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ORIGINAL ARTICLE

Prophylactic intravesical chemotherapy decreases bladder tumor recurrence after nephroureterectomy for primary upper tract urothelial carcinoma: A systematic review and meta-analysis

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Summary

Purpose: *A high incidence of bladder tumor (BT) occurs after radical nephroureterectomy (NU) for primary upper tract urothelial carcinoma (UTUC). Although some studies have shown that prophylactic intravesical chemotherapy could prevent BT recurrence, it has not become standard practice at this stage. The purpose of this study was to evaluate the effect of intravesical instillation chemotherapy in preventing BT recurrence in patients with primary UTUC after nephroureterectomy.*

Methods: *A comprehensive literature search was performed in July 2014 using the Medline, Embase, and Cochrane Library databases, as well as the China National Knowledge Infrastructure and Wanfang Data. All clinical trials compared the effect of prophylactic intravesical chemotherapy after radical NU for primary UTUC. Analysis was performed using the Stata 12.0 SE software.*

Results: *Eight trials were analyzed with a total of 979 patients including 521 patients receiving intravesical chemotherapy instillation and 458 without instillation. The BT incidence rate was 125 out of 521 patients (24.0%) with intravesical instillation chemotherapy after NU, and 169 out of 458 patients (36.9%) without intravesical chemotherapy after NU. Compared with those who didn't receive instillation, the pooled odds ratio (OR) of BT recurrence was 0.45 (95% confidence interval/CI 0.34–0.61, p<0.0001) in instillation patients. In the sub-analyses, the OR of single instillation was similar to repeated instillations (0.48 and 0.42). The OR of beginning the first instillation within 24 hrs, 48 hrs and 2 weeks was 0.34, 0.48 and 0.46, respectively.*

Conclusions: *This systematic review demonstrates that prophylactic intravesical instillation chemotherapy can prevent BT recurrence in primary UTUC patients after NU. It also suggests that single instillation may have a similar effect to repeated instillations. The first instillation beginning within 24 hrs seems to show lower BT recurrence than at 48 hrs or 2 weeks. However, given that some limitations exist, well-designed randomized controlled trials are needed to further evaluate these results.*

Key words: *bladder tumor, intravesical chemotherapy, meta-analysis, nephroureterectomy, recurrence, upper tract urothelial carcinoma*

Introduction

UTUC is a rare disease accounting for approximately 5-10% of all urothelial carcinomas in Western countries [1,2]. However, a remarkably high incidence of UTUC occurs in Asian regions. Recently, it has been reported that 20-25% of UTUC on the southwest coast of Taiwan may be

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Table 1. Quality assessment

Potential bias	*Items to be considered for assessment of potential bias* *Score: Yes =2, Partly =1, No/Unsure =0)*
Study participation	Sampling method, period of recruitment and key characteristics are adequately described. Inclusion and exclusion criteria are adequately described.
Study attrition	Proportion of study sample completing the study and providing outcome data is adequate. There is no important difference in participants who completed the study and those who did not.
Prognostic factor	A clear description of intravesical instillation method is provided. The instillation method is the same for all study participants.
Outcome	A clear description of BT recurrence rate is provided, including follow-up duration. A clear description of adverse drug reactions is described.
Confounding	Important potential confounders are matched in the study design. Important potential confounders are accounted for in the analysis.
Analysis	The selected method of analysis is adequate for the design of the study. There is no selective reporting of results.

due to eating the traditional Chinese medicines, aristolochic acid herbs [3,4].

Up to 23-47.2% of the patients may develop BT after radical NU for primary UTUC [5-8]. BT needs transurethral resection, which is associated with costs of treatment and potential poor prognosis. Since the first randomized controlled trial (RCT) on the prevention of BT recurrence reported by Sakamoto et al. [9], a few clinicians realized the importance of prophylactic intravesical chemotherapy after radical surgery of UTUC [7,10-12]. So far, no definitive recommendations exist about the prophylactic intravesical chemotherapy in reducing the BT recurrence after NU.

In recent years, several studies have shown that prophylactic intravesical chemotherapy could decrease BT recurrence [13]. But the conclusions are still uncertain, as the results were limited by small sample size and the retrospective nature of the studies. As a result, to determine the role of prophylactic intravesical chemotherapy on BT recurrence after NU for primary UTUC, a systematic review and meta-analysis of relative studies was performed.

Methods

Search strategy

This meta-analysis was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [14]. A comprehensive search was carried out to identify all clinical trials that compared the effect of prophylactic intravesical chemotherapy after radical NU for UTUC before July 2014. The keywords used were: upper urinary tract, urothelial carcinoma, nephroureterectomy, prophylactic intravesical chemotherapy, intravesical instillation, bladder recurrence, and comparative study in Medline, Embase, and Cochrane Library electronic database. As clinical trials reported in English were rare, we also performed a similar search in China National Knowledge Infrastructure (CNKI) and Wanfang Data (http://www.wanfangdata.com.cn). The search was restricted to full-text papers containing English abstract.

Study selection

Clinical trials included in this study met the following criteria: (*i*) trials had to compare the different BT recurrence with or without prophylactic intravesical chemotherapy; (*ii*) studies only focused on radical NU, while neoadjuvant chemotherapy or conservative surgery studies were excluded; (*iii*) the diagnosis of UTUC had to be confirmed pathologically; (*iv*) patients should have primary UTUC without a prior history of bladder or a synchronous bladder cancer; (*v*) for studies with the same or overlapping data by the same authors, the most recent study with the greatest number of subjects was chosen.

Data extraction

Two investigators (Wu PJ and Wang XM) independently extracted data, and all disagreements about eligibility were resolved by a third reviewer (Zhu G). For each study, the following information was extracted: first author's name, year of publication, number of enrolled patients, number of patients in treatment and control, gender, median or mean age, tumor location, tumor stage and grade, types of study design, article language, information of treatment such as treatment regimens, retained time in bladder, first instillation time, treatment duration, length of the follow-up period and number of BT recurrence.

Quality assessment

The checklist of quality used was the applicable elements from existing tools (Quality in Prognosis Studies tool) [15]. The criteria included exploring domains of participation, attrition, prognostic factors, outcome, confounding factors, and analysis. We evaluated and scored studies to quantify the assessment (Table 1). The maximum score for each item was 2. Studies scoring

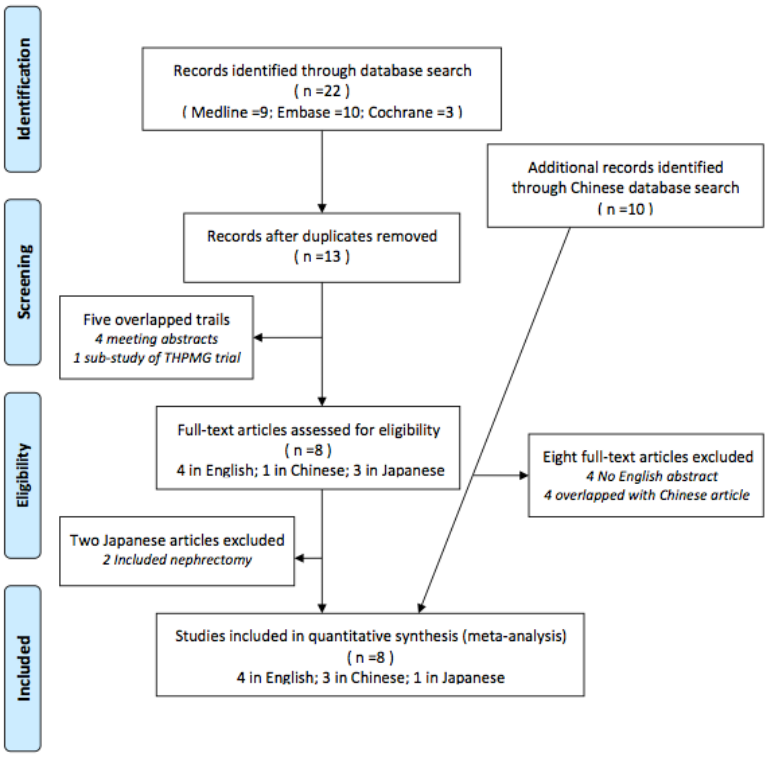

Figure 1. Preferred reporting items for systematic reviews and meta-analysis flowchart.

Table 2. Quality scoring

Study (First author)	*Participation*	*Attrition*	*Prognostic factor*	*Outcome*	*Confounding*	*Analysis*	*Score*	*Quality*
Ito, 2013 [7]	Y	Y	Y	Y	Y	Y	12	H
O'Brien, 2011 [10]	P	Y	P	Y	Y	Y	10	H
Sakamoto, 2001 [9]	Y	Y	Y	Y	Y	Y	12	H
Wu, 2010 [11]	Y	P	P	Y	P	Y	9	L
Nagashima, 2013 [12]	Y	P	Y	P	P	Y	9	L
Tian, 2011 [20]	Y	U	Y	Y	Y	Y	10	H
Fu, 2009 [21]	P	Y	P	P	P	Y	8	L
Miao, 2009 [22]	P	U	P	P	P	P	5	L

Y =yes (2), P =partial (1), U = unsure (0), H =high quality, L =low quality

10-12 were defined as high quality, while scoring 0–9 were considered low quality, just as previously defined by Maan et al. [16]. The quality scoring was assessed by two independent investigators. Any disagreement was resolved by discussion.

Statistics

Dichotomous data were analyzed by Stata 12.0 SE software (StataCorp, College Station, TX, USA) and presented as OR with 95% CI. Statistical heterogeneity was tested using the chi-square test, and the I-square statistic. A p value of <0.10 was used to indicate heterogeneity. If no heterogeneity existed, the Mantel-Haenszel fixed effect model was used. The Begg's funnel plot was conducted to identify potential publication bias. In the Begg's funnel plot, a symmetrical plot suggests an acceptable publication bias. If asymmetry was detected, then the funnel plot asymmetry was assessed by the Egger's test. For all statistical analyses, a two-sided $p<0.05$ was considered to be statistically significant.

Results

Study selection and characteristics

Figure 1 shows the flowchart depicting the

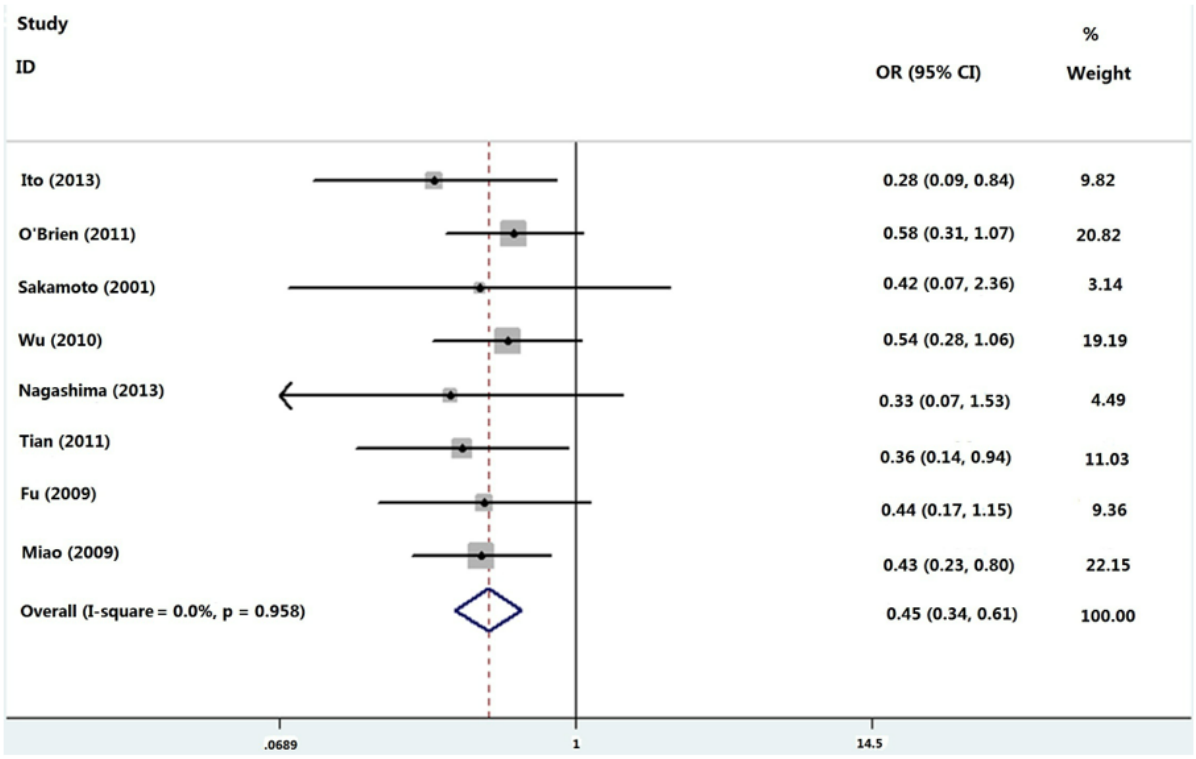

Figure 2. A Forest plot of odds ratio of bladder tumor recurrence in instillation patients compared with those who didn't receive intravesical the chemotherapy after nephroureterectomy.

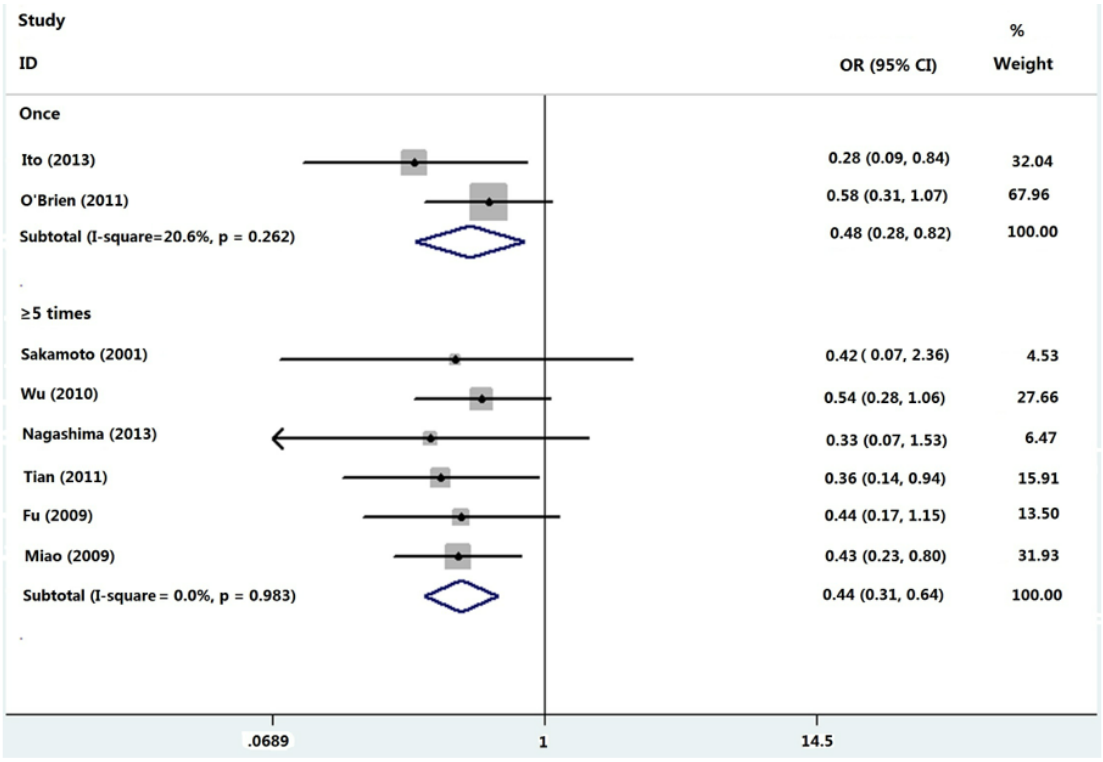

Figure 3. Forest plot for sub-analysis of the bladder tumor recurrence by times of intravesical instillation chemotherapy.

Table 3. Patient and disease characteristics

Study	*Ito, 2013[7] N=77*		*Nagashima, 2013[12] N=42*		*O'Brien, 2011[10] N=284*		*Sakamoto, 2001[9] N=27*		*Wu, 2010[11] N=196*			*Tian, 2011[20] N=82*		*Fu, 2009[21] N=96*	*Miao, 2009[22] N=227*	*Total N=1031*
Characteristics	*Group*	*Control*	*Group*	*Control*	*Group*	*Control*	*Group*	*Control*	*Group1*	*Group2*	*Control*	*Group*	*Control*	*Total*	*Total*	
Sex																
Male	22	21	15	13	-	-	8	8	16	14	62	26	26	63	126	420
Female	14	15	8	6	-	-	5	4	15	13	76	15	15	33	101	320
Unknown	-	-	-	-	120	119	-	-	-	-	-	-	-	-	-	239
Age (years)	<69 18 ≥69 18	<69 19 ≥69 17	69 (58-81)	71 (42-81)	70 (44-87)	71 (36-90)	69.4 (55-85)	69.3 (59-80)	<65 15 ≥65 16	<65 14 ≥65 13	<65 58 ≥65 80	57.6±8.1	58.2±7.8	62.2 (37-81)	62.0 (34-78)	≈65.4
Tumor site																
P	21	19	14	8	-	-	-	-	15	7	42	23	23	57	227	456
U	13	16	8	7	-	-	-	-	10	14	71	11	11	24	0	185
PU	2	1	1	4	-	-	-	-	-	-	-	7	7	15	0	37
NA	-	-	-	-	120	119	13	12	6	6	25-	-	-	-	-	301
Stage																
pTa-pT1	19	20	5	7	68	71	3	6	11	8	67	17	17	11	96	426
T2	6	2	6	0	19	13	10	6	12	12	39	13	13	43	131 (T2-T3)	194+NA
T3	11	14	11	10	29	28	0	0	8	7	32	7	7	42 (T3-T4)		164+NA
T4	0	0	1	2	2	2	0	0	0	0	0	4	4		0	15+NA
NA	-	-	-	-	2	5	-	-	-	-	-	-	-	-	-	7
Grade																
Low	24	15	7	5	10	8	2	2	8	12	61	15	14	21	85	289
High	12	21	16	14	107	107	11	10	23	15	77	26	27	75	142	683
NA	-	-	-	-	3	4	-	-	-	-	-	-	-	-	-	7
Total	72		42		239		25		196			82		96	227	979

P: calyx or pelvis, PU: pelvis and ureter, U: ureter, NA: not available

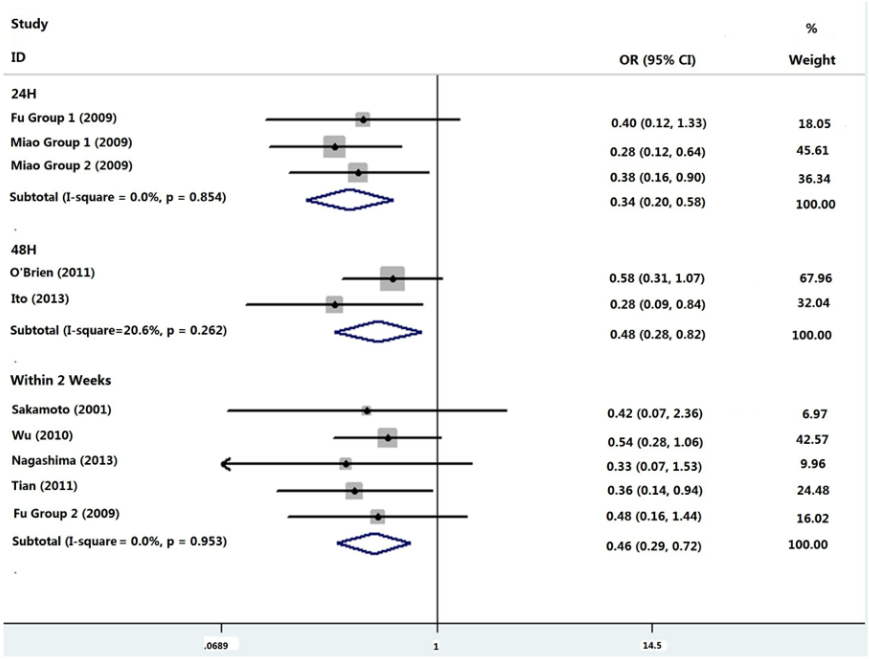

Figure 4. Forest plot for sub-analysis of the bladder tumor recurrence by the beginning time of first prophylactic intravesical chemotherapy.

literature search processes based on PRISMA statement. Thirteen articles were found in Medline, Embase and Cochrane Library databases. Four meeting abstracts overlapped the published articles. Another paper was excluded due to the sub-study of THPMG trial [17]. Two Japanese trials were excluded because some patients underwent nephrectomy [18,19]. In addition, 2 studies were identified by further analysis of potentially relevant studies in CNKI and Wanfang database [20,21]. In total, 8 eligible trials were identified according to our predefined selection criteria [7,9-12,20-22].

For quality assessment, 4 studies [7,9,10,20] were defined as high quality scoring from 10 to 12, while 4 studies [11,12,21,22] as low quality scoring from 5-9 (Table 2).

As shown in Table 3, 6 out of the 8 papers described different information about instillation within group and control in terms of gender, age, tumor location, stage, and grade [7,9-12,20]. The majority of studies lacked information about patient characteristics in BT recurrence, hence separate analysis could not be performed to show which characteristic would benefit from prophylactic chemotherapy instillation postoperatively.

As shown in Table 4, there were 3 RCT and 5 retrospective trials containing 979 patients suitable for analysis. Two studies used a single instillation, while the other 6 made use of repeated instillations over time. A high number of articles came from China and Japan, and this phenomenon was consistent with the incidence of UTUC in the world [1].

Prophylactic intravesical chemotherapy reduces the BT recurrence rate

A total of 521 patients received prophylactic intravesical chemotherapy, while 458 did not. As shown in Table 4, the BT recurrence rate was 125 out of 541 patients (24.0%) with intravesical chemotherapy after NU, while 169 out of 458 patients (36.9%) without instillation had recurrence. The absolute reduction of risk was 12.9% and the relative reduction of risk was 35.0%. Compared with those who didn't receive instillation, the pooled OR of BT recurrence was 0.45 (95% CI 0.34–0.61, p<0.0001) in instillation patients (Figure 2). These trials had no significant heterogeneity (I-square=0%; chi-square=2.03; p=0.958), so a fixed-effects model was used.

In the subgroup stratified by trial types and languages, we found that the OR of RCT was 0.48 (95% CI 0.28-0.79, p=0.008). This was similar to ≥5 instillation 0.44 (95% CI 0.31-0.64 p<0.0001). The OR of 1-5 and >5 courses of instillation was 0.46 (95% CI 0.28-0.77, p=0.003) and 0.45 (95% CI 0.31-0.65, p<0.0001), respectively.

How many courses of bladder instillation could benefit patients after NU?

Table 4. Trials on prophylactic intravesical chemotherapy after NU for primary UTUC

Study	*Type*	*Language*	*Drug*	*Solution*	*Retained time (hrs)*	*Beginning time*	*Duration*	*BT recurrence*				*Follow-up (months) median (range)*	*Patient number Total=979*
								Instillation		*Non-instillation*			
								Cases	*Total*	*Cases*	*Total*		
								N=125	*N=521*	*N=169*	*N=458*		
Ito, 2013 [7]	RCT	English	THP 30mg	Saline 30ml	0.5	48 hrs	once	6	36	15	36	24.9 (2.6~39.3)	72
O'Brien, 2011 [10]	RCT	English	MMC 40mg	Saline 40ml	NA	Immediately prior to removal of the urethral catheter	once	21	120	32	119	12	239
Sakamoto, 2001 [9]	RCT	English	MMC 20mg plus Ara-C 200mg	Saline 30ml	2	1-2 weeks	2, weekly, 5, fortnightly, 21, monthly	3	13	5	12	45 (6-65)	25
Wu, 2010 [11]	Retro	English	MMC 10mg Epirubicin 20mg	Saline 20ml	1	Within 2 weeks	6-8, weekly	7 9	27 31	57	138	55.6 (12-182)	196
Nagashima, 2013 [12]	Retro	Japanese	THP 30mg	Saline 40ml	1	Within 2 weeks	5, weekly	2	23	6	19	50 (4-94)	42
Tian, 2011 [20]	Retro	Chinese	HCPT 40mg	NA	2	Within 2 weeks	6-8, weekly	9	41	18	41	46.0 (26-66)	82
Fu, 2009 [21]	Retro	Chinese	MMC 30mg or THP 30mg	Saline 40ml	1 2 weeks	24 hrs	10, weekly	5 7	29 35	11	32	61.4 (6 -132)	96
Miao, 2009 [22]	Retro	Chinese	MMC 30mg or HCPT 30mg	Saline 50ml	1 24 hrs 3 weeks	24 hrs	10, weekly	11 10 17	67 48 51	25	61	58 (1-120)	227

RCT: randomized controlled trial, Retro: retrospective study, NU: nephroureterectomy, UTUC: upper tract urothelial cancer, BT: bladder tumor, THP: pirarubicin, MMC: mitomycin C, Ara-C: arabinoside, HCPT: hydroxycamptothecin, NA: not available

Two studies used a single instillation of chemotherapy, one trial used 5 cycles of instillations and the remaining 5 trials made use of >5 courses of instillation. Within the sub-grouped by instillation courses (Figure 3), we found that the OR of a single instillation was 0.48 (95% CI 0.28-0.82, p=0.008). This was similar to ≥5 instillation 0.44 (95% CI 0.31-0.64, p<0.0001). The OR of 1-5 and >5 courses of instillation was 0.46 (95% CI 0.28-0.77, p=0.003) and 0.45 (95% CI 0.31-0.65, p<0.0001), respectively.

When to begin prophylactic intravesical chemotherapy for primary UTUC after NU?

According to clinical experience, the majority of patients after UTUC surgery have removal of their urethral catheter within 2 weeks. We classified the instillation time of ODMIT-C Trial as within 2 weeks for analysis. The first prophylactic bladder instillation was divided into 3 time points: 24 hrs, 48 hrs, and within 2 weeks. The details of the drug instillation and duration are shown in Table 4.

In the subgroup analysis stratified by different starting times of instillation, we found that the OR of 24 hrs (0.34, 95% CI 0.20-0.58, p<0.0001) was less than the OR of 48 hrs (0.48, 95% CI 0.28-0.82, p=0.008) and within 2 weeks (0.46, 95% CI 0.29-0.72, p=0.001) (Figure 4). It seems that instillation within 24 hrs had better efficacy in preventing BT recurrence than the other two subgroups.

Which agent is outstanding in reducing BT recurrence?

Different doses of different agents, such as epirubicin, pirarubicin (THP), hydroxycamptothecin (HCPT), mitomycin C (MMC), and MMC plus arabinoside (Ara-c), were used in the trials. As depicted in Table 4, 6 out of the 8 trials used the same drugs for all study participants. However, due to differences in dosaging schedules, we were unable to accurately compare the efficacy between drugs.

Drug toxicity

No study reported any severe toxicity or systemic side effects. The incidence of local side effects was 19.5-23.1% [9,20], which mainly were bladder irritation symptoms including frequency, urgency, and pain on urination.

Publication bias and sensitivity analysis

No significant evidence of publication bias was detected for reducing the BT recurrence rate in any of these trials based on Begg's test (p=0.174). Sensitivity analysis was conducted to evaluate the stability of the meta-analysis. The statistical significance of the results was not altered when any single study was omitted.

Discussion

The data of the present systematic review suggest that the intravesical instillation of chemotherapy significantly decreased the risk of BT recurrence in primary UTUC patients after NU without severe adverse effects. In the subgroup analysis, a single instillation, which is not inferior to repeated instillations, significantly decreased the BT recurrence. Although confounding factors did exist, our analysis suggests beginning instillation within 24 hrs results in fewer BT occurrences than at 48 hrs or 2 weeks.

To our knowledge, this research represents the latest systematic review and meta-analysis investigating whether intravesical instillation can prevent BT recurrence after NU for primary UTUC, including 8 studies and 979 patients. Publication bias was not detected by the Begg's test. The overall results did not change remarkably after subgroup analyses by language and study type. Sensitivity analysis showed the stability of the meta-analysis. Therefore, we are confident of the validity of our findings.

There is no consensus on how many courses of instillation should be performed after NU. In Asian regions 5-8 courses of instillation were popular [11,12,22], while a single instillation is widely used in European countries [10]. In our study, irrespective of instillation courses, intravesical chemotherapy significantly decreased BT recurrence. In all, the efficacy of intravesical instillation is confirmed, but the courses of intravesical chemotherapy need to be further determined by well-designed clinical trials.

When to begin the first instillation after NU still confuses urologists. This study has shown that beginning the first instillation within 24 hrs results in better efficacy than within 48 hrs and 2 weeks. This result is consistent with the BT research: the best time to administer the first instillation is within 24 hrs to prevent BT recurrence after transurethral resection of BT (TURBT) [23]. UTUC is different from BT, as the bladder needs to be repaired after NU. With the fear of chemical extravasation, urologists believe it is not good choice to administer the chemotherapy immediately after surgery. In clinical practice, they usu-

ally perform instillation within 48 hrs or immediately after removal of the urethral catheter [7,10]. However, Tian et al. [20] found that after suturing the bladder, BT recurrence rates using 24 hrs instillation intravesical chemotherapy were lower than 48 hrs without severe adverse effects, but the result was not statistically significant. The same result was found in Fu et al. trial that compared 24 hrs instillation with 2 weeks ($p>0.05$) [21]. So, whether patients could benefit from earlier instillation should be proved by high-level evidence in the future.

However, we should acknowledge certain inherent limitations in some of the studies, which cannot be ignored when interpreting the data of this meta-analysis. Firstly, most studies included were retrospective trials or small sample sized. Secondly, factors of the clinical and pathologic characteristics of the patients, such as gender [24], surgical procedures [25], distal ureter management [26], tumor stage and grade [8], tumor location [27], multifocal carcinoma [28], preoperative urine cytology [29], adjuvant chemotherapy [30], which are of great importance for the BT recurrence, were mixed in the included trials. Due to lack of risk stratification for BT relapse, it is difficult to determine which one could benefit from instillation. Thirdly, it is well known that BT recurrence rates vary with time. Nevertheless, there were differences in the length of the patient follow-up period, ranging from 12 to 58 months. Finally, trials utilized different intravesical chemotherapy regimens with various instillation agents retained for different times in the bladder. In addition, the majority of studies lacked grading of complications of instillation.

Conclusions

This systematic review demonstrates that prophylactic intravesical instillation of chemotherapy could reduce BT recurrence. It also suggests that patients could benefit from a single instillation. Beginning the first instillation within 24 hrs seems to achieve fewer BT recurrences compared with 48 hrs and 2 weeks. However, these findings need to be confirmed by well-designed RCT without inherent limitations.

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