesical chemotherapies: BCG, BCG+EPI, BCG+ Isoniazid (INH), BCG+MMC, EPI, GEM and MMC.

RESULTS

Baseline characteristics of the included studies

In total 23 randomized clinical trials (RCTs) were finally included in our study after screening out irrelevant papers (Table 1) [6, 20–41]. Among the total 5,822 subjects

with follow-up periods ranging from 1 to 7.2 years, 2,399 (41.21%) individuals were treated with BCG and 1,064 (18.28%) individuals were treated with MMC (Figure 1). There are 2 three-arm trials and 21 two-arm trials which contain a total of seven comparisons. Moreover, there are 22 studies in which TR was assessed as the primary endpoint. TP and disease-specific mortality (DM) was assessed by 20 and 12 trials, respectively. Secondary endpoints including fever, cystitis and haematuria were researched in 9, 8 and 11 studies, respectively. The quality of included studies was assessed by using the Jadad scale (Supplementary Table S1).

Pair-wise meta-analysis

The summary odds ratios (ORs) of the corresponding outcomes (TR, TP, DM, fever, cystitis, haematuria) for each direct comparison were calculated. The results of pair-wise meta-analysis were showed in Table 2. Patients with EPI exhibited an increased risk of TR compared to those with BCG (OR = 1.58, 95% CI = 1.23–1.90, $P < 0.001$). By contrast, patients with BCG+MMC exhibited a significantly lower risk of TR than those with BCG (OR = 0.25, 95% CI = 0.10–0.61, $P = 0.002$). Besides that, patients with EPI or MMC exhibited a higher risk of TP than those with BCG (EPI: OR = 1.71, 95% CI = 1.16–2.53, $P = 0.007$; MMC: OR = 3.05, 95% CI = 2.24–4.17, $P < 0.001$). Moreover, patients with MMC were associated with a reduced risk of fever compared to those with BCG (OR = 0.22, 95% CI = 0.13–0.38, $P < 0.001$), while those with BCG + INH were associated with an increased risk of fever in relation to patients with BCG (OR = 1.92, 95% CI = 1.25–2.94, $P = 0.003$). Furthermore, both EPI (OR = 0.64, 95% CI = 0.48–0.86, $P = 0.003$) and BCG + EPI (OR = 0.44, 95% CI = 0.23–0.86, $P = 0.016$) appeared to be more effective than BCG in reducing the risk of cystitis. Finally, patients with MMC (OR = 0.55, 95% CI = 0.41–0.75, $P = 0.011$) and EPI (OR = 0.54, 95% CI = 0.39–0.74, $P < 0.001$) were associated with approximately 45% reduction in the risk of haematuria.

As suggested by Table 2, heterogeneity among studies did not appear to be significant and thereby the fixed-effect model was incorporated in our analysis for some the comparisons. However, significant heterogeneity was presented in some comparisons (GEM vs. BCG, $I^2 = 52.37%$, in TR; MMC vs. BCG, $I^2 = 91.64%$, in TP; EPI vs. BCG, $I^2 = 51.78%$, in DM; BCG+MMC vs. BCG, $I^2 = 56.00%$, in fever; MMC vs. BCG, $I^2 = 57.80%$, in cystitis and MMC vs. BCG, $I^2 = 66.89%$, in haematuria) and hence the random-effects model was implemented for these comparisons.

Network meta-analysis

Table 3 demonstrated the mixed comparisons results by synthesizing all evidence within the network. Patients

Table 1: The main characteristics of included studies

Author	Year	Follow-up (yr)	Size	Age	Male (%)	Intervention	Induction	Outcomes					
								TR	TP	DM	Fever	Cystitis	Haematuria
Solsona	2015	7.1	407	67	89.9	MMC+BCG	30 mg + 81 mg Connaught strain	44	26	10			
						BCG	81 mg Connaught strain	68	24	15			
Gontero	2013	1	120	67.4	85.8	BCG	27 mg Connaught strain	14	3				
						GEM	2000 mg	16	5				
Järvinen	2012	7.2	68	68	80.9	MMC	-	35	14	12			
						MMC+BCG	-	19	8	8			
Oosterlinck	2011	4.7	96	69	86.5	MMC+BCG	40 mg + TICE 5 × 10 ⁸ CFU	23	2	0			
						BCG	TICE 5 × 10 ⁸ CFU	26	5	6			
Hinotsu	2011	2	115	NR	90.4	BCG	81 mg Connaught strain	19	3				69
						EPI	40 mg	22	7				
Sylvester	2010	9.2	837	67	NR	EPI	50 mg	147	24	19			
						BCG	TICE 5 × 10 ⁸ CFU	103	19	9			
						BCG+INH	TICE 5 × 10 ⁸ CFU + 300 mg	110	23	10			
Porena	2010	3.7	64	69.4	84.4	BCG	TICE 5 × 10 ⁸ CFU	9	5		2		
						GEM	2000 mg	17	10		0		
Di Lorenzo	2010	1.3	80	70.4	61.2	GEM	2000 mg	21	7		1		2
						BCG	81 mg Connaught strain	35	13		3		5
Addeo	2010	3	120	66.4	85.3	MMC	40 mg	22	10			12	4
						GEM	2000 mg	15	6		3		2
Cai	2008	1.3	161	NR	85.7	EPI+BCG	80 mg + TICE 5 × 10 ⁸ CFU	34	2				
						BCG	TICE 5 × 10 ⁸ CFU	40	4				
Ojea	2007	4.4	430	64.5	87	BCG	27 mg Pasteur	88	32	8			
						MMC	30 mg	58	141	7			
Friedrich	2007	2.9	495	67.4	80.2	BCG	RIVM 2 × 10 ⁸ CFU	41			15		19
						MMC	20 mg	62			8		15
de Reijke	2005	5.6	168	NR	92	BCG	81 mg Connaught strain	9		9	6	15	33
						EPI	50 mg	21		13	0	7	23
Cheng	2005	5.1	209	69.9	71.2	BCG	81 mg Connaught strain	30	9	13			
						EPI	50 mg	59	16	7			
Kaasinen	2003	4.7	304	70.5	80.3	MMC+BCG	40 mg				13		
						BCG	120 mg Connaught				10		
Di Stasi	2003	3.6	108	NR	73	BCG	81 mg Pasteur	19	6		7	24	26
						MMC	40 mg	46	14		0	22	14
van der Meijden	2001	3.5	957	66	77	EPI	50 mg	142	19	12	34	82	45
						BCG	TICE 5 × 10 ⁸ CFU	98	9	5	38	111	93
						BCG+INH	TICE 5 × 10 ⁸ CFU + 300 mg	100	15	8	72	113	78
Bilen	2000	1.5	41	55	95.1	BCG	81 mg Connaught strain	4	2	0	3		8
						EPI+BCG	50 mg and 81 mg Connaught strain	3	1	0	2		4
Ali-El-Dein	1999	2.5	139	58.2	77.4	EPI+BCG	50 mg and 150 mg Pasteur strain	7	3		0	18	0
						BCG	150 mg Pasteur strain	12	5		3	36	4
Witjes	1998	7.2	344	NR	81.7	BCG	RIVM strain	76	21	12		30	
						MMC	30 mg	72	12	8		37	
Rintala	1996	2.8	188	68	75.5	MMC	20–40 mg	58	3				
						MMC+BCG	20–40 mg	57	3				
Melekos	1996	2.9	94	NR	NR	BCG	150 mg Pasteur strain	16	5			33	11
						EPI	50 mg	22	7			12	6
Lamm	1995	2.5	377	67	83	BCG	TICE 50 mg	77	15	8	38	19	85
						MMC	20 mg	101	25	12	8	19	61

*yr: year; BCG: Bacille Calmette Guerin; MMC: Mytomycin C; GEM: Gemcitabine; EPI: Epirubicin; INH: Isoniazid; TR: tumor recurrence; TP: tumor progression; DM: disease-specific mortality.

with all other treatments exhibited a significantly lower risk of TR than those with EPI (OR = 0.40, 95% CrI = 0.25–0.62; OR = 0.25, 95% CrI = 0.10–0.60; OR = 0.51, 95% CrI = 0.26–0.96; OR = 0.26, 95% CrI = 0.11–0.54; OR = 0.33, 95% CrI = 0.15–0.73; OR = 0.45, 95% CrI = 0.25–0.83). On the other hand, patients with MMC exhibited experienced 84% and 91% reduction in the risk of fever compared to those treated with BCG and BCG+INH, respectively (OR = 0.16, 95% CrI = 0.04–0.50; OR = 0.09, 95% CrI = 0.01–0.97). As suggested by Figures 2–5, no significant inconsistency between direct and indirect evidence was presented with respect to TR, TP, DM or haematuria and thereby a consistent model was used in our analysis.

The estimated probabilities and their corresponding SUCRA are displayed in Figure 6. Incorporating EPI or MMC into BCG (EPI+BCG, MMC+BCG) appeared to be the most preferred interventions with respect to TR, TP and DM. As for fever, cystitis and haematuria, BCG+EPI also exhibited a satisfied SUCRA value. Overall, incorporating EPI or MMC into BCG (EPI+BCG, MMC+BCG) was potentially more preferable than others when all of the six endpoints were taken into account.

DISCUSSION

Instillation therapy with BCG has been considered as the standard treatment for patients with NMIBC [42]. The limitation of BCG motivates researchers to

seek alternative chemotherapeutic agents that may have equivalent efficacy. We extracted data from 23 studies which incorporate a total of seven bladder intravesical instillation methods for NMIBC patients. Our objective is to determine whether these approaches have comparable efficacy with an increased safety and tolerability level. Direct evidence from conventional meta-analysis indicates that BCG is more preferred than EPI with respect to TR and TP. On the other hand, our network-meta analysis indicates that EPI is the worst with respect to TR. As shown by the corresponding ranking based on SUCRA values, both BCG + EPI and BCG + MMC have superior performance in comparison to other bladder intravesical instillations.

Adjuvant instillation of BCG has been verified as the most effective intravesical therapy that is able to prevent TR and progression [43–45]. Studies have concluded that the TR rate and TP rate can range from 23% to 49% and 4.8% to 25.6% over a five-year period among patients with intermediate and high-risk NMIBC [46, 47]. Furthermore, several studies reported that maintenance instillation of BCG is more effective than both chemotherapy and BCG monotherapy with respect to recurrence prevention for NMIBC patients [44, 48, 49]. However, maintenance instillation of BCG is not recommended for all NMIBC patients due to potential side effects [47].

EPI (4'-epidoxorubicin) is an antineoplastic agent which is derived from doxorubicin and it exerts antitumor effects by affecting DNA synthesis and such a mechanism

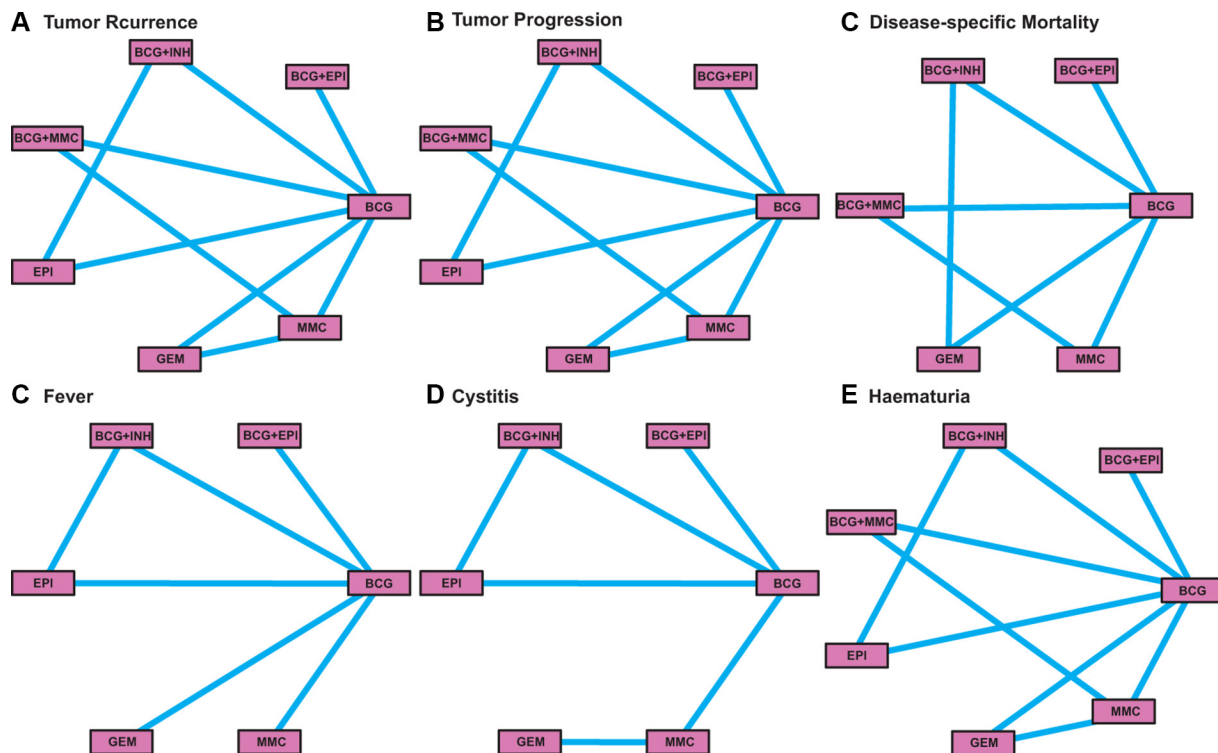


Figure 1: The network plot of intravesical chemotherapies included in this meta-analysis.

Table 2: Pair-wise meta-analyses of direct comparisons between the five drugs

Endpoints	Direct comparisons	I^2	P_H values	OR (95% CI)	P_{OR} values
Tumor Recurrence	MMC vs. BCG	31.58%	0.234	1.07 (0.89, 1.29)	0.593
	GEM vs. BCG	52.37%	0.122	1.01 (0.64, 1.61)	0.829
	EPI vs. BCG	0.00%	0.402	1.58 (1.32, 1.90)	< 0.001
	BCG + MMC vs. BCG	0.00%	0.058	0.25 (0.10, 0.61)	0.002
	BCG + EPI vs. BCG	0.00%	0.672	0.76 (0.48, 1.21)	0.254
	BCG + INH vs. BCG	0.00%	0.764	1.07 (0.85, 1.35)	0.547
	MMC vs. GEM	-	-	1.44 (0.68, 3.07)	0.345
	MMC vs. BCG + MMC	0.00%	0.630	1.11 (0.75, 1.64)	0.617
Tumor Progression	MMC vs. BCG	91.64%	< .0001	3.05 (2.24, 4.17)	< 0.001
	GEM vs. BCG	42.79%	0.182	1.09 (0.55, 2.17)	0.797
	EPI vs. BCG	0.00%	0.351	1.71 (1.16, 2.53)	0.007
	BCG + MMC vs. BCG	2.30%	0.312	0.91 (0.52, 1.59)	0.741
	BCG + EPI vs. BCG	0.00%	0.999	0.52 (0.19, 1.44)	0.209
	BCG + INH vs. BCG	0.00%	0.582	1.40 (0.84, 2.32)	0.193
	MMC vs. GEM	-	-	1.64 (0.56, 4.82)	0.371
	MMC vs. BCG + MMC	0.00%	0.852	1.17 (0.50, 2.72)	0.722
Disease-specific Mortality	MMC vs. BCG	17.96%	0.303	1.14 (0.66, 1.98)	0.634
	EPI vs. BCG	51.78%	0.102	1.42 (0.89, 2.24)	0.324
	BCG + MMC vs. BCG	22.63%	0.204	0.76 (0.43, 1.34)	0.335
	BCG + EPI vs. BCG	-	-	1.05 (0.06, 17.95)	0.973
	BCG + INH vs. BCG	0.00%	0.646	1.32 (0.65, 2.69)	0.442
	MMC vs. BCG + MMC	-	-	1.05 (0.38, 2.90)	0.925
Fever	MMC vs. BCG	0.00%	0.807	0.22 (0.13, 0.38)	< 0.001
	EPI vs. BCG	0.00%	0.813	0.40 (0.08, 2.16)	0.289
	BCG + MMC vs. BCG	56.00%	0.132	0.83 (0.51, 1.34)	0.428
	BCG + EPI vs. BCG	0.00%	0.565	0.49 (0.11, 2.11)	0.340
	BCG + INH vs. BCG	-	-	1.92 (1.25, 2.94)	0.003
Cystitis	MMC vs. BCG	57.80%	0.096	0.89 (0.62, 1.27)	0.513
	EPI vs. BCG	46.53%	0.166	0.64 (0.48, 0.86)	0.003
	BCG + EPI vs. BCG	-	-	0.44 (0.23, 0.86)	0.016
	BCG + INH vs. BCG	-	-	1.03 (0.76, 1.41)	0.839
	MMC vs. GEM	-	-	3.93 (1.05, 14.70)	0.042
Haematuria	MMC vs. BCG	66.89%	0.040	0.55 (0.41, 0.75)	0.011
	GEM vs. BCG	-	-	0.40 (0.07, 2.18)	0.290
	EPI vs. BCG	0.00%	0.627	0.54 (0.39, 0.74)	0.0001
	BCG + EPI vs. BCG	0.00%	0.511	0.42 (0.13, 1.31)	0.135
	BCG + INH vs. BCG	-	-	0.85 (0.60, 1.20)	0.357
	MMC vs. GEM	-	-	1.96 (0.35, 11.17)	0.447

*H: heterogeneity; OR: odds ratio; CI: confidence interval; BCG: Bacille Calmette Guerin; MMC: Mytomycin C; GEM: Gemcitabine; EPI: Epirubicin; INH: Isoniazid.

Table 3: The efficacy and tolerability of seven treatments according to the network meta-analysis using odds ratios (ORs) and corresponding 95% credible intervals (CrIs)

Tumor Recurrence						
BCG	0.63 (0.28, 1.35)	1.27 (0.67, 2.49)	0.64 (0.34, 1.18)	2.51 (1.62, 4.05)	0.83 (0.43, 1.63)	1.14 (0.76, 1.73)
1.59 (0.74, 3.57)	BCG_EPI	2.03 (0.75, 5.91)	1.02 (0.38, 2.80)	3.98 (1.66, 10.31)	1.34 (0.48, 3.78)	1.81 (0.77, 4.59)
0.79 (0.40, 1.49)	0.49 (0.17, 1.34)	BCG_INH	0.50 (0.20, 1.20)	1.96 (1.04, 3.82)	0.65 (0.25, 1.61)	0.90 (0.41, 1.92)
1.56 (0.84, 2.90)	0.98 (0.36, 2.66)	1.99 (0.83, 5.04)	BCG_MMC	3.90 (1.85, 8.74)	1.30 (0.54, 3.10)	1.78 (0.96, 3.36)
0.40 (0.25, 0.62)	0.25 (0.10, 0.60)	0.51 (0.26, 0.96)	0.26 (0.11, 0.54)	EPI	0.33 (0.15, 0.73)	0.45 (0.25, 0.83)
1.20 (0.61, 2.35)	0.75 (0.26, 2.08)	1.54 (0.62, 4.00)	0.77 (0.32, 1.84)	3.04 (1.36, 6.86)	GEM	1.37 (0.66, 2.83)
0.87 (0.58, 1.31)	0.55 (0.22, 1.30)	1.12 (0.52, 2.42)	0.56 (0.30, 1.04)	2.20 (1.20, 4.04)	0.73 (0.35, 1.51)	MMC
Tumor Progression						
BCG	0.46 (0.06, 3.07)	1.73 (0.27, 10.98)	1.16 (0.22, 5.92)	2.23 (0.60, 8.60)	1.35 (0.29, 6.27)	2.69 (0.80, 8.99)
2.19 (0.33, 17.18)	BCG_EPI	3.75 (0.26, 58.16)	2.57 (0.18, 36.01)	4.89 (0.49, 54.05)	3.01 (0.24, 36.91)	5.92 (0.60, 62.73)
0.58 (0.09, 3.70)	0.27 (0.02, 3.87)	BCG_INH	0.69 (0.05, 7.84)	1.31 (0.20, 8.01)	0.79 (0.07, 8.40)	1.59 (0.17, 14.16)
0.86 (0.17, 4.63)	0.39 (0.03, 5.42)	1.45 (0.13, 18.85)	BCG_MMC	1.89 (0.25, 16.30)	1.15 (0.14, 10.37)	2.31 (0.45, 12.15)
0.45 (0.12, 1.67)	0.20 (0.02, 2.03)	0.76 (0.12, 4.91)	0.53 (0.06, 4.04)	EPI	0.61 (0.08, 4.36)	1.19 (0.20, 6.98)
0.74 (0.16, 3.45)	0.33 (0.03, 4.19)	1.26 (0.12, 14.80)	0.87 (0.10, 7.31)	1.64 (0.23, 12.63)	GEM	1.99 (0.32, 11.86)
0.37 (0.11, 1.25)	0.17 (0.02, 1.65)	0.63 (0.07, 5.75)	0.43 (0.08, 2.23)	0.84 (0.14, 5.06)	0.50 (0.08, 3.09)	MMC
Disease-specific Mortality						
BCG	0.94 (0.02, 62.49)	1.02 (0.34, 3.21)	0.66 (0.24, 1.50)	1.45 (0.61, 3.36)	1.04 (0.44, 2.39)	
1.06 (0.02, 50.15)	BCG_EPI	1.08 (0.01, 58.75)	0.67 (0.01, 33.01)	1.51 (0.02, 77.52)	1.06 (0.01, 53.12)	
0.98 (0.31, 2.95)	0.93 (0.02, 71.92)	BCG_INH	0.65 (0.13, 2.41)	1.41 (0.45, 4.02)	1.02 (0.22, 4.01)	
1.52 (0.67, 4.24)	1.49 (0.03, 108.70)	1.54 (0.41, 7.68)	BCG_MMC	2.19 (0.68, 8.20)	1.56 (0.58, 5.14)	
0.69 (0.30, 1.63)	0.66 (0.01, 46.96)	0.71 (0.25, 2.20)	0.46 (0.12, 1.48)	EPI	0.72 (0.22, 2.37)	
0.96 (0.42, 2.30)	0.94 (0.02, 66.73)	0.98 (0.25, 4.45)	0.64 (0.19, 1.73)	1.40 (0.42, 4.63)	MMC	
Fever						
BCG	0.40 (0.04, 2.88)	1.87 (0.23, 10.82)	0.61 (0.08, 2.16)	0.33 (0.03, 2.78)	0.16 (0.04, 0.50)	
2.48 (0.35, 23.42)	BCG_EPI	4.39 (0.26, 71.94)	1.40 (0.08, 18.35)	0.78 (0.04, 17.48)	0.40 (0.03, 4.84)	
0.54 (0.09, 4.42)	0.23 (0.01, 3.89)	BCG_INH	0.32 (0.04, 1.89)	0.18 (0.01, 3.79)	0.09 (0.01, 0.97)	
1.64 (0.46, 12.65)	0.71 (0.05, 12.55)	3.10 (0.53, 26.47)	EPI	0.57 (0.04, 11.29)	0.26 (0.04, 2.67)	
3.02 (0.36, 37.16)	1.29 (0.06, 28.39)	5.68 (0.26, 109.10)	1.76 (0.09, 26.83)	GEM	0.48 (0.04, 7.08)	
6.31 (2.01, 25.05)	2.50 (0.21, 29.69)	11.60 (1.03, 123.98)	3.78 (0.37, 23.27)	2.06 (0.14, 27.16)	MMC	
Cystitis						
BCG	0.68 (0.16, 2.59)	0.13 (0.01, 2.32)	0.34 (0.08, 1.31)	0.22 (0.02, 2.31)	0.79 (0.08, 6.14)	
1.47 (0.39, 6.09)	MMC	0.19 (0.01, 2.49)	0.49 (0.07, 3.74)	0.32 (0.02, 5.47)	1.13 (0.08, 13.65)	
7.72 (0.43, 159.74)	5.23 (0.40, 79.26)	GEM	2.59 (0.10, 71.24)	1.69 (0.04, 79.64)	5.95 (0.15, 231.17)	
2.97 (0.76, 12.83)	2.03 (0.27, 15.33)	0.39 (0.01, 9.53)	EPI	0.65 (0.04, 11.41)	2.31 (0.27, 19.31)	
4.56 (0.43, 47.81)	3.13 (0.18, 48.99)	0.59 (0.01, 23.00)	1.54 (0.09, 23.08)	BCG+EPI	3.49 (0.13, 80.12)	
1.27 (0.16, 12.04)	0.88 (0.07, 12.54)	0.17 (0.00, 6.87)	0.43 (0.05, 3.76)	0.29 (0.01, 7.99)	BCG + INH	
Haematuria						
BCG	0.31 (0.04, 2.28)	0.21 (0.01, 4.65)	0.19 (0.02, 1.17)	0.27 (0.01, 5.02)	0.55 (0.02, 16.14)	
3.22 (0.44, 26.17)	MMC	0.68 (0.03, 15.37)	0.60 (0.03, 9.25)	0.85 (0.02, 32.72)	1.80 (0.03, 94.56)	
4.75 (0.21, 104.85)	1.46 (0.07, 33.05)	GEM	0.87 (0.02, 27.84)	1.23 (0.02, 99.40)	2.61 (0.03, 233.17)	
5.37 (0.86, 41.23)	1.66 (0.11, 29.78)	1.15 (0.04, 46.72)	EPI	1.43 (0.05, 53.28)	3.00 (0.10, 96.15)	
3.76 (0.20, 80.76)	1.18 (0.03, 45.96)	0.81 (0.01, 64.93)	0.70 (0.02, 20.87)	BCG + EPI	2.09 (0.02, 194.73)	
1.82 (0.06, 57.61)	0.56 (0.01, 28.65)	0.38 (0.00, 35.66)	0.33 (0.01, 9.75)	0.48 (0.01, 45.77)	BCG + INH	

*BCG: Bacille Calmette Guerin; MMC: Mytomicin C; GEM: Gemcitabine; EPI: Epirubicin; INH: Isoniazid.

is stimulated during the S phase of the cell cycle [50]. EPI has very limited effectiveness because it is a single

chemotherapy agent against tumors and its effectiveness can be enhanced if combined with other chemotherapy

agents [50]. A common conclusion obtained from both network-meta analysis and the ranking based on SUCRA values is that introducing BCG into EPI appears to be more effective than EPI monotherapy and this strategy is associated with a decrease in the risk of TR.

MMC is another chemotherapy agent which also inhibits DNA synthesis and there is no consensus about the difference between BCG+MMC and BCG monotherapy with respect to preventing TR and TP [51, 52]. Results from direct evidence showed that BCG + MMC are more effective than BCG monotherapy, and such a conclusion is supported by indirect evidence. Taking TR, TP and DM into consideration, BCG + MMC have several strengths with respect to these endpoints. A recent study also found that BCG + MMC appeared to be more effective than BCG or MMC monotherapy (5-year TR rate: 20.6% vs. 33.9%) [45].

The SUCRA ranking plot suggests that GEM may exhibit a safety profile with respect to the risk of fever, cystitis and haematuria. However, this trend is not reflected by our pairwise or network meta-analysis. We suspect this inconsistency for several reasons. Firstly,

there may exist significant study heterogeneity which potentially causes the inconsistency between direct and indirect evidence. Secondly, the corresponding SUCRA values were produced by using the Bayesian Framework in conjunction with the MCMC sampling technique. Compared to the frequentist approach, the Bayesian framework does not lead to an unbiased estimator and such a characteristic may be reflected in the SUCRA values. The current literature indicates that GEM pyrimidine antimetabolite with approved efficacy and mild toxicity [53]. Nevertheless, the safety of GEM should be warranted in the future if it is used as a monotherapy or polytherapy for bladder patients. On the other hand, the current literature suggests that INH could cause chronic liver dysfunction and its application is restricted in clinical practices [27, 54] and our results also showed a worse performance of BCG + INH in TR.

This study is the first Bayesian network meta-analysis which simultaneously compares seven bladder intravesical instillation methods for patients with NMIBC. However, there are still some limitations affecting the results of our analysis. On one hand, there are large

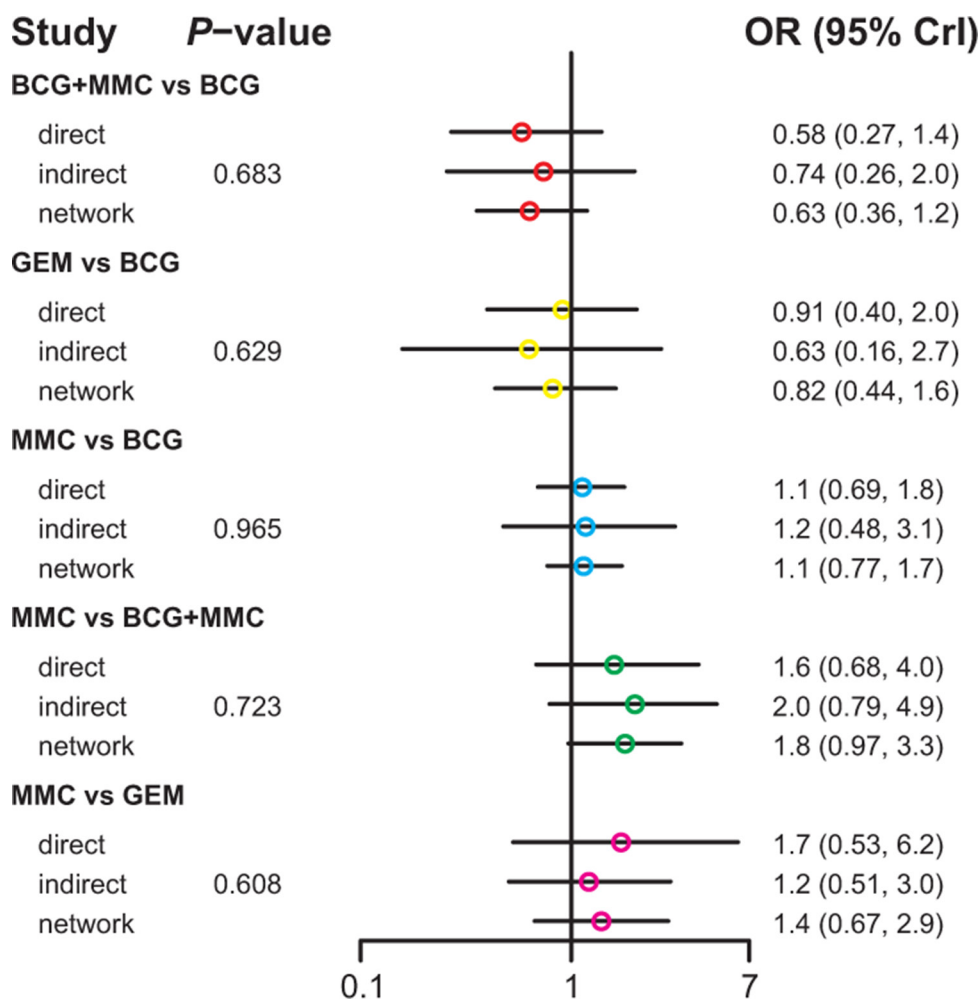


Figure 2: The network node-split plot of tumor recurrence.

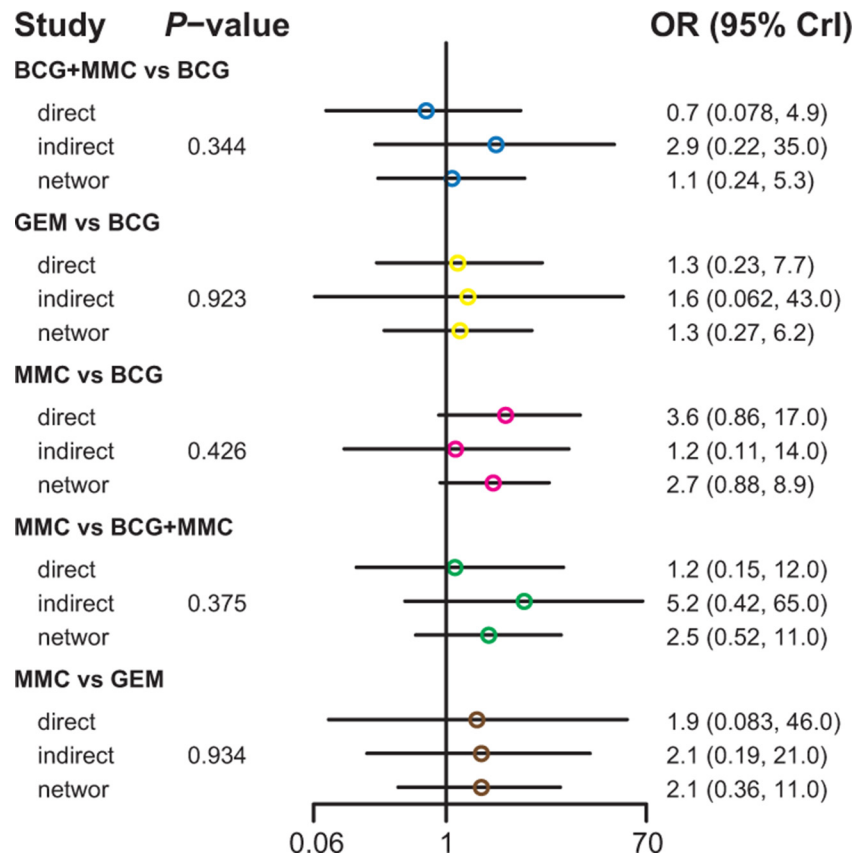


Figure 3: The network node-split plot of tumor progression.

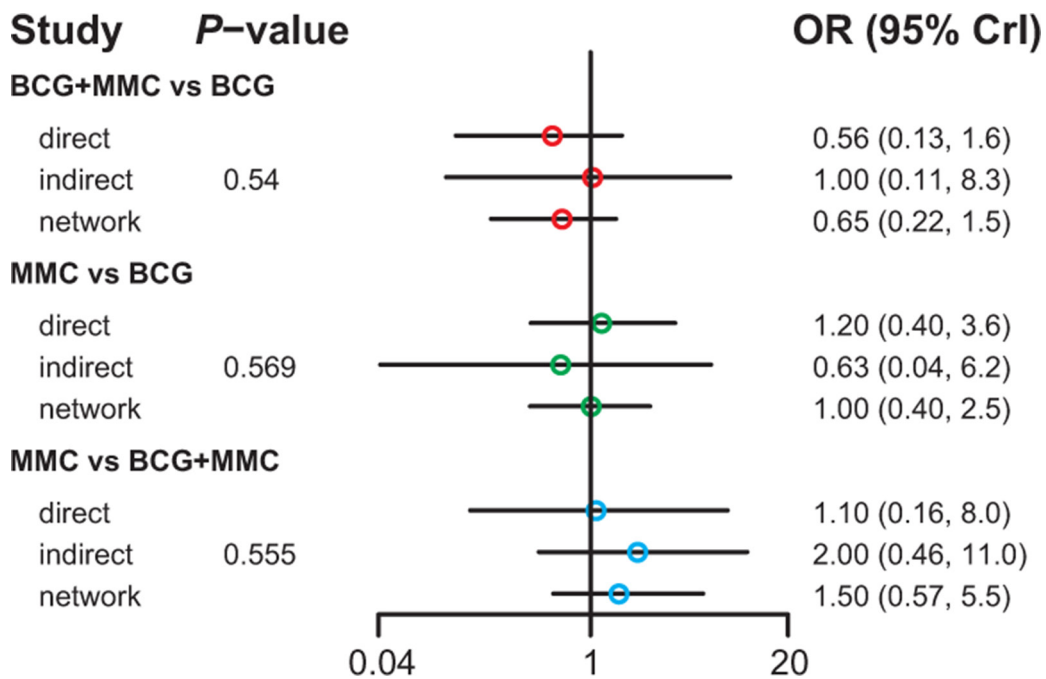


Figure 4: The network node-split plot of disease-specific mortality.

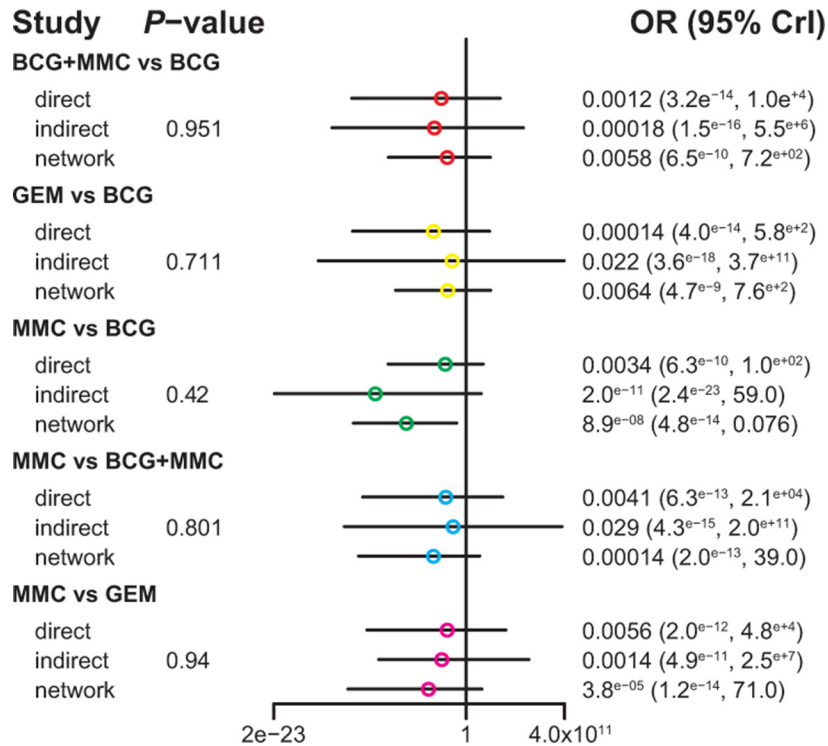


Figure 5: The network node-split plot of haematuria.

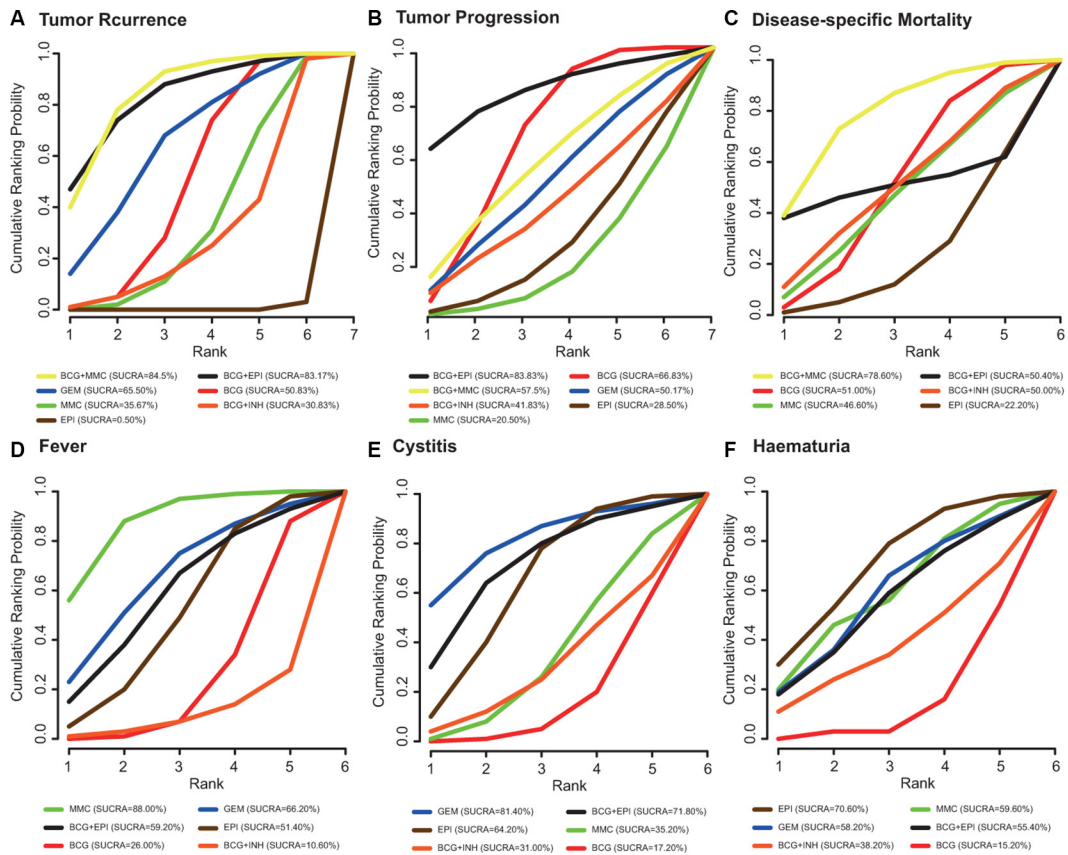


Figure 6: The corresponding results of SUCRA with respect to six endpoints (A) tumor recurrence; (B) tumor progression; (C) disease-specific mortality; (D) fever; (E) cystitis; (F) haematuria.

deviations in the sample size among different studies and such unbalanced sample size may have significant influence on the overall conclusions. On the other hand, we only analyzed the short-term effects of intravesical instillation methods on NMIBC patients due to the lack of evidence and thereby prognoses like survival rate of these approaches are still unclear.

In conclusion, combined intravesical instillation methods such as BCG + EPI and BCG + MMC exhibited outstanding efficacy for NIMBC patients. Nevertheless, future studies should further investigate the long-term effects of these intravesical instillation methods on NMIBC patients and the selection of appropriate methods should be validated by using well designed trials.

MATERIALS AND METHODS

Search strategy

Randomized control trials (RCTs) with “Bacillus Calmette - Guerin” or “mytomicin C” or “gemcitabine” or “epirubicin” or “isoniazid” matched with “bladder Cancer” was searched in PubMed, Embase, China National Knowledge Internet (CNKI), which were update to April, 2016 without any restriction on language. A manual search was also performed on the reference list of each relevant study, previous meta-analyses and earlier reviews of intravesical instillation therapies in relation to bladder tumor so that inappropriate omission can be prevented. The literature searching and retrieving process were carried out by two reviewers independently. All the arguments were solved by a third reviewer.

Inclusion and exclusion criteria

Studies are eligible if: (1) their sample size were greater than 30 and (2) belonged to Randomized control trials (RCTs); (3) patients were above 18 years old and pathologically diagnosed with bladder cancer; (4) the efficacy of two or more intravesical instillation therapies (BCG, MMC, GEM, EPI, INH) were compared; (5) sufficient outcome data were provided. Articles are excluded if: (1) patients had history of muscle-invasive disease, upper urinary tract tumor or chronic urinary tract infection; (2) patients had other disease with immunodeficiency. The literature search, screen and selection flow chart was shown in Supplementary Figure S1.

Outcome measures and data extraction

The following data was extracted from eligible studies, including gender, age, sample size, duration of follow-up, treatment and dosage. The effectiveness and tolerability of intravesical instillation therapies were assessed by using multiple endpoints including TR, TP, DM, fever, cystitis and haematuria. Data extraction

was performed by two reviewers independently. Risk of complications such as fever, cystitis and haematuria were considered as secondary outcomes which evaluated the tolerability of intravesical instillation therapies.

Statistical analysis

Conventional pair-wise meta-analysis was initially carried out and it incorporates direct evidence for each pair of treatment comparison. The fixed-effect model or random-effects model was implemented in pair-wise meta-analysis and the odds ratios (ORs) with their corresponding 95% confidence intervals (CI) were pooled in order to produce a summary effect size for each endpoint. Heterogeneity among studies was assessed by using the statistic of I^2 and Q . No significant heterogeneity was suggested if $P > 0.05$ or $I^2 < 50\%$ and thereby a fixed-effect model was selected. Otherwise, a random-effects model was taken into account due to the presence of significant heterogeneity.

Next, we carried out a network meta-analysis which is based on the Bayesian framework using R 3.2.3 software. Both direct and indirect evidence were synthesized from selected studies in order to produce summary statistics for each endpoint. Aside from that, intravesical instillation interventions are ranked by using the surface under the cumulative ranking curve (SUCRA) which produces a comprehensive ranking with respect to each endpoint. The corresponding ranking probabilities were defined as cumulative probabilities that each treatment being ranked as the first, second and so on. The larger SUCRA values, the more preferred ranking for each intravesical instillation intervention.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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