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Original Article

Prognostic value and efficacy valuation of postoperative intravesical instillation in primary urothelial carcinomas of upper urinary tract

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Abstract: Bladder tumor recurrence after surgery for upper urinary tract urothelial carcinoma (UUT-UC) is frequent. Intravesical instillation has been widely accepted as an effective way to prevent bladder tumor recurrence. We aimed to find whether postoperative instillation have benefits for bladder tumor recurrence of UUT-UC. A meta-analysis based on 6 studies from 5 publications was performed. Published literature from PubMed, EMBASE and Web of science was pooled and the hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated to estimate the benefits. Conclusively, our results indicate a 62% benefit (HR = 0.38; 95% CI: 0.16-0.87) in recurrence free survival (RFS) among those treated with postoperative intravesical instillation compared with those not. Mitomycin C (MMC) and pirarubicin were found to provide more benefits than other regimens in stratified analysis. Further, after excluding one study for its heterogeneity, the results demonstrated a more reliable results of a 34% benefit (HR = 0.66; 95% CI = 0.44-0.98). This study reveals a relative benefit for postoperative instillation to improve the RFS of UUT-UC patients.

Keywords: Intravesical instillation, upper urinary tract urothelial carcinoma, bladder tumor, recurrence, postoperative chemotherapy

Introduction

Upper urinary tract urothelial carcinoma (UUT-UC), accounts for merely 5-10% of all urothelial tumors [1]. Radical nephroureterectomy (RNU) with excision of an ipsilateral bladder cuff and retroperitoneal lymph node (LN) dissection has commonly been accepted as a gold standard therapy for this so-called "field-change" disease [2]. Adjuvant therapies such as neo-adjuvant chemotherapy, adjuvant chemotherapy, intravesical instillation and radiotherapy have also been applied to UUT-UC treatment [3]. Adjuvant chemotherapy can provide a therapeutic benefit for high-risk UUT-UC (including stage pT2), while neoadjuvant chemotherapy was conducive to locally advanced bladder carcinoma [4]. In addition, radiotherapy is often limited to patients who are medically unfit and/or who are considered unresectable, representing a comparatively longer-term tumor control and survival [5]. Overall, neoadjuvant chemotherapy, adjuvant chemotherapy and radiotherapy continues to be defined, as receipt of them has been suggested to improve survival and prohibit bladder recurrence [6].

Despite advantages of neoadjuvant chemotherapy, adjuvant chemotherapy and radiotherapy for treating UUT-UC, limitations are also elucidated which mainly cause tiredness and sore, sometimes even irritates the bladder and bowel. Furthermore, though RNU is the standard procedure to treat UUT-UC, it cannot avoid the bladder tumor recurrence. Prophylactic intravesical chemotherapy has been widely used for bladder cancer treatment for over 40 years and it was found to be effective for delaying and preventing bladder tumor recurrence and progression [7]. The rate of bladder tumor

recurrence following surgery for UUT-UC was frequent, predominantly in the first two years after surgery [8]. Niijima *et al* [9] and Omoto *et al* [10] showed that earlier postoperative instillation appeared to be more effective during the initial one year after surgery. Fang *et al* [11] conducted a meta-analysis to compare radical surgery alone or surgery plus postoperative intravesical chemotherapy and found that intravesical chemotherapy might significantly decrease the risk of bladder tumor recurrence after nephroureterectomy for primary UUT-UCs.

Epirubicin, mitomycin C (MMC) and pirarubicin have been widely used as intravesical instillation chemotherapy regimens to reduce bladder tumor recurrences. Epirubicin, a stereoisomer of doxorubicin and anthracycline-containing combination regimen, has been considered the standard treatment for various cancers. Kurth et al [12] found that a direct relationship between epirubicin dose and effect on tumor in situ in patients or side effects caused by treatment. MMC, another standard chemotherapy agent for treating superficial bladder cancer, is recommended in intravesical infusion at the dose of 20 to 40 mg by the European Urological Association guidelines [13]. An immediate instillation of pirarubicin ([2'R]-4-O-tetrahydropyranyl-doxorubicin), which has a greater distribution volume and less cardiac toxicity than those of epirubicin and mitomycin [14], was demonstrated to be well tolerated and more effective for preventing tumor recurrence, especially in intermediate-risk non-muscle invasive bladder cancer (NMIBC) patients [15]. Ito *et al.* [16] found that intravesical instillation of pirarubicin after surgery significantly reduced the bladder tumor recurrence rate for UUT-UC patients with positive voided urine cytology. However, Wu *et al.* found no statistically significant association between prophylactic intravesical chemotherapy after surgery and the cancer specific survival rate [17]. Tari *et al* [18] and Kudoh *et al* [19] have reported that bladder tumor recurrence rate was noteworthy diminished in patients with instillation of different anticancer regimens or bacillus Calmette-Guerin after surgery for UUT-UC patients. On the contrary, Wu *et al* [17] found that this instillation benefit was limited to early recurrence and not maintained at long-term follow-up. Currently, no consensus has been reached on the prophylactic capability of intravesical chemotherapy in preventing bladder tumor recurrence rate after surgery for UUT-UCs.

Recurrence free survival (RFS), which was commonly defined as the time from surgery to recurrence of bladder tumor, was more sensitive to reveal the prognosis of UUT-UCs. This meta-analysis was thus to elucidate and confirm the potential impact of postoperative intravesical chemotherapy in preventing bladder recurrence after RNU and found a significant benefit for postoperative instillation to improve the RFS of UUT-UC patients especially for MMC and pirarubicin.

Methods

Identification of relevant studies

A comprehensive search of PubMed, EMBASE and Web of Science was conducted for relevant studies on the association between the impact of postoperative intravesical chemotherapy and bladder tumor recurrence, covering all the papers published through May 21st, 2014. Publications were identified using the following search terms: "intravesical instillation", "upper tract urinary carcinoma", "bladder tumor" and "recurrence". Additional literatures were collected from a hand search from the references of identified original articles or review articles. No language restrictions were executed. Selected Studies must meet the following inclusion exclusion: the local treatment should be performed in control and experimental groups, which differed only in the addition of intravesical instillation. The major exclusion criterion was conservative surgery instead of radical surgery, other neoadjuvant or adjuvant treatment, metastatic disease and non-urothelial carcinomas.

Data extraction

Two reviewers independently assessed all articles identified by search strategies for relevance and reached a consensus on all items. The following information was obtained from each publication: author's first name, publication year, country, study type, number of patients in treatment and control group, instillation regimens, instillation duration, patients

Table 1. Characteristics of studies included in the meta-analysis

ID	First author	Year	Country	Patients Charateristic	Study type	No. of patients		Instillation Duration	Instillation Regimens	RFS
						Instillation	Non-Instillation			HR (95% CI)
1	Sakamoto	2001	Japan	Nonselective[#]	Multi-center	13	12	24 months	MMC 20 mg + Ara-C 200 mg	0.12 (0.01-1.07)
2	Wu[&]	2010	Taiwan	Nonselective	Single-center	31	138	6-8 times	MMC 10 mg	0.63 (0.28-1.45)
3	Wu[&]	2010	Taiwan	Nonselective	Single-center	27	138	6-8 times	Epirubicin 20 mg	1.19 (0.55-2.56)
4	O'Brien	2011	UK	Nonselective	Multi-center	120	119	Once	MMC 40 mg	0.66 (0.35-1.28)
5	Ito A[&]	2013	Japan	Nonselective	Multi-center	36	36	Once	Pirarubicin 30 mg	0.26 (0.07-0.91)
6	Ito A[&]	2013	Japan	Positive urine cytology[*]	Multi-center	17	14	Once	Pirarubicin 30 mg	0.02 (0.01-0.53)

MMC, mitomycin C; Ara-C, Arabinoside C; RFS, Recurrence free survival; HR, Hazard Ratio; 95% CI, 95% confidence intervals. [#]Patients of non-instillation groups contained both patients with or without positive voided urine cytology. [*]Patients of non-instillation groups were both patients with positive voided urine cytology. [&]In the studies by Wu *et al* and Ito *et al*, non-instillation patients utilized were the same group of people respectively.

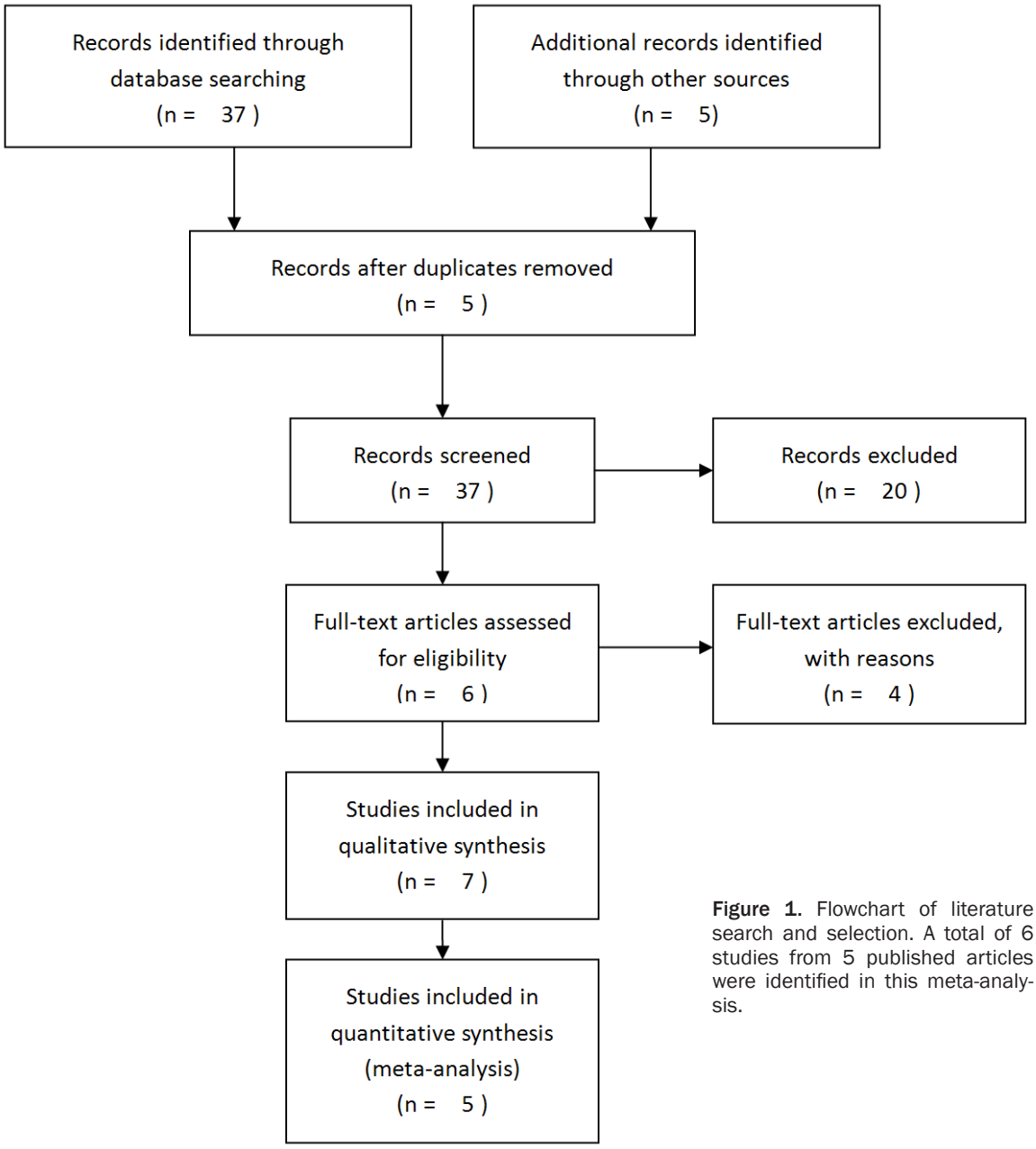

Figure 1. Flowchart of literature search and selection. A total of 6 studies from 5 published articles were identified in this meta-analysis.

characteristic and RFS. RFS was defined as the time from the date of surgery to the date of recurrence. The data was presented as "Hazard Ratio (HR)" and "95% confidence intervals (95% CI)" for RFS. The instillation regimens were classified as MMC, epirubicin and pirarubicin. The HR and 95% CI were obtained using two methods: (i) from articles that offer them directly; (ii) generated from published Kaplan-Meier curves by the software Engauge Digitizer version 4.1 (free software downloaded from http://sourceforge.net).

Statistical analysis

With the method of Dersimonian *et al* [20], HR estimates were pooled via random-effects analysis, and heterogeneity across studies was assessed by the I^2 statistic from Higgins *et al* measuring the percentage of total variation [21]. Significant heterogeneity was denoted by a Cochran Q $P < 0.05$ and an $I^2 > 50\%$. The random-effects model is more appropriate for one of the studies [22] that contains a much smaller sample size than other studies and there

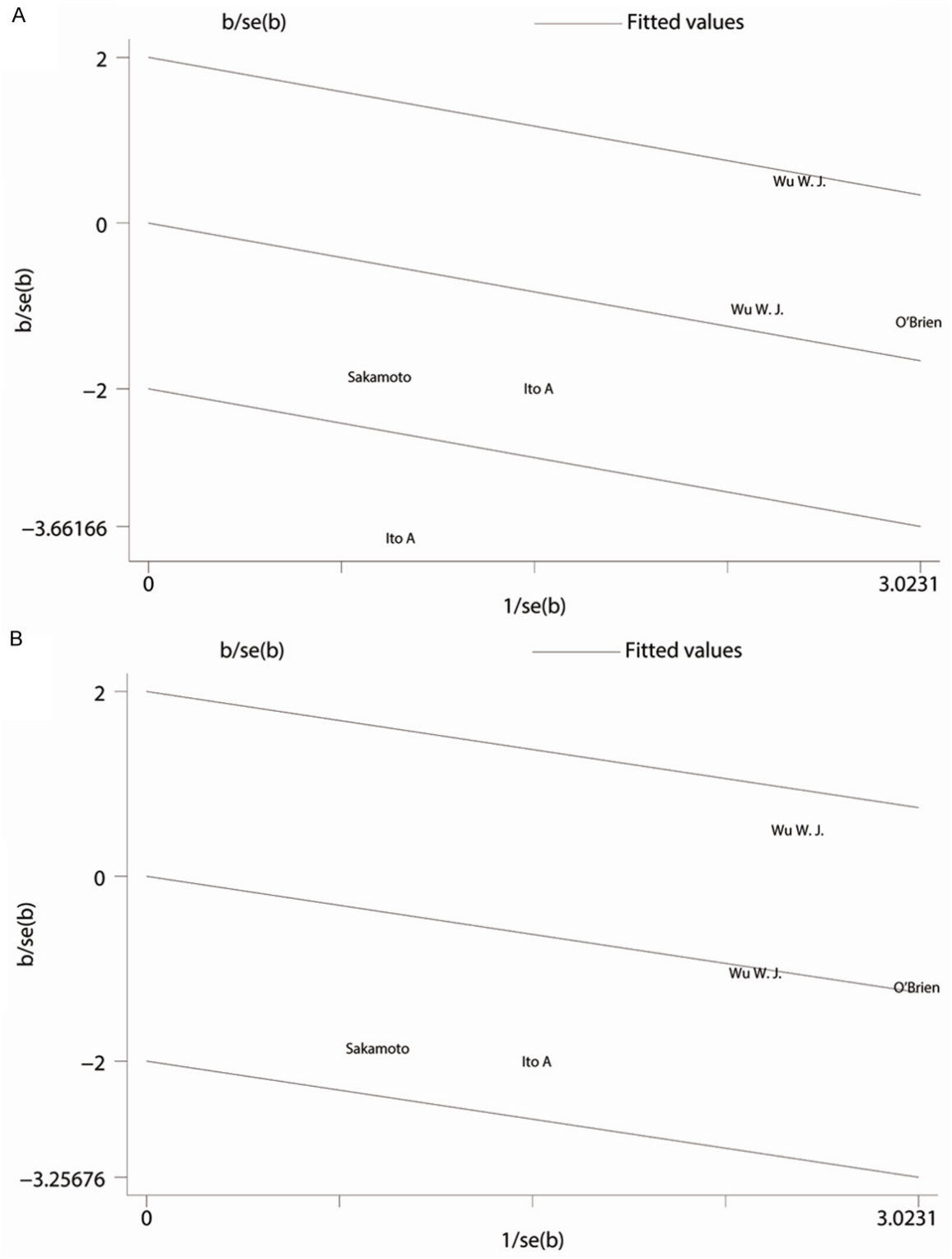

Figure 2. A. Galbraith radial plot for the overall meta-analysis. The figure shows the contribution of individual studies to the heterogeneity. B. Galbraith radial plot after the exclusion of Ito's study. The figure shows the contribution of individual studies to the heterogeneity.

was significant heterogeneity. We first analyzed the pooled HR of RFS rates from the data acquired. Next, stratified analysis was performed in accordance with instillation regi-

Table 2. Results of recurrence free survival hazard ratios of studies investigating overall regimens, MMC and pirarubicin regimens and results after the exclusion of Ito A *et al*'s study

RFS Pooled analysis	Pooled HR (95% CI)	*P* value
Primary analysis	0.378 (0.165-0.866)	0.021
Stratified analysis		
MMC	0.594 (0.362-0.974)	0.039*
Pirarubicin	0.081 (0.007-0.990)	0.049
Exclusion of one study	0.660 (0.444-0.981)	0.076*

MMC, mitomycin C; Ara-C, Arabinoside C; RFS, Recurrence free survival; HR, Hazard Ratio; 95% CI, 95% confidence intervals. *The analysis was conducted with the fixed-effects model. The rest analysis was conducted with the random-effect model.

mens. In addition, we performed sensitivity analysis by removing each study one at a time to determine the impact on the overall pooled results. The presence of publication bias was examined using Begg's funnel plot and $P < 0.05$ was considered significant [23]. All analysis was performed with Stata software (version 11.0; StataCorp LP, College Station, TX) with two-sided *P* values.

Results

Characteristics of accessible studies

The analysis included 6 studies from 5 publications on the postoperative intravesical instillation and UUT-UCs bladder tumor recurrence, including total 227 cases and 305 controls (**Table 1**). The flow chart of selection is shown in **Figure 1**. All studies were single or multi-center studies. Three studies [17, 22, 24] utilized MMC for the instillation regimens while in one of them [22] MMC and Ara-C were simultaneously instilled into bladder. Epirubicin and pirarubicin were respectively applied for the instillation in additional studies. A single instillation of regimens was performed in 3 studies and in another 3 studies more than 1 instillation was given during a period of over a month.

Test of heterogeneity and sensitivity analysis

Heterogeneity between studies was observed in the overall comparison as well as in the subgroup analysis. There was significant heterogeneity in the primary analysis ($P = 0.003$, $I^2 = 72.4\%$). Meta-regression was utilized to evaluate the source of heterogeneity for instillation regimens (MMC, epirubicin, pirarubicin) ($P_{regimen} = 0.64$) and patient characteristic (non-selected, positive urine cytology) ($P_{patient} = 0.05$). $P < 0.1$ was considered significant and therefore heterogeneity was existed. The results show that patient characteristic did contribute to substantial altered heterogeneity. Next, a Galbraith radial plot was performed to delineate which study was the cause of the heterogeneity (**Figure 2A**). After the elimination of the study by Ito *et al* [16], the results exhibited that no heterogeneity was observed in the analysis (**Table 2**, **Figure 2B**).

Sensitivity analysis was performed to distinguish each study's influence on the pooled HR by repeating the meta-analysis while omitting each study one at a time [25]. No individual study significantly affected the pooled HR showed by **Figure 3**, suggesting that our results are reliable and robust.

Quantitative synthesis

When the eligible studies had data for RFS, they were pooled for the meta-analysis. The pooled HR was 0.38 (95% CI: 0.16-0.87) demonstrating a 62% benefit in RFS among those treated with postoperative intravesical instillation compared with those not (**Figure 4**). Hence a random-effects model was practiced in the primary analysis. Next, stratified analysis was conducted based on the instillation regimens (**Figure 5**). Respectively, a 41% benefit of MMC (HR = 0.59; 95% CI, 0.36-0.97) and a 92% benefit of pirarubicin (HR = 0.08; 95% CI, 0.01-0.99) in RFS was exhibited versus those who merely underwent surgeries. Considering $P = 0.331$ and $I^2 = 9.7\%$, we practiced a fixed-effect model to assess the significance of prophylactic instillation of MMC to prevent recurrent bladder tumors. The exclusion of one study [16] for its heterogeneity revealed the pooled HR was 0.66 (95% CI, 0.44-0.98; $P = 0.154$ for heterogeneity test; $I^2 = 40.1\%$) (**Figure 6**) and intravesical instillation did appear to reduce the risk of a bladder tumor recurrence following nephroureterectomy for UUT-UC.

Publication bias

Begg's funnel plot and Egger's test were conducted to evaluate the publication bias and the

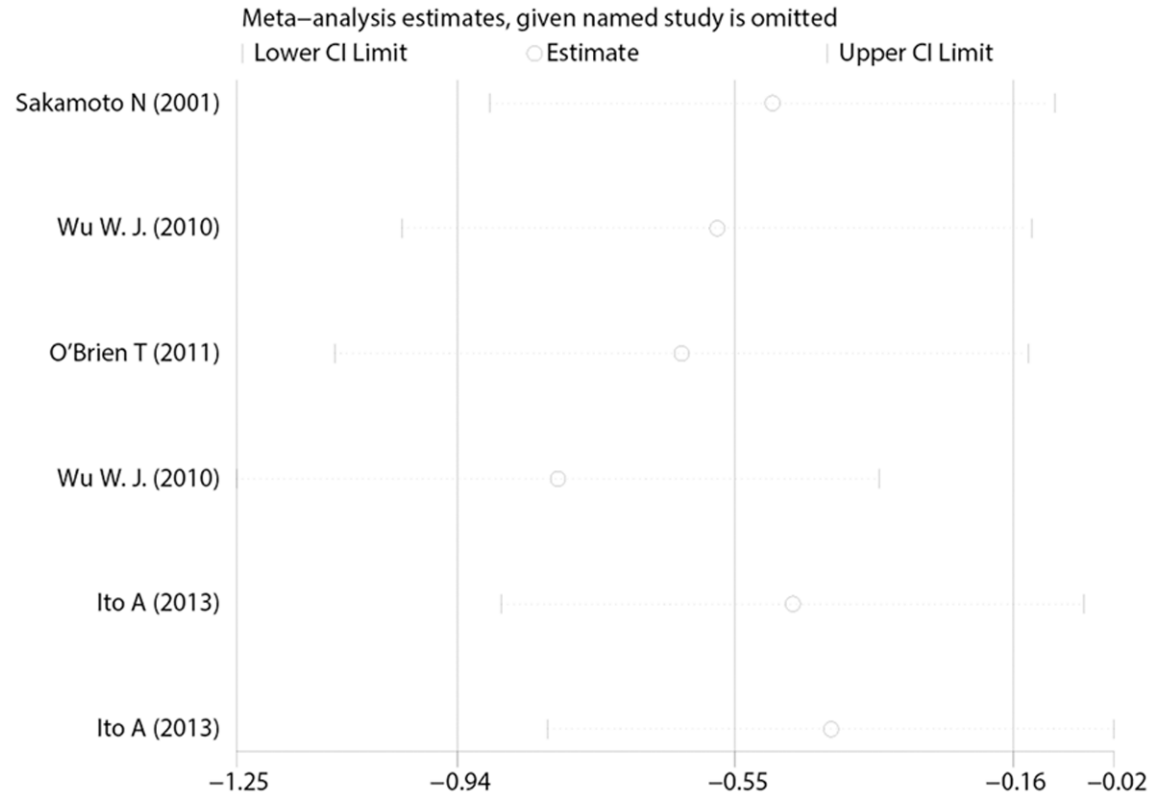

Figure 3. Sensitivity analysis in the overall meta-analysis. The figure shows the influence of individual studies on the summary HR.

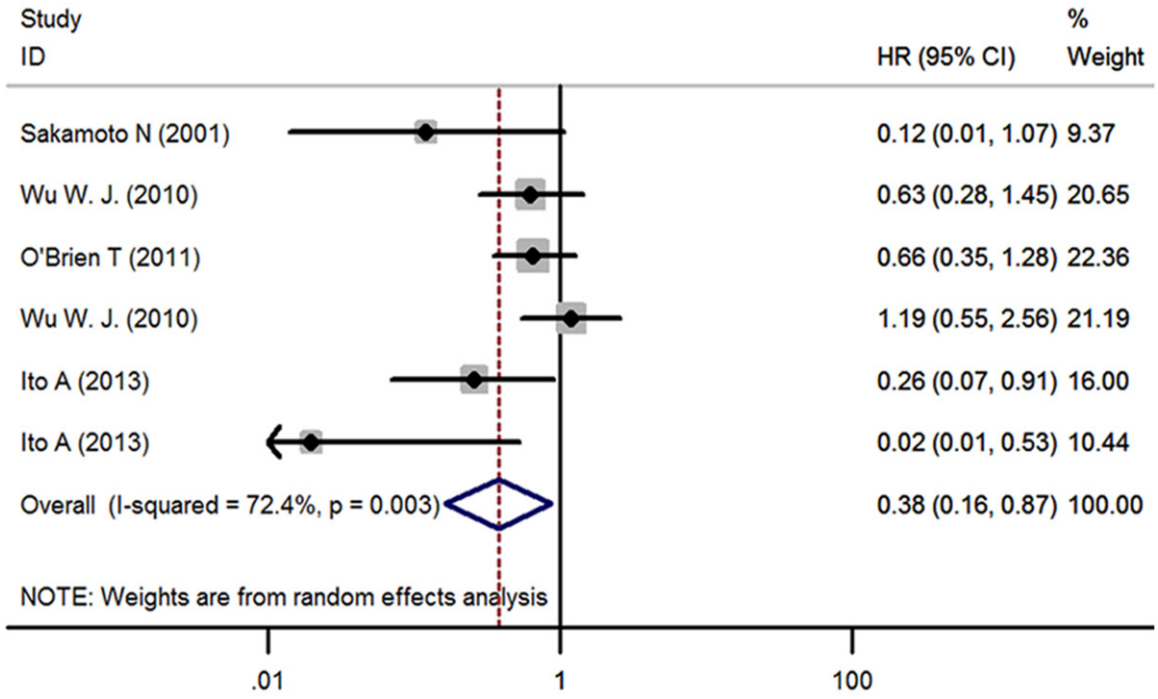

Figure 4. Forest plot of overall studies to estimate intravesical instillation benefits to prevent bladder tumor recurrence. HR: Hazard ratio. CI: confidence interval.

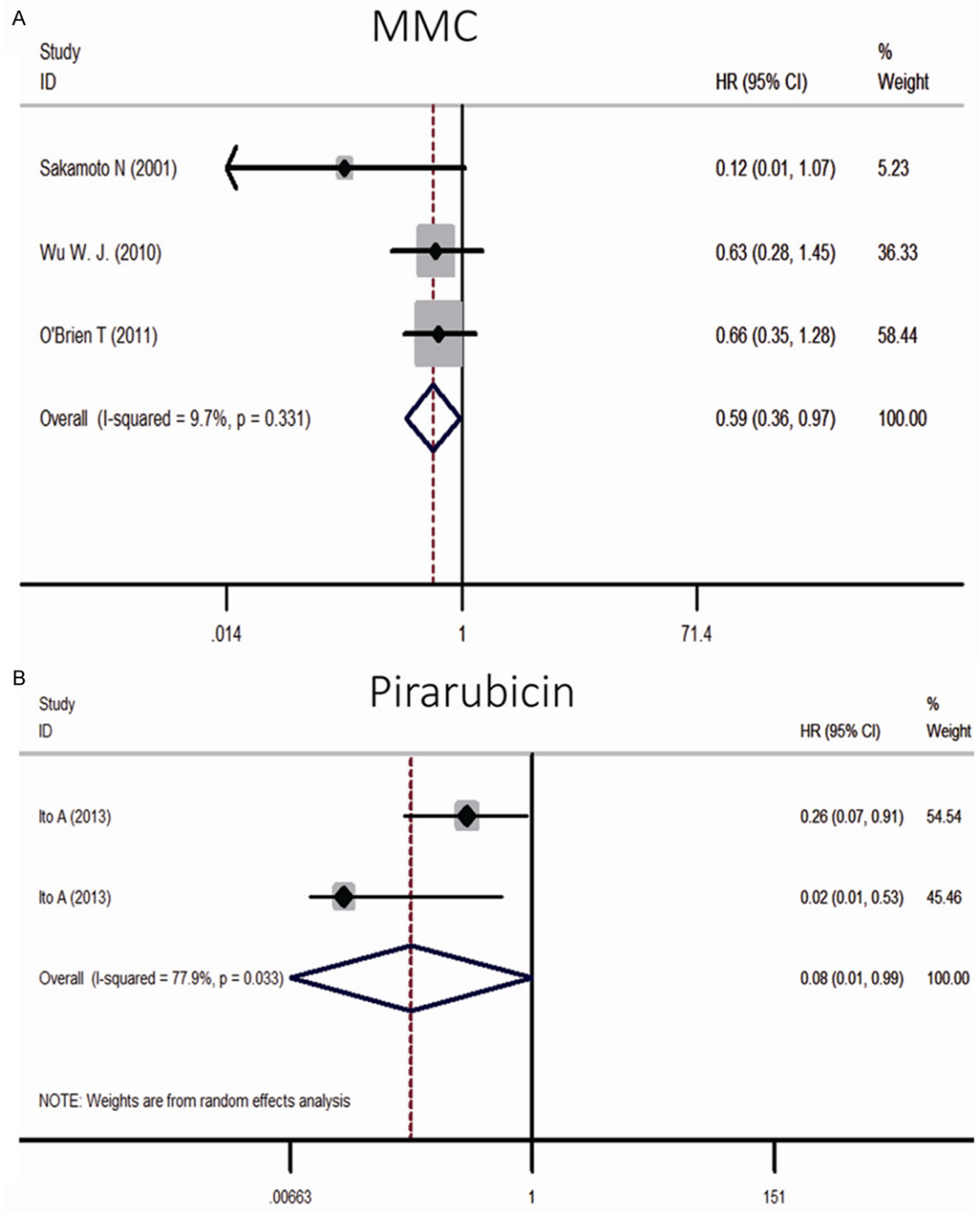

Figure 5. Forest plot of stratifies analysis to estimate different instillation regimens benefits to prevent bladder tumor recurrence. HR: Hazard ratio. CI: confidence interval.

results are shown in **Figure 6**. However, publication bias was present (t = -3.36, *P = 0.028*) and after the removal of the study [16], the results of the funnel plots showed no evidence of obvious asymmetry (t = -2.25, *P = 0.110*) (**Figure 7**).

Discussion

In general, our results supported more benefits of RFS among patients treated with instillation regimens for UUT-UC bladder tumor recurrence compared to those who underwent surgery

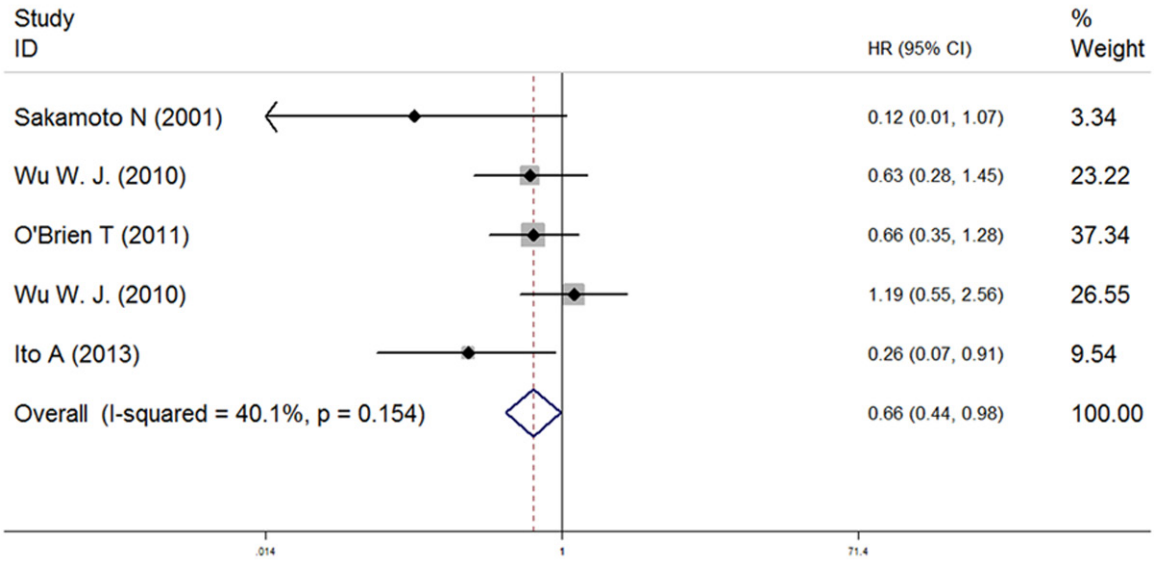

Figure 6. Forest plot of the rest 5 studies to estimate intravesical instillation benefits to prevent bladder tumor recurrence. HR: Hazard ratio. CI: confidence interval.

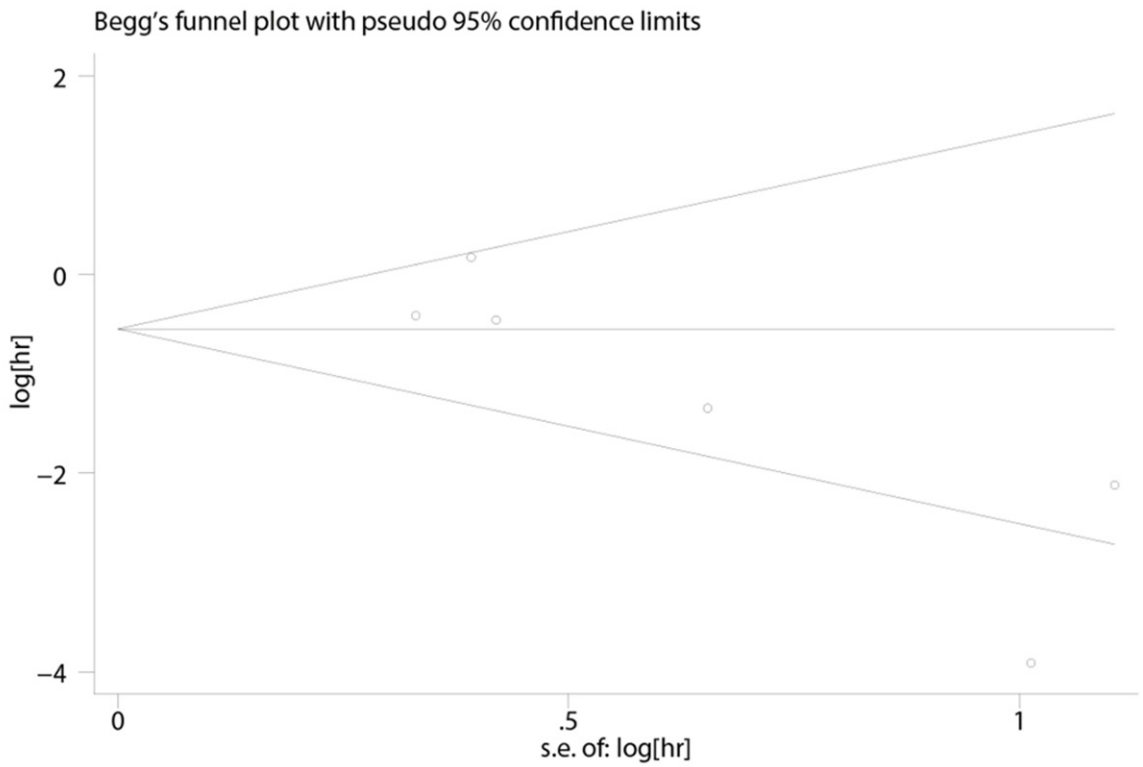

Figure 7. Begg's funnel plot of publication bias test. Each point represents an isolated study for the indicated association. Log (HR): natural logarithm of HR. Horizontal line mean effect size.

alone (HR = 0.38, 95% CI: 0.16-0.87). Furthermore, after assumption of stratified analysis by instillation regimens, we found that MMC and pirarubicin would provide more benefits to patients after the prophylactic instillation (HR = 0.59, 95% CI = 0.36-0.97 for MMC and HR = 0.08, 95% CI = 0.01-0.99 for pirarubicin).

Currently, though intravesical instillation is widely used to prevent recurrence after transurethral resection of superficial bladder tumors, there are still controversial results on the prophylactic ability of intravesical chemotherapy to prevent bladder tumor recurrence after surgery for UUT-UCs [22]. In this study, we found an RFS benefit among patients treated with postoperative intravesical instillation for UUT-UC compared with those who underwent surgery alone. Studies have shown that intraluminal seeding and implantation of cancer cells [26, 27] and field cancerization [28, 29] may be two significant mechanisms for bladder tumor recurrence. The milieu of the bladder at the time of surgery could also be incipient tumor growth for three reasons: tumor cell shedding acceleration on account of the manipulation of tumor, bladder wound resulting in angiogenic factors release and surgery wound immunocompromised [24]. Intravesical instillation chemotherapy will significantly annihilate tumor cells and inhibit the cancer cell implantation and field cancerization [30]. What's more, intravesical chemotherapy was pondered to be most effective if it is instilled within six hours after surgery [30]. Interestingly, a meta-analysis have illustrated that a single immediate instillation of chemotherapy after transurethral resection of bladder tumor (TURBT) significantly diminished the risk of recurrence in patients with Ta/T1 stage bladder cancer [31]. Likewise, three of pooled studies utilized a single-dose early instillation of various drugs and the scale of the pooled treatment effect (HR = 0.19) was similar to the results in trials of postoperative single-dose intravesical chemotherapy to prevent bladder tumor recurrence after TURBT [32-34]. Compared to the period instillation, we found similar consequencess with the results from three of the pooled studies [16, 24, 35] which merely instilled regimens once immediately after the surgery. And it turned out that risks of bladder tumor recurrence for UUT-UCs are also strikingly reduced.

The heterogeneity may emanate from various factors, such as instillation regimens, instillation duration and even population characteristic diversities. Thus, we conducted a meta-regression ($P_{patients}$ = *0.05*) and Galbraith radial plots to discover the source of heterogeneity. The results showed that a study by Ito *et al* [16] was a key spring of the analysis heterogeneity. As far as we concerned, patients with positive voided urine cytology had more frequent recurrence when compared with the patients with negative urine cytology. Based on the multivariate analysis in the control group by Ito *et al*, they discovered that voided urine cytology was an independent predictor of bladder tumor recurrence. Studies have suggested that preoperative positive urine cytology was a prognostic factor for bladder tumor recurrence after surgery because the cancer cells from UUT-UCs unceasingly fell onto the bladder mucosa in the preoperative period [16]. The patients of Ito's study from the non-instillation group were patients with positive voided urine. The instillation method of this study would provide 98% benefit (HR = 0.02) indicating that instillation of pirarubicin immediately after surgery significantly reduced bladder tumor recurrence rate for patients with positive urine cytology. This observation suggests that the intravesical seeding and implantation of cancer cells from UUT-UC might occur during surgery not before surgery. Physical injury to the bladder is a possible contribution to the striking increase in the adherence of bacteria, tumor cells or crystals to the urothelium [36]. That's a reason that most of the patients had bladder tumor recurrence in the areas around the wall of cystectomy or the bladder neck [16]. Hence, we excluded this study and the meta-analysis was conducted again. The pooled results showed a significant anti-tumor recurrence effect than the non-instillation group (HR = 0.66, 95% CI = 0.44-0.98, *P = 0.154*, I^2 = 40.1%) and publication bias also vanished (*P = 0.274*). The results presented herein are more reliable after this study was excluded for homogeneity [16].

MMC, which is a cross-linking agent and typical micronucleus inducer [37] could possibly prevented cells that implanted themselves from establishing a significant new tumor. Our stratified analysis demonstrated that the consumption of MMC would provide more benefit to the instillation group than to the surgery group. (HR = 0.59, 95% CI: 0.36-0.97). Interestingly, the doses of MMC used by Wu *et al* [17] (10 mg) was much lower than the recommended dose (30 mg) after transurethral resection of bladder cancer, which has the potential to decrease therapeutic costs and side effects. Studies have been demonstrated that higher intravesical chemotherapy doses with maintenance

instillations would provide no more benefit than the doses (10 mg) in Wu *et al*'s study [38]. The Pirarubicin Monotherapy Study Group trial reported that a single instillation of pirarubicin within 48 h of surgery was independently associated with a significantly reduced rate of bladder tumor recurrence [35]. In a single intravesical instillation of MMC after TURBT, the instillation was retained for 60 minutes while an appropriate intravesical retention time of pirarubicin was 30 minutes [39], which indicated that pirarubicin required shorter time than MMC for representing antitumor effect [40]. We discovered that pirarubicin may also function as a recurrence scavenger and reduce the risk of bladder recurrence in the UUT-UCs (HR = 0.08, 95% CI: 0.01-0.99). One of the pooled studies by Sakamoto *et al*, which instilled MMC 20 mg and Arabinoside C (Ara-C) 200 mg simultaneously presented a HR = 0.12 indicating a much higher benefits than remaining studies. Moreover, this combination instillation was investigated to show a relatively low incidence of side-effects as compared to other anticancer agents [10]. Thus, MMC and Ara-C might be consequently chosen as a prior instillation regimens in the future study.

To the best of our knowledge, this is the first meta-analysis describing the relationship between postoperative intravesical instillation benefits and the risk of bladder tumor recurrence. After the exclusion of one study for its heterogeneity [16], all the pooled studies showed a 34% benefit for chemotherapy instillation than the non-instillation group patients. However, our analysis had some limitations which should be declared: First of all, the studies contained a relatively small sample sizes and the results need to be further validated and confirmed. Secondly, only studies with full text from English databases were selected, and this may have led to publication bias. Thirdly, the major studies pooled were investigations in Asians. Finally, we extracted the HR following an internationally acknowledged methodology. Although this methodology cannot extract data from all studies and not get the absolute accurate HR, it might not cause a great impact on our result due to our relative consistent result. Conclusively, this study reveals a relative benefit for postoperative instillation to improve the RFS of UUT-UC patients. Moreover, it would be exciting to extend the investigation to a wider range of experiments which may result in a better, comprehensive understanding of the intravesical chemotherapy.

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Disclosure of conflict of interest

None.

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