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Prospective Randomized Phase II Trial of a Single Early Intravesical Instillation of Pirarubicin (THP) in the Prevention of Bladder Recurrence After Nephroureterectomy for Upper Urinary Tract Urothelial Carcinoma: The THP Monotherapy Study Group Trial

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ABSTRACT

Purpose
We evaluated the efficacy of a single early intravesical instillation of pirarubicin (THP) in the prevention of bladder recurrence after nephroureterectomy for upper urinary tract urothelial carcinoma (UUT-UC).

Patients and Methods
From December 2005 to November 2008, 77 patients clinically diagnosed with UUT-UC from 11 institutions participating in the Tohoku Urological Evidence-Based Medicine Study Group were preoperatively enrolled in this study. Patients were randomly assigned to receive or not receive a single instillation of THP (30 mg in 30 mL of saline) into the bladder within 48 hours after nephroureterectomy. Cystoscopy and urinary cytology were repeated every 3 months for 2 years or until the occurrence of first bladder recurrence.

Results
Seventy-two patients were evaluable for efficacy analysis, 21 of whom had a subsequent bladder recurrence. Significantly fewer patients who received THP had a recurrence compared with the control group (16.9% at 1 year and 16.9% at 2 years in the THP group *v* 31.8% at 1 year and 42.2% at 2 years in the control group; log-rank $P = .025$). No remarkable adverse events were observed in the THP-treated group. Based on multivariate analysis, THP instillation (hazard rate [HR], 0.26; 95% CI, 0.07 to 0.91; $P = .035$) and open surgery (HR, 0.28; 95% CI, 0.09 to 0.84; $P = .024$) were independently predictive of a reduced incidence of bladder recurrence.

Conclusion
In this prospective randomized phase II study, a single intravesical instillation of THP seemed to reduce bladder recurrence after nephroureterectomy. A phase III, large-scale, multicenter study is needed to confirm these observations.

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INTRODUCTION

Approximately 20% to 50% of patients with upper urinary tract urothelial carcinoma (UUT-UC) experience bladder recurrence after nephroureterectomy.[1-5] Although many agents have been administered for the prevention of bladder recurrence,[3,6,7] the standard prophylactic treatment has yet to be established.

Pirarubicin, or (2′′R)-4′-*O*-tetrahydropyranyldoxorubicin (THP), is an anthracycline derivative that is absorbed into tumor cells with greater speed than is doxorubicin.[8,9] A meta-analysis found that a single instillation of chemotherapy immediately after transurethral resection of bladder tumor (TURBT) significantly decreased the risk of recurrence in patients with bladder cancer.[10] Indeed, a single early instillation of THP was found to reduce the post-TURBT bladder recurrence rate among patients with bladder cancer.[11]

In this prospective, randomized, phase II study, we evaluated the efficacy of a single, early, intravesical instillation of THP in the prevention of bladder recurrence after nephroureterectomy for UUT-UC. Factors associated with bladder recurrence were also investigated.

PATIENTS AND METHODS

Eligibility Criteria

Patients who were clinically diagnosed with UUT-UC, had no distant metastasis, had an Eastern Cooperative Oncology Group performance status of ≤ 2, and who were expected to receive curative surgery were eligible to participate in this study. UUT-UC was mainly diagnosed with voided urine cytology and computed tomography or retrograde pyelography. In cases that were hard to diagnose with these examinations, diagnostic ureteroscopy was performed. Cystoscopy was performed to confirm the absence of bladder tumors before nephroureterectomy. Written informed consent was obtained from all patients before participation in the study.

Exclusion criteria included a prior history of bladder or synchronous bladder cancer, administration of neoadjuvant chemotherapy, or the presence of severe complications. However, patients who received adjuvant chemotherapy according to a postoperative pathologic diagnosis were eligible to participate.

All eligible patients were included in the intent-to-treat analysis.[11] However, patients whose urothelial carcinoma was not confirmed via pathology of surgical specimens and patients who did not receive postoperative cystoscopic examination as a result of perioperative death were excluded.

The study protocol was approved by the ethics committee of the Tohoku University Graduate School of Medicine and by the ethics committee or institutional review board of each participating institution. Patients were enrolled from 11 institutions, including the Tohoku Urological Evidence-Based Medicine Study Group, Tohoku University Hospital, Sendai Shakai Hoken Hospital, Osaki Citizen Hospital, Miyagi Cancer Center, Tohoku Rosai Hospital, Senseki Hospital, Shirakawa Kosei General Hospital, Sen-en General Hospital, Kesennuma City Hospital, Iwate Prefectural Iwai Hospital, and Ogachi Central Hospital.

Treatment Schedule

Enrolled patients were stratified at University Hospital Medical Information Network Clinical Trials Registry according to institution, sex, location of urothelial tumor, and operative method and then randomly assigned using a minimization method.[12] Open nephroureterectomy was performed in a standard manner. In laparoscopic surgery, a retroperitoneal approach was used for mobilization of the kidney, and the cuff resection of the bladder wall was performed with a lower abdominal incision. The distal ureter was dissected down to its intramural segment, and the entire ureter and orifice were completely excised through a posterolateral cystotomy. Then the bladder wall was tightly sutured in both approaches. Regional lymphadenectomy was not performed routinely. Patients were randomly assigned to receive a single instillation of THP or no instillation within 48 hours after nephroureterectomy. THP 30 mg in 30 mL of normal saline was delivered into the bladder through a catheter and was retained for 30 minutes. All surgical specimens were processed according to standard pathologic procedures, and all slides were reviewed by pathologists at each participating institution. The pathologist in each institution standardly diagnosed according to the 2002 International Union Against Cancer TNM system and the 2004 WHO Classification of Tumors. The study protocol is available online at the University Hospital Medical Information Network Clinical Trials Registry Web site.[13]

Patient Assessment

All patients were followed up with cystoscopy, urinary cytology, and urinalysis every 3 months for 2 years or until first bladder recurrence was observed. Bladder recurrence was judged on visual appearance, and histopathologic proof of recurrence was required. Electrocardiography, hematology, and biochemistry data were collected, and local and systemic toxicities were evaluated at the first postnephroureterectomy visit; severity of adverse events was graded using National Cancer Institute Common Toxicity Criteria version 2.0. Patients who showed disease progression or died of other disease or moved to a distant place within 2 years were censored.

Sample Size Calculation and Statistical Analysis

A previous prospective randomized study of intravesical instillation of mitomycin and cytarabine for the prevention of bladder recurrence after nephroureterectomy reported recurrence-free rates of 57.1% and 92.3% at 12 months in the control and treatment groups, respectively.[6] Assuming a similar treatment effect, the present study required 58 patients to achieve 80% power of detecting a treatment difference at the 5% level of two-sided significance. Similarly, 72 patients would be required to achieve 90% power. The sample size was calculated based on the χ^2 test. Bladder recurrence–free rates after nephroureterectomy were estimated using the Kaplan-Meier method. The log-rank test was used for comparing recurrence-free survival rates between the two groups. Covariates included in the analyses consisted of sex, age, tumor side, operation method (laparoscopic or open surgery), urinary cytology, histologic type, pathologic T stage, tumor grade, tumor location, concomitant carcinoma in situ, and adjuvant chemotherapy. Univariate and multivariate

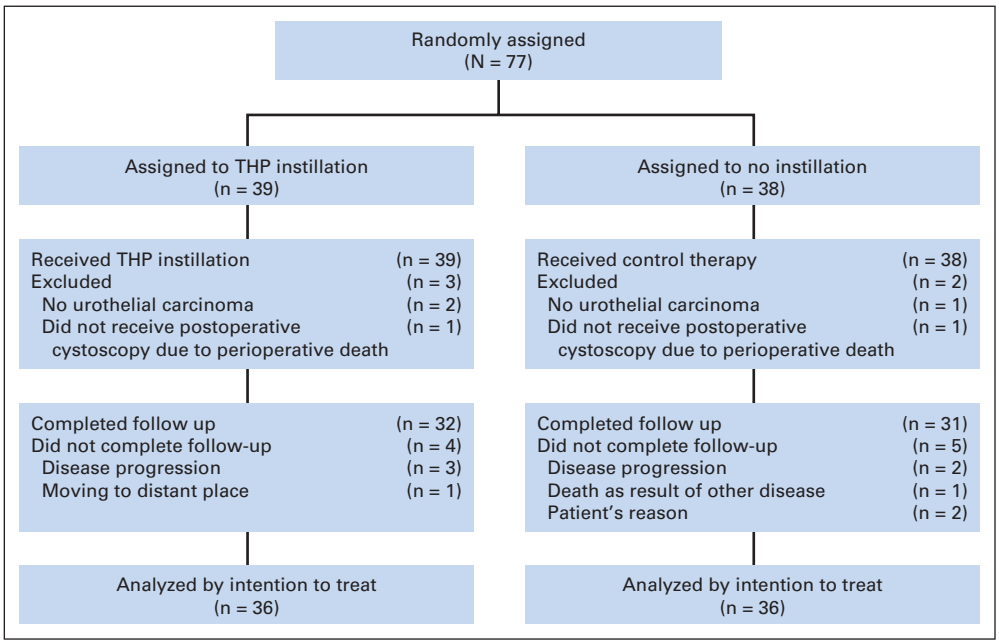

Fig 1. CONSORT diagram of this study. THP, pirarubicin.

analyses using Cox proportional hazards were performed to determine independent predictors of bladder recurrence after nephroureterectomy. All reported *P* values were two-sided, and statistical significance was set at .05. Statistical analyses were performed with SAS Release 8.2 software (SAS Institute, Cary, NC).

RESULTS

Baseline Patient Characteristics

Between December 2005 and November 2008, 77 patients with clinically diagnosed UUT-UC were preoperatively enrolled in this study. The 77 patients were randomly assigned into the THP (n = 39) or control groups (n = 38). Two patients in THP group and one patient in control group were excluded from efficacy analysis because of a lack of pathologically confirmed urothelial carcinoma. One patient in the THP group and one patient in the control group were excluded from all analyses due to a lack of postoperative cystoscopic examination as a result of perioperative death. As illustrated in Figure 1, the remaining 72 patients were included in the efficacy analysis on the basis of the intent-to-treat analysis. Of these 72 patients, 20 patients who were included in the analysis warrant special mention. One patient died of another disease within 2 years, five patients continued to receive cystoscopy until the diagnosis of metastatic disease, and 14 patients (seven in each group) received adjuvant chemotherapy as a result of worsening pathologic findings of extirpated specimens. Patient characteristics of the two groups are outlined in Table 1.

Treatment Efficacy and Toxicity

Figure 2 shows the bladder recurrence–free survival curve of all 72 patients. As illustrated, a total of 21 patients experienced a subsequent bladder recurrence, most of which were observed at the first cystoscopic examination after nephroureterectomy. Figure 3 shows the bladder recurrence–free survival curves for patients in the THP and control groups. The median follow-up period was 24.9 months (range, 2.6 to 39.3 months) in the THP group and 13.7 months (range, 2.8 to 34.1 months) in the control group. Significantly fewer patients in the THP group than in the control group had a recurrence (16.9% at 1 year and 16.9% at 2 years in the THP group *v* 31.8% at 1 year and 42.2% at 2 years in the control group; log-rank $P = .025$). Bladder symptoms of grade 1 or worse associated with instillation of THP were not observed. At first visit 1 month after surgery, there were no electrocardiographic changes from presurgical examination, and hematologic or biochemical adverse events and bladder symptoms of grade 1(eg, mild bladder symptoms without requiring intervention) or worse were not observed.

Factors Affecting Bladder Recurrence

Univariate and Cox multivariate analyses of factors associated with bladder recurrence are described in Table 2. In univariate analyses, THP instillation, age, presence of a ureter tumor, operation method, and tumor grade were significantly associated with bladder recurrence. Multivariate analysis revealed that THP instillation (hazard ratio, 0.26; 95% CI, 0.07 to 0.91; $P = .035$) and open surgery (hazard ratio, 0.28; 95% CI, 0.09 to 0.84; $P = .024$) were the only factors to independently predict better recurrence-free survival rates.

Table 1. Patient Characteristics

Characteristic	THP Group (n = 36) No.	THP Group (n = 36) %	Control (n = 36) No.	Control (n = 36) %
Sex				
Male	22	61.1	21	58.3
Female	14	38.9	15	41.7
Age, years				
< 69	18	50	19	52.8
≥ 69	18	50	17	47.2
Tumor side				
Right	17	47.2	21	58.3
Left	19	52.8	15	41.7
Tumor site				
Calix or pelvis	21	58.3	19	55.9
Pelvis and ureter	2	5.6	1	2.8
Ureter	13	36.1	16	44.4
Operation				
Laparoscopic	16	44.4	17	47.2
Open	20	55.6	19	52.8
Urinary cytology				
Positive	26	72.2	20	55.6
Negative	10	27.7	16	44.4
Pathology				
UC	33	91.7	32	88.9
UC and SCC	3	8.3	2	5.6
UC and AC	0		2	5.6
Grade				
Low	24	66.7	15	41.7
High	12	33.3	21	58.3
Tumor stage				
pTa	10	27.7	6	16.7
pT1	9	25	14	38.9
pT2	6	16.7	2	5.6
pT3	11	30.6	14	38.9
Nodal status				
pN0	20	55.6	19	55.9
pN1	0	0	1	2.8
pNx	16	44.4	16	44.4
Concomitant CIS				
No	32	88.9	36	100
Yes	4 (1 in ureter)	11.1	0	0
Adjuvant chemotherapy				
Yes	7	19.4	7	19.4
No	29	80.6	29	80.6

Abbreviations: AC, adenocarcinoma; CIS, carcinoma in situ; SCC, squamous cell carcinoma; THP, pirarubicin; UC, urothelial carcinoma.

DISCUSSION

Nearly a third (29.2%) of patients in the current study had a subsequent bladder recurrence after nephroureterectomy for UUT-UC. Most recurrences were observed at the first postnephroureterectomy cystoscopic examination. Multivariate analysis revealed that a single instillation of THP within 48 hours of nephroureterectomy was independently associated with a significantly reduced rate of bladder recurrence. To date, two hypotheses have been proposed to explain subsequent bladder recurrence after nephroureterectomy: intraluminal seeding and implantation of cancer cells[14,15] and field cancerization.[16,17] A previous meta-analysis demonstrated that the use of a

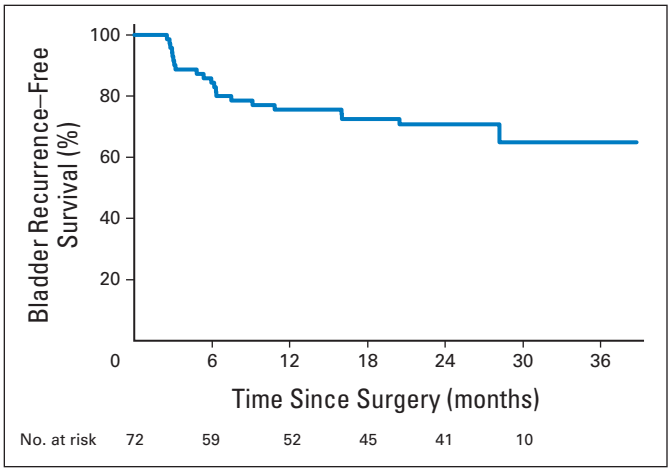

Fig 2. Bladder recurrence–free survival curve for all patients.

Table 2. Univariate and Multivariate Analysis of Factors Associated With Bladder Recurrence

Variable	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
THP instillation	0.35	0.14 to 0.91	.032	0.26	0.07 to 0.91	.035
Sex, male *v* female	1.37	0.55 to 3.41	.494	2.52	0.85 to 7.50	.094
Age	1.04	1.00 to 1.09	.034	1.02	0.97 to 1.08	.438
Tumor side, right *v* left	0.81	0.34 to 1.91	.633	2.00	0.61 to 6.64	.255
Presence of ureter tumor	2.99	1.20 to 7.48	.019	2.95	0.99 to 8.83	.053
Open or laparoscopic	0.27	0.10 to 0.69	.007	0.28	0.09 to 0.84	.024
pT stage	1.70	0.71 to 4.04	.230	1.02	0.29 to 3.58	.973
Urinary cytology	1.98	0.73 to 5.42	.182	2.11	0.64 to 7.00	.222
Tumor grade	2.66	1.07 to 6.62	.036	1.25	0.38 to 4.09	.708
Concomitant CIS	2.19	0.51 to 9.43	.293	8.25	0.71 to 95.83	.092
Histology type	0.57	0.17 to 1.95	.369	0.33	0.07 to 1.52	.153
Adjuvant chemotherapy	1.29	0.47 to 3.54	.615	1.13	0.30 to 4.19	.855

Abbreviations: CIS, carcinoma in situ; HR, hazard ratio; THP, pirarubicin.

single immediate instillation of chemotherapy after TURBT significantly decreases the risk of recurrence in patients with bladder cancer.[10] Similarly, the present study suggests that a single early instillation of THP also prevented the implantation of cancer cells and reduced the rate of bladder recurrence after nephroureterectomy.

A prospective randomized clinical trial using a single dose of intravesical instillation for the prevention of bladder cancer after nephroureterectomy for primary UUT-UC was reported by O'Brien et al.[3] The study consisted of 284 patients who were randomly assigned to receive standard postoperative care or a single dose of intravesical mitomycin. Although the incidence of bladder cancer during follow-up seemed to be lower in the mitomycin arm than in the standard treatment arm, it did not reach statistical significance ($P = .055$). As stated in the accompanying editorial, the major flaw of this study was the lack of standardized timing for the administration of mitomycin.[18] Indeed, in an effort to mitigate the risk of extravasation, mitomycin was given at the time of catheter removal, at least a week after nephroureterectomy. Given the inappropriate timing, the authors noted that although mitomycin could not have prevented implantation, it could have prevented cells from establishing a significant new tumor. A meta-analysis of seven randomized trials confirmed that a single immediate intravesical instillation decreased the risk of recurrence among patients with nonmuscle invasive bladder cancer.[10] Interestingly, in all seven of these trials, the instillation was given within 24 hours after TURBT. Therefore, clinicians should consider administering a single dose of intravesical therapy within 24 hours of resection for the purpose of preventing the implantation and dissemination of tumor cells. In a single intravesical instillation of mitomycin after TURBT, the instillation was retained for 60 minutes.[19,20] However, it was reported that an appropriate intravesical retention time of THP was 30 minutes.[21] This indicated that THP required shorter time than mitomycin for presenting antitumor effect. Therefore, we selected THP rather than mitomycin in our study. Because the timing of THP administration in the current study was standardized to within 48 hours of nephroureterectomy, this may have contributed to the reduced risk of bladder recurrence.

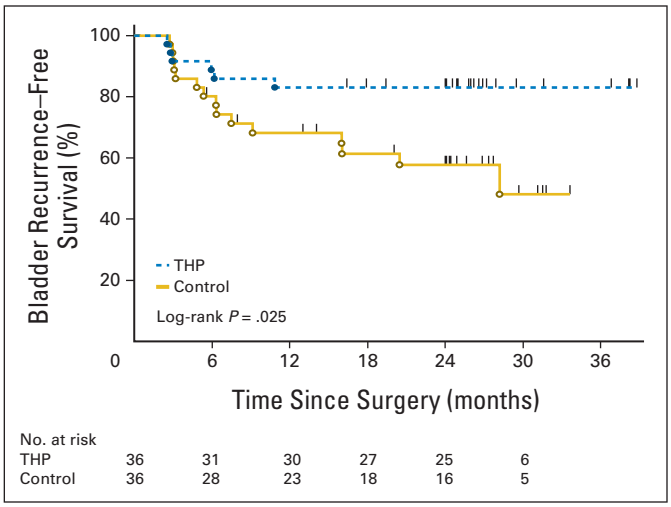

Fig 3. Bladder recurrence–free survival rates after nephroureterectomy of the treatment and control groups estimated using the Kaplan-Meier method. The log-rank test was used for comparing recurrence-free survival rates between the two groups. Closed circles represent the THP-treated group; open circles represent the control group. THP, pirarubicin.

No severe local toxicities were observed in response to THP instillation, and no hematologic, biochemical, and electrocardiographic abnormalities were observed at first visit after surgery. In our study group, urethral catheter removal occurred on average on the seventh postoperative day (range, 2 to 15 days, data not shown), whereas THP was instilled into the bladder within 48 hours after surgery. Thus, at the time of catheter removal, bladder symptoms caused by instillation of THP had been resolved. During laparoscopic nephroureterectomy, the cuff resection of the bladder wall was performed under an open procedure with a lower abdominal small incision. Subsequently, the bladder wall was tightly sutured. Therefore, the extravasation of urine was not observed in our study group.

According to univariate analysis, THP instillation, age younger than 69 years, no ureter lesion, open surgery, and lower tumor grade were associated with improved recurrence-free survival rates. Previous reports have indicated a number of factors that affect bladder recurrence, including tumor multiplicity, location, stage, and grade; operative modality; preoperative urine cytology; and sex.[1,2,4,6,22-24] In our study, multivariate analysis revealed THP instillation and open

surgery as independent predictors of recurrence-free survival. The difference between the findings of previous reports and those of the present study may be explained by the small number of patients in this study or the fact that THP instillation or operative method may simply be the strongest predictors of outcome. Although the central pathology review was absent in this study, the pathologist in each institution standardly diagnosed according to the 2002 International Union Against Cancer TNM system and the 2004 WHO Classification of Tumors. Because the patients of each institution were randomly assigned to both groups, the difference of pathologic diagnosis between institutions should have affected both groups equally. Therefore, the absence of central pathology review may have minimal effect on the results. Additionally, in contrast to prior studies,[6] patients who received adjuvant chemotherapy as a result of worsening of pathologic findings were included in our study. However, multivariate analysis showed that adjuvant chemotherapy was not associated with intravesical recurrence in the current study, a finding that is concurrent with previous retrospective studies.[2,4,24]

Patients in the current study who underwent laparoscopic operation were at increased risk of intravesical recurrence. Although some reports found no difference between open and laparoscopic operations,[25-27] others showed that patients who received laparoscopic surgery were at increased risk of intravesical recurrence.[1,2,28] It has been suggested that the high gas pressure during the procedure might promote tumor cell dissemination within the urinary tract[22] and that a longer operative time owing to lack of operator experience might prolong tumor exposure.[28] However, skilled teams, whose operative times are not prolonged by laparoscopic surgery, report no increase in the risk of bladder recurrence.[28] Recently, a systematic review and cumulative analysis of comparative studies noted that bladder recurrence rates were lower for patients who underwent laparoscopic versus open nephroureterectomy.[29] Nevertheless, most series in this review were retrospective studies and included a small number of cases, and the results were controversial.

In conclusion, in this prospective randomized phase II study, we revealed that a single immediate intravesical instillation of THP can prevent bladder recurrence after nephroureterectomy. A phase III, large-scale, multicenter study is needed to confirm the therapeutic efficacy of this treatment.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Final approval of manuscript: All authors

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