

Prophylactic Intravesical Chemotherapy to Prevent Bladder Tumors after Nephroureterectomy for Primary Upper Urinary Tract Urothelial Carcinomas: A Systematic Review and Meta-Analysis

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Key Words

Bladder cancer · Intravesical chemotherapy · Meta-analysis · Nephroureterectomy · Upper urinary tract urothelial carcinoma

Abstract

Introduction: Intravesical recurrence after treatment of primary upper urinary tract urothelial carcinomas (UUT-UCs) is common. While intravesical instillation is widely used to prevent recurrence after transurethral resection for primary bladder tumors, there is still no consensus on the prophylactic capability of intravesical chemotherapy in preventing bladder tumor recurrence after surgery for UUT-UCs. **Methods:** A meta-analysis of the published results of clinical trials was performed to compare radical surgery alone or surgery plus postoperative intravesical chemotherapy. The primary end point was to determine the percentage of patients with recurrence in the different groups. **Results:** Our study includes five trials with recurrence information on 614 patients. During follow-up, 55 of 268 (20.5%) patients who received postoperative instillation had bladder recurrence compared to 127 of 346 (36.7%) patients who had no adjuvant treatment – a decrease of 41% in the odds of recurrence with chemotherapy (odds ratio 0.48, 95% confidence interval 0.33–0.69, $p = 0.0001$). No serious adverse events were

reported. Subgroup analyses were temporarily unavailable. **Conclusions:** Postoperative intravesical chemotherapy significantly decreases the risk of bladder recurrence after nephroureterectomy for primary UUT-UCs. Postoperative intravesical instillation is considered the treatment of choice after nephroureterectomy.

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Introduction

Urothelial carcinomas are the fourth most common tumors after prostate and/or breast cancer, lung cancer and colorectal cancer [1, 2]. They can be located in the lower urinary tract (bladder and urethra) or the upper urinary tract (pyelocaliceal cavities and ureter). Upper urinary tract urothelial carcinomas (UUT-UCs) are uncommon and account for only 5–10% of urothelial carcinomas [1, 3].

As a localized disease, radical nephroureterectomy with excision of the bladder cuff is the gold standard treatment for UUT-UCs [4, 5]. The reported recurrence rate within the bladder after treatment of a primary UUT-UC is thought to be 20–50% [6–11]. Recurrent bladder tumors require transurethral resection, which is associated with surgical complications, higher costs of treatment and potential further radical cystectomy [12].

Generally speaking, the field cancerization hypothesis [13, 14] and intraluminal seeding [15–17] are currently the two main concepts to explain multifocality of urothelial cancer and the recurrent bladder tumor. Independent multiclonal tumor development after carcinogenic exposure of the entire urothelial and intraluminal implantation followed by clonally induced single progenitor cell evolution are the mechanisms suggested. While the two mechanisms could co-exist [18], the intraluminal seeding hypothesis is becoming more prevalent with the emergence of more evidence from molecular studies. Thus postoperative intravesical chemotherapy could potentially remove the implantation cell and prevent recurrence. While intravesical instillation is widely used to prevent recurrence after transurethral resection for primary bladder tumors [19, 20], there is no consensus on the prophylactic capability of intravesical chemotherapy in preventing bladder tumor recurrence after surgery for UUT-UCs.

To determine the effect of postoperative intravesical chemotherapy in preventing bladder tumor recurrence after surgery for UUT-UCs, a systematic review and a meta-analysis of the results of clinical trials was performed to reach a more precise estimate of the size of the overall treatment effect and the effect of different kinds of intravesical drugs.

Methods

Data Collection

To limit publication bias, both published and unpublished trials were included. By using key words ('upper urinary tract', 'urothelial carcinoma', 'intravesical instillation', 'bladder tumor' and 'recurrence'), we searched Medline, Cochrane Database, China National Knowledge Infrastructure and Elsevier. Cited references from included trials and reviews of similar trials were also searched. There were no restrictions on the inclusion of publications by language. Two reviewers independently assessed all articles identified by search strategies for relevance.

Inclusion and Exclusion Criteria

To be included in the meta-analysis, trials needed to be aimed toward patients who underwent radical surgery with or without postoperative intravesical chemotherapy. The local treatment should have been used in each group – the control and experimental groups had to differ only by the addition of intravesical instillation. Nephroureterectomy could be performed by open or laparoscopic approach, and postoperative histologic proof of transitional cell carcinoma was needed. Conservative surgery instead of radical surgery, other neoadjuvant or adjuvant treatment besides postoperative instillation, metastatic disease and non-urothelial carcinomas were excluded.

Quality Assessments

The risk of bias was assessed according to The Cochrane Collaboration's tool for assessing risk of bias.

Study Outcomes

Since not all publications provided the necessary information to compare time to first recurrence, the primary end point was the percentage of patients with a recurrence in different groups. The decrease in the odds of recurrence for patients receiving intravesical instillation was thus calculated without taking into account the time to recurrence.

Statistical Analysis

The odds ratios (ORs) for each trial were calculated based on the number of eligible patients with follow-up after nephroureterectomy (evaluable patients) and the number of patients with recurrence in each treatment group. ORs from the individual trials were combined based on a Mantel-Haenszel fixed effects model to get an overall estimate of the OR. Absolute risk reduction was calculated according to risk difference. Forest plots provide the OR for each individual trial and overall, along with 2-sided 95% confidence intervals. A test for heterogeneity assessed whether there was a difference in the size of the treatment effect among trials. Subgroup analysis concerning different drugs was also calculated.

Results

A total of 7 trials focused on this topic and potentially met the selection criteria [21–27]. Two trials were excluded because some patients underwent radical nephrectomy instead of nephroureterectomy [26, 27] and because some patients received intravesical instillation before surgery in one trial [26]. Five trials were retained, including four published articles [21–23, 25] and one meeting program abstract from the AUA annual meeting [24].

Trial Characteristics

The trials began patient accrual between 1985 and 2005 and were published from 2001 to 2012 (table 1). The median follow-up was 12, 55.6, 46 and 45 months respectively (data were incomplete in one trial), with a maximum of 182 months. Epirubicin, hydroxycamptothecin and pirarubicin were each used in one trial, and mitomycin C was used in three trials (one of which simultaneously used arabinoside). In two studies a single instillation was given within a week after surgery, while in the other three studies the instillation was given 6–8 times with the first within 2 weeks after surgery. Patients retained the solution for at least 1 h in all studies. Intention to treat analysis was used in one study. The assessment of risk of bias for published articles is shown in table 2.

Table 1. Trial characteristics

Trial (first author)	Accrual period	Drugs	Follow-up time	Instillation duration	Patients, total
O'Brien, 2011 [21]	2000–2006	MMC 40 mg	12 months	just once	239
Wu, 2010 [22]	1985–2007	MMC 10 mg/epirubicin 20 mg	12–182 months	6–8 times*	196
Tian, 2011 [23]	1995–2007	HCPT 40 mg	46 (26–66) months	6–8 weekly	82
Ito, 2012 [24]	2005–2008	THP 30 mg	NA	just once	72
Sakamoto, 2001 [25]	1993–1996	MMC 20 mg plus Ara-C 200 mg	6–65 months	2 weekly + 5 fortnightly + 21 months	25

Ara-C = Arabinoside; HCPT = hydroxycamptothecin; MMC = mitomycin C; THP = pirarubicin; NA = not available.

*No detailed data for intervals between instillations.

Table 2. Risk of bias assessment (only published articles were assessed)

	O'Brien, 2011 [21]	Wu, 2010 [22]	Tian, 2011 [23]	Sakamoto, 2001 [25]
Adequate sequence generation	yes	non-random approach	non-random approach	yes
Allocation concealment	yes	no	no	yes
Blinding	unclear	unclear	unclear	unclear
Incomplete outcome data addressed	yes	yes	yes	yes
Free of selective reporting	yes	yes	yes	yes
Free of other bias	yes	yes	yes	yes

Patient Characteristics

A total of 666 eligible patients were initially enrolled in all trials: 614 (92.2%) had follow-up and were included in the final analysis, 346 (56.4%) after nephroureterectomy and 268 (43.6%) after nephroureterectomy plus instillation (table 3). There was no significant difference between groups in terms of gender, number of tumors, age, T category and G grade at study entry.

Recurrence

As shown in the forest and funnel plot (fig. 1, 2), recurrence was reported in 182 (29.6%) of the 614 patients, in 127 patients (36.7%) after nephroureterectomy alone and in 55 patients (20.5%) receiving instillation (OR 0.48, 95% confidence interval 0.33–0.69, $p = 0.0001$). The size of the treatment effect was similar in the trials using epirubicin and in those using mitomycin C with or without arabinoside (fig. 3). The absolute reduction in risk is 15%, and the relative reduction in risk is 41%. Separate analysis for different T categories and for single/multiple tumors could not be made for lack of information.

Table 3. Patient characteristics (data were unavailable in Ito [2012])

	Instillation group (n = 268)	Non-instillation group (n = 346)	Total (n = 614)
Sex			
Male	64	96	160
Female	48	95	143
Unknown	156	155	311
T stage			
T0–1	117	167	284
T2	56	65	121
T3	51	67	118
T4	6	6	12
Unknown	38	41	79
Number of tumors			
Multiple	53	64	117
Solitary	178	244	422
Unknown	37	38	75
G grade			
Well	27	24	51
Moderate	84	94	178
Poor	60	50	110
Unknown	97	178	275

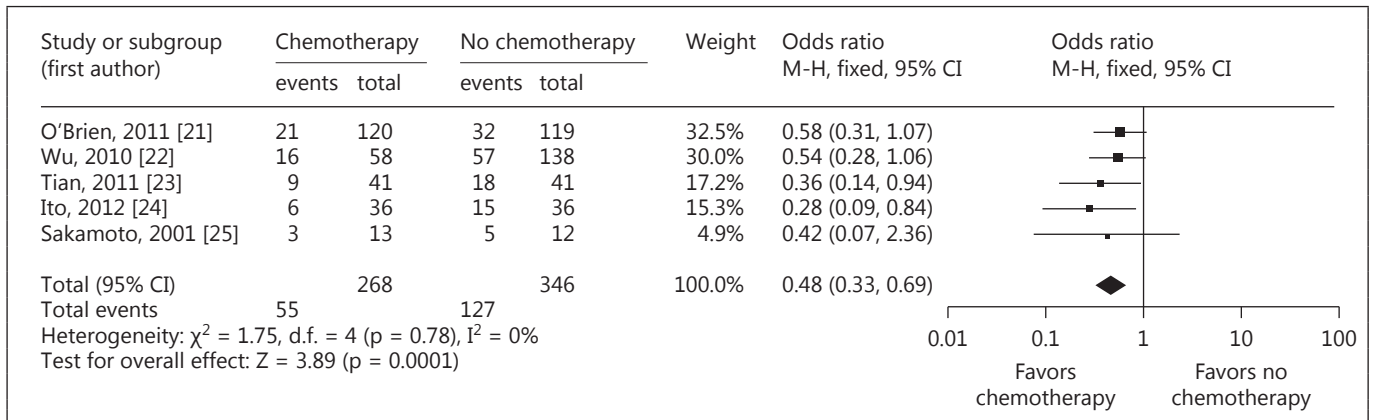


Fig. 1. Forest plot for recurrence rate.

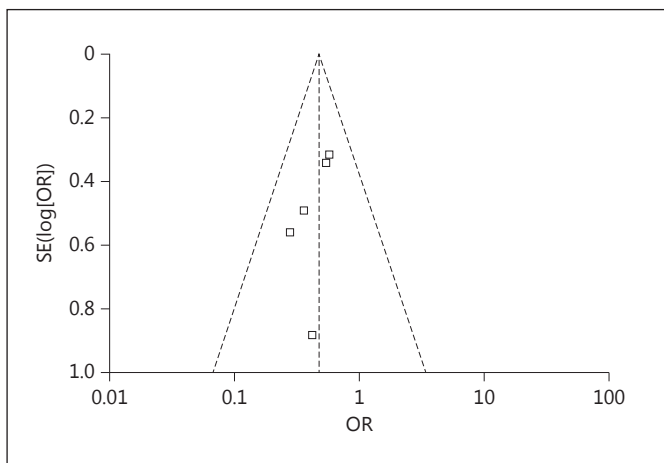


Fig. 2. Funnel plot of recurrence rate.

Toxicity

Mild transient, irritable bladder symptoms including frequency, urgency and pain on urination were noted in very few patients. Neither systemic toxicity nor abnormal laboratory data were observed.

Discussion

This meta-analysis showed that intravesical instillation of chemotherapy after nephroureterectomy decreases the risk of recurrence by 41% in patients with UUT-UCs (OR 0.48, $p = 0.0001$) without serious adverse events.

The absolute risk reduction is 15%, which more or less means that fewer than seven patients need to be treated to prevent one recurrence. This meta-analysis demonstrated the prophylactic role of instillation and is more persuasive than any individual trial.

The instillation drugs including mitomycin C, hydroxycamptothecin, pirarubicin and epirubicin seemed to be associated with similar treatment results, but a conclusion could not be made since the data was limited. More randomized clinical trials are needed for comparison of treatment effects between different drugs. We have insufficient evidence to formally test whether any of the specific combinations of chemotherapy was more or less effective.

The risk factors for bladder recurrence after surgery for UUT-UCs were analyzed in previous articles. Tumor multifocality [6, 7, 28] and prior history of bladder cancer [8, 9, 28] are the most frequently reported risk factors for bladder recurrence. Other variables such as tumor location [10], tumor stage [6, 7] and gender [11] have also been discussed. The identification of factors that allow accurate risk stratification for future bladder relapse is disappointing [28], and it is difficult to select high-risk patients before instillation. In the trials included in our meta-analysis little attempt was made to match the two arms for their risk factors for recurrence. In the study by Sakamoto et al. [25], none of these factors were found to significantly influence the non-recurrence rate. Under re-comparison with the data in the article by O'Brien et al. [21], no difference in recurrence rate between different grades, stages or single/multiple focus was discovered. No related data were provided in the remaining trials. As for

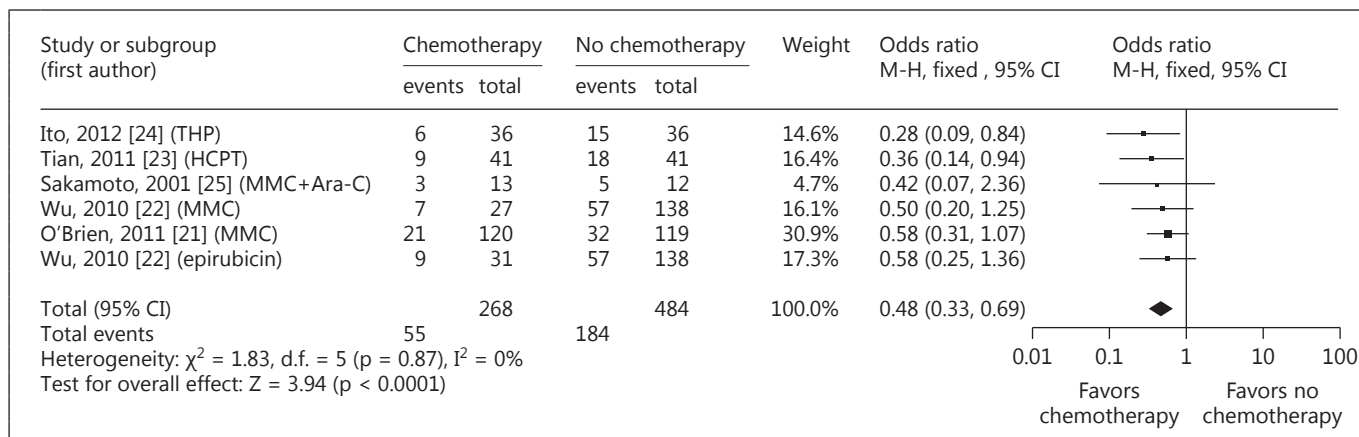


Fig. 3. Forest plot of treatment effects of different drugs. Ara-C = Arabinoside; HCPT = hydroxycamptothecin; MMC = mitomycin C; THP = pirarubicin.

the size of the effect of treatment for each subgroup, the only article which compared these factors found no difference in the effect of treatment across patient subgroups [21].

As for the primary superficial bladder tumor, a single immediate postoperative as well as a series of further instillations is needed [20]. The best time to administer the first instillation is within 24 h after transurethral resection [29], while the instillation times and schedule after nephroureterectomy are uncertain. The first instillation in all trials was given about 1–2 weeks after surgery, and additional instillations were given in three trials [22, 23, 25]. Implantation might already have irreversibly occurred 7–10 days after nephroureterectomy, but the investigators believe it is better not to administer the chemotherapy before the bladder heals to prevent extravasation [21]. As for the instillation times, Sakamoto et al. [25] conclude that a shorter instillation period may also be sufficient to obtain a good prophylactic effect for the high-risk period of bladder recurrence, which seemed to be relatively short in the non-instillation group; Badalament et al. [19] found long-term maintenance therapy

had no apparent benefit in terms of recurrence and was associated with increased local toxicity in a previous research study about bladder cancer. In all, while the effect of intravesical instillation is confirmed, the proper schedule and duration of intravesical chemotherapy needs further clinical trials to be determined.

This study is hampered by the inclusion of patients with different drugs and different instillation schedules and durations. Thus since only five trials and no unpublished trials were included in our meta-analysis, publication bias is inevitable and more randomized clinical tests are needed to further justify the effects.

Conclusions

Prophylactic intravesical chemotherapy significantly decreases the risk of bladder tumor recurrence after nephroureterectomy for primary UUT-UCs. With little adverse effects, postoperative intravesical instillation is considered the treatment of choice for nephroureterectomy.

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