Outcomes of stage II-IV upper-tract urothelial carcinoma and adjuvant chemotherapy for locally advanced cancer

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Abstract. The present retrospective study aimed to examine the outcomes of stage II-IV upper-tract urothelial carcinoma (UTUC) and determine whether adjuvant chemotherapy is a beneficial treatment for patients with locally advanced UTUC (specifically, stage III-IV). The analysis included 126 patients with muscle-invasive UTUC who were treated between June 2003 and June 2012. All patients underwent laparoscopic or open nephroureterectomy and bladder cuff excision. Overall survival (OS), disease-free survival (DFS), distant metastasis-free survival (DMFS) and locoregional recurrence-free survival (LRFS) were assessed. Outcomes were compared between groups of patients with stage II (high-stage localized) disease, stage III-IV (high-stage locally advanced) disease treated with chemotherapy, and stage III-IV disease not treated with chemotherapy. Among patients with high-stage locally advanced UTUC (stage III-IV), those who received adjuvant chemotherapy had significantly better rates of OS (67.1 vs. 33.7%; P=0.004), DFS (70.2 vs. 46.0%; P=0.030) and DMFS (86.3 vs. 65.2%; P=0.048) at 5-years compared with those who did not undergo adjuvant chemotherapy. However, there was no significant difference between the 5-year LRFS rates in these two groups (78.2 vs. 62.5%; P=0.525). Importantly, the survival curve of patients with high-stage UTUC who received adjuvant chemotherapy was similar to that of patients with low-stage UTUC who underwent surgery only. Multivariate analysis revealed that adjuvant chemotherapy was an independent risk factor for OS [without adjuvant chemotherapy vs. with adjuvant chemotherapy: Hazard ratio (HR), 0.29; 95% confidence interval (CI), 0.129-0.654; P=0.003] and DFS (without adjuvant chemotherapy vs. with adjuvant chemotherapy: HR, 0.381; 95% CI, 0.168-0.865; P=0.021). In conclusion, adjuvant chemotherapy may improve the outcome for patients with high-stage locally advanced UTUC.

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Introduction

Urothelial carcinoma (UC) is the ninth most common type of tumor globally (1). In Western countries, urinary bladder UC (UBUC) is the most common malignancy of the urinary tract, and upper-tract UC (UTUC) is comparatively rare, accounting for 5-10% of all urinary tract malignancies (2). However, in Taiwan, UTUC accounts for 40% of all types of urothelial tumor due to the prevalent use of Chinese herbs containing aristolochic acids including *Aristolochia fangchi*, named 'Guang Fang Ji' in Mandarin (3). *Aristolochia fangchi* is used in slimming pills, in addition to being used as a diuretic and immune modulator (3). The Aristolochia herb results in Aristolochic acid-induced urothelium damage (4). As human urothelial tissue is rich in peroxidases, the aristolactams activated by peroxidase may result in the formation of aristolactam (AL)-DNA adducts in urothelial tissue (4,5) resulting in mutations in the TP53 tumor suppression gene which may promote cell-cycle checkpoints, DNA repair and apoptosis (6). The overexpression of TP53 protein in patients is highly observed in Aristolochic acid nephropathy resulting in urothelial carcinoma (7).

Nephroureterectomy is the gold standard in the initial management of invasive localized UTUC (8,9). However, in patients with high-stage (AJCC 7th edition stage II-IV) (10) tumors, the survival rate is poor. The 5-year survival rate is <50% for patients with tumor (T) stage T2/3 and <10% for patients with T4 UTUC (11). The high recurrence and mortality rates in patients with high-stage tumors indicates the necessity for additional effective adjuvant treatments (12).

UC is a chemosensitive tumor (13), and the effectiveness of chemotherapy in treating UBUC is well established (8,14). Therefore, considering the high prevalence of distant metastasis of upper tract urothelial cancer (15), chemotherapy in a neoadjuvant or adjuvant setting appears to be a reasonable approach for the treatment of high-stage UTUC. Kwak *et al* (16) studied 32 patients receiving cisplatinum-based chemotherapy

compared with 11 patients without chemotherapy. Based on multivariate analysis, this previous study concluded that chemotherapy improved survival.

The objective of the present study was to observe the outcome of high-stage UTUC and determine whether adjuvant chemotherapy is beneficial for patients with high-stage UTUC.

Patients and methods

Patients. The present study was approved by the Research Ethics Committee of China Medical University and Hospital (IRB approval no. CMUH103-REC1-094; Taichung, Taiwan). Personal records and data were retrospectively collected and analyzed anonymously. A tertiary referral center (China Medical University Hospital, Taichung, Taiwan) database was used, and included 139 patients who underwent nephroureterectomy between June 2003 and December 2012 for pathological stage II to IV UTUC at the China Medical University Hospital. Patients with concomitant UBUC (n=5); patients with incomplete data (n=2); patients with a follow-up duration of <3 months (n=4); or patients receiving neoadjuvant chemotherapy (n=2) were excluded. Finally, the study population comprised 126 patients with UTUC of pathological stage II [pT2, node (N)0/X, metastasis (M)0], stage III (pT3, N0/X, M0) and stage IV (T4, N0/X, M0; or T1-4, N1-3, M0).

The present retrospective study analyzed age at surgery, sex, tumor location, adjuvant chemotherapy status and regimen, estimated glomerular filtration rate (eGFR), tumor pathology (grade and lymphovascular invasion), tumor recurrence and cause of mortality. All patients underwent open or laparoscopic nephroureterectomy with bladder cuff excision and achieved free pathological margins. Lymph node dissection was performed if preoperative computerized tomography (CT) of the abdomen and pelvis revealed lymph node enlargement or if palpable lymph nodes were identified during surgery. Extended lymphadenectomy was not routinely performed due to potential complications, including lymphocele development, vascular injury and bowel injury. Regional lymph node recurrence was defined according to a previous study by Kondo *et al* (17).

Tumor staging and follow-up. Tumor stage was determined according to the American Joint Committee on Cancer TNM classification (18) and tumor grade was defined according to the 2004 World Health Organization grading system (19). Lymphovascular invasion was defined as the presence of tumor cells within an endothelium-lined space without underlying muscular walls (20). Postoperative renal function was calculated as per the following equation: eGFR=186 x (serum creatinine/88.4)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) (21).

Patients were followed up by physical examination, blood tests and cystoscopy postoperatively every 3 months for the first 3 years after surgery, every 6 months for the subsequent 2 years, and then annually for up to 10 years. Abdominal CT or magnetic resonance imaging were performed every 6 months to evaluate tumor recurrence, lymph node metastasis and distant metastasis.

Measurements and definitions. Patients with a stage I tumor were defined as low-stage while those with stage II-IV were defined as high-stage. In the high-stage group, patients with pathological stage II tumors were categorized as the localized UTUC group, and patients with T3, T4 and/or node-positive non-distant metastatic UTUC were categorized as the locally advanced UTUC group.

The endpoints assessed were overall survival (OS), disease-free survival (DFS), distant metastasis-free survival (DMFS) and locoregional recurrence-free survival (LRFS).

Local recurrence was established by urine cytology, cystoscopy, retrograde ureteropyeloscopy or biopsy, and/or CT or magnetic resonance imaging scans of the abdomen and pelvis. Distant metastasis was diagnosed on the basis of physical examination and imaging methods. OS was defined as the time from treatment until mortality; the follow-up of the patients that survived was censored at the latest date of follow-up (date of mortality). DFS was defined as the time from treatment until the earliest occurrence of recurrence or mortality from any cause. For analysis of LRFS and DMFS, the latencies were recorded (time from date of treatment) to the first detection of locoregional recurrence or distant metastasis, respectively.

Statistical analysis. χ^2 or Fisher's exact tests were used to assess differences between groups. All survival data were analyzed using the Kaplan-Meier method with a log-rank test to compare the disease free survival and overall survival rate. Multivariate analysis was carried out using a Cox proportional hazards regression model. $P<0.05$ was considered to indicate a statistically significant difference. Statistical analysis was performed using SPSS statistical software (version 22.0; IBM Corp., Armonk, NY, USA).

Results

Patient characteristics. The median follow-up period was 23.6 months (range, 3.1-120.9 months). Clinicopathological characteristics are listed in Table I. A total of 38 patients with pathological stage II (T2, N0, M0) UTUC were categorized as the localized group, and 88 patients with stage III/IV and/or node-positive non-distant metastatic UTUC were categorized as the locally advanced group.

In the localized group, the 5-year OS, DFS, LRFS and DMFS were 70.7, 82.2, 82.0 and 97.3%, respectively; whereas, in the locally advanced group with and without chemotherapy, these rates were 49.5, 56.8, 71.1 and 75.2%, respectively. Overall, in the locally advanced group, 29 patients (33.3%) succumbed to UTUC, and 5 patients (5.7%) succumbed to other causes. Furthermore, 19 patients with locally advanced UTUC presented with distant metastasis at diagnosis of disease recurrence and 17 presented with locoregional recurrence. By contrast, in the localized UTUC group, 4 patients (10.5%) succumbed to UTUC and 4 (10.5%) succumbed to other causes; 1 patient presented with distant metastasis at diagnosis of disease recurrence; and 5 patients presented with locoregional recurrence.

Lymph node metastasis was detected in 5 patients, and all of these patients received adjuvant chemotherapy. The mean age was 60.6 years. Of the 5 patients, 3 (60%) survived for >5 years and 1 patient (20%) developed distant metastasis. No patients suffered from local recurrence. These patients were

Table I. Clinicopathological characteristics of patients with high stage (II-IV) upper-tract urothelial carcinoma.

Clinicopathological characteristic	Value
Age (years); median (range)	70.0 (26-86)
Sex[a]	
Male	43 (34.1)
Female	83 (65.9)
eGFR (ml/min)[a]	
>60	30 (23.8)
<60	96 (76.2)
Pathological stage[a]	
II	38 (30.2)
III	73 (57.9)
IV	15 (11.9)
Grade[a]	
Low	35 (27.8)
High	91 (72.2)
Lymphovascular invasion[a]	
No	80 (63.5)
Yes	46 (36.5)
Perineural permeation[a]	
No	104 (82.5)
Yes	22 (17.5)
Location[a]	
Ureter	52 (41.3)
Renal pelvis	74 (58.7)
Lymph node metastasis[a]	
Negative	121 (96.0)
Positive	5 (4.0)

[a]Data are presented as number of patients (%). eGFR, estimated glomerular filtration rate.

Table II. Univariate analysis of overall survival in patients with high stage (II-IV) upper-tract urothelial carcinoma.

Variable	5-year overall survival rate (%)	P-value
Age (years)		0.018
>70	39.9	
<70	70.8	
Sex		0.900
Male	38.9	
Female	60.5	
Location		0.681
Renal pelvis	56.9	
Ureter	53.3	
Grade		0.231
Low	59.0	
High	52.7	
Lymphovascular invasion		0.002
With	42.4	
Without	61.3	
Stage		<0.001
II	70.7	
III	56.7	
IV	16.0	
eGFR (ml/min)		0.303
<60	51.0	
>60	63.1	

eGFR, estimated glomerular filtration rate.

included in the locally advanced with chemotherapy group to expand the case number.

Univariate log-rank analysis was performed for OS. Age, pathological stage and lymphovascular invasion were identified as significant prognostic factors for OS, while there were no significant differences in terms of sex, tumor location, tumor grade or renal function (eGFR) (Table II).

Chemotherapy regimens. Adjuvant chemotherapy was not administered to the localized group. Of the locally advanced group, 38 (43.2%) received adjuvant chemotherapy. These patients were scheduled to receive >4 courses of carboplatin-based chemotherapy, including the carboplatin, methotrexate and vinblastine (CarMV) regimen (13 patients), and the gemcitabine and carboplatin (GCar) regimen (25 patients). The median interval between surgery and the beginning of systemic therapy was 1.2 months (range, 0.7-2.3 months).

Patients treated with the CarMV regimen received methotrexate (30 mg/m^2), vinblastine (3 mg/m^2), and carboplatin [area under the plasma drug concentration-time curve (AUC)=5] intravenously on day 1, and methotrexate (30 mg/m^2) and vinblastine (3 mg/m^2) intravenously on days 15 and 22. Cycles were repeated every 4 weeks.

The GCar regimen was administered in a 4-week cycle, with gemcitabine (1,000 mg/m^2) administered intravenously on days 1, 8, and 15, and carboplatin (AUC=5) administered intravenously on day 1. The majority of patients received >4 cycles of chemotherapy (median, 5 cycles; range, 2-6 cycles), with the exception of 1 patient who received 2 cycles, and 3 patients who received 3 cycles of chemotherapy.

Survival analysis. In the locally advanced UTUC group, there were no significant differences in clinicopathological characteristics between patients who received and those who did not receive adjuvant chemotherapy, except that an eGFR of <60 ml/min was more prevalent among patients who did not receive adjuvant chemotherapy (Table III).

Of the 50 patients who did not receive adjuvant chemotherapy, 14 (28%) developed distant metastasis, and 10 (20%) developed locoregional recurrence. On the other hand, of the 38 patients administered with adjuvant chemotherapy, 5 (13.2%) developed distant metastasis and 7 (18.4%) developed locoregional recurrence.

Kaplan-Meier curve analysis revealed that, in locally advanced patients, those who received adjuvant chemotherapy

Table III. Characteristics of patients in the locally advanced group stratified by adjuvant chemotherapy.

Clinicopathological characteristics	Adjuvant chemotherapy	No adjuvant chemotherapy	P-value
Age (years), mean	63.57	68.86	0.735
Sex[a]			
Male	17	13	0.107
Female	21	37	
eGFR (ml/min)[a]			
>60	15	8	0.025
<60	23	42	
Pathological stage[a]			
III	30	43	0.558
IV	8	7	
Grade[a]			
Low	8	13	0.774
High	30	37	
Lymphovascular invasion[a]			
No	21	27	1.000
Yes	17	23	
Perineural permeation[a]			
No	30	38	0.944
Yes	8	12	
Location[a]			
Ureter	13	15	0.850
Renal pelvis	25	35	

[a]Data are presented as the number of patients. eGFR, estimated glomerular filtration rate.

had significantly better 5-year OS (67.1 vs. 33.7%, P=0.004; Fig. 1), DFS (70.2 vs. 46.0%, P=0.030; Fig. 2) and DMFS (86.3 vs. 65.2%, P=0.048; Fig. 3) rates compared with those who did not receive adjuvant chemotherapy. However, there was no significant difference in 5-year LRFS rates (78.2 vs. 62.5%, P=0.525; Fig. 4). Notably, the survival curves of the locally advanced group who received adjuvant chemotherapy were similar to those of the localized group who underwent surgery only (Figs. 1-4).

Log-rank analysis was performed for OS and DFS. Administration of adjuvant chemotherapy (without vs. with) was a significant independent risk factor for OS [hazard ratio (HR), 0.291; 95% CI, 0.129-0.654; P=0.003] and DFS (HR, 0.381; 95% CI, 0.168-0.865; P=0.021). Additionally, tumor stage (III vs. IV) was an independent predictor of OS and DFS, while lymphovascular invasion (absent vs. present) predicted OS only (HR, 2.248; 95% CI, 1.124-4.497; P=0.022) (Table IV).

Discussion

In the present study, 65.9% of the patients with UTUC were female. Although the majority of UTUC cases occur in men, the high prevalence of UTUC in Taiwan is notably impacted by the high use of *Aristolochia fangchi* by women for weight-loss and immune modulation to become healthy, which results in an increased female incidence in Taiwan compared with men (22). The present study aimed to determine whether adjuvant chemotherapy is beneficial for patients with high-stage UTUC. It was revealed that patients with localized UTUC had good survival outcomes without adjuvant chemotherapy compared with patients with locally advanced UTUC. The results of the present study demonstrated that adjuvant chemotherapy following nephroureterectomy may improve the survival of patients with locally advanced high-stage UTUC. In particular, the significant improvement in DMFS implies that the eradication of micrometastasis by systemic chemotherapy is feasible, but warrants further research.

A carboplatin-based regimen was selected for adjuvant chemotherapy, as carboplatin had been demonstrated to provide an equivalent effect and improved tolerability compared with cisplatin in numerous other types of cancer (23). However, it has not been well studied whether carboplatin is an adequate alternative for patients who are considered fit for the administration of cisplatin. Only one phase III study compared a cisplatin-based regimen (methotrexate, vinblastine, doxorubicin and cisplatin) to carboplatin/paclitaxel in patients with metastatic urothelial cancer, which revealed no significant differences in the response and OS rates of patients (24); however, the study was terminated early, meaning no definitive conclusions could be drawn due to the slow accrual rate (the accrual rate was 31 cases per year). A previous meta-analysis (25) demonstrated an apparent lack of efficacy of non-cisplatin regimens with regard to OS, DFS and disease-specific survival in patients with UTUC, whereas it

Table IV. Multivariate analysis for overall survival and disease-free survival in patients in the locally advanced group.

	Overall survival		Disease-free survival	
Clinicopathological characteristic	HR (95% CI)	P-value	HR (95% CI)	P-value
Adjuvant chemotherapy: Without vs. with	0.291 (0.129-0.654)	0.003	0.381 (0.168-0.865)	0.021
Age: <70 vs. >70 years	2.042 (0.987-4.224)	0.054	1.750 (0.841-3.645)	0.135
Stage: III vs. IV	4.286 (2.006-9.159)	<0.001	3.928 (1.755-8.794)	0.001
Lymphovascular invasion: Without vs. with	2.248 (1.124-4.497)	0.022	1.235 (0.603-2.530)	0.564
eGFR: <60 vs. >60 ml/min	1.072 (0.464-2.473)	0.871	0.816 (0.346-1.928)	0.644

eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval.

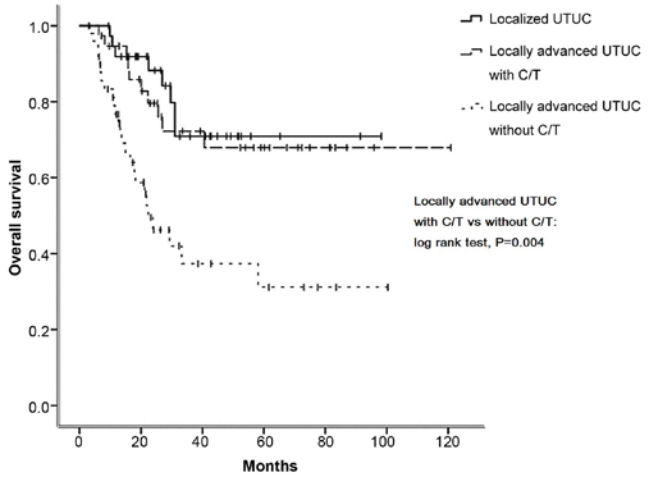

Figure 1. Kaplan-Meier plot of overall survival estimation for patients with localized UTUC, and locally advanced UTUC with and without C/T. UTUC, upper-tract urothelial carcinoma; C/T, chemotherapy.

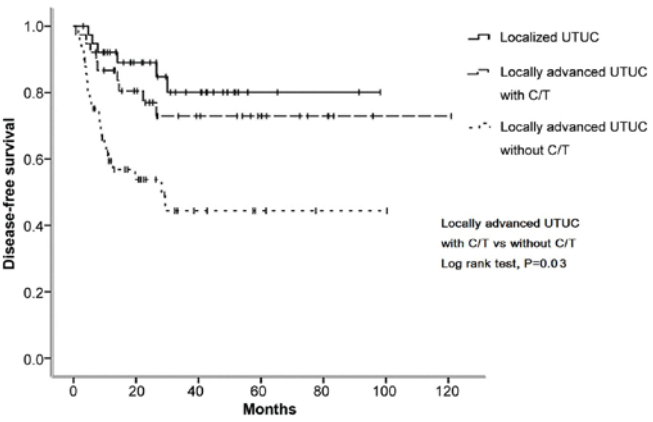

Figure 2. Kaplan-Meier plot of disease-free survival estimation for patients with localized UTUC, and locally advanced UTUC with and without C/T. UTUC, upper-tract urothelial carcinoma; C/T, chemotherapy.

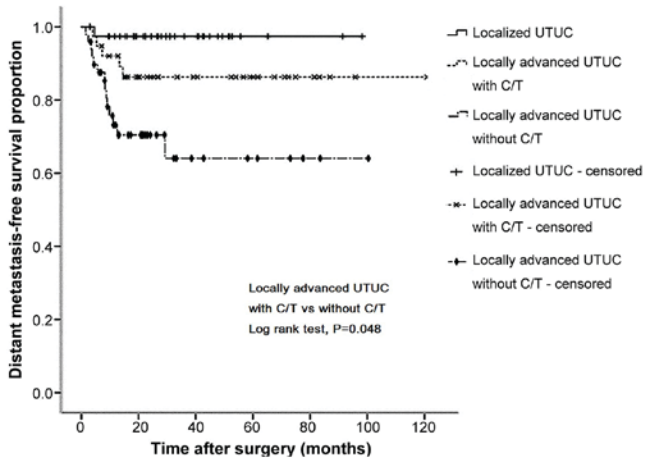

Figure 3. Kaplan-Meier plot of distant metastasis-free survival estimation for patients with localized UTUC, and locally advanced UTUC with and without C/T. UTUC, upper-tract urothelial carcinoma; C/T, chemotherapy.

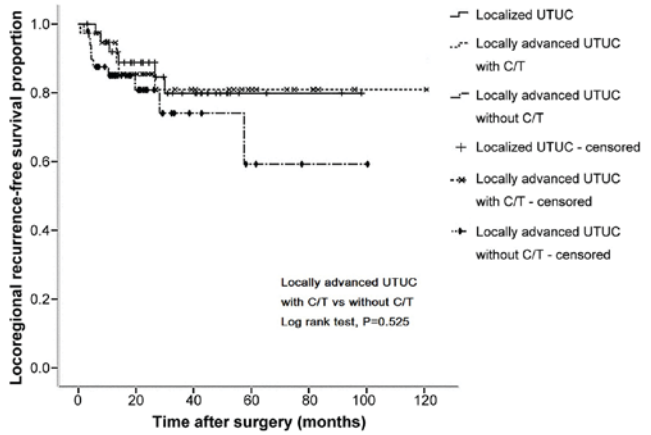

Figure 4. Kaplan-Meier plot of locoregional recurrence-free survival estimation for patients with localized UTUC, and locally advanced UTUC with and without C/T. UTUC, upper-tract urothelial carcinoma; C/T, chemotherapy.

demonstrated improved OS and DFS rates for patients treated with cisplatin-based regimens. The single prospective cohort (n=36) of patients treated with a non-cisplatin-based regimen in the meta-analysis indicated that carboplatin-based chemotherapy is feasible and may reduce the risk of distant metastasis. Another retrospective analysis enrolled patient groups with unbalanced characteristics between the adjuvant chemotherapy and patients who had not received adjuvant chemotherapy, and used non-uniform treatment regimens (cisplatin-based and non-cisplatin-based regimens were all included) (16). Therefore, the efficacy of carboplatin in the treatment of upper tract urothelial cancer remains unclear (16). In the present

study, a carboplatin-based regimen was selected due to the fact that a majority of patients with upper UC will have declining renal function and decreased tolerability for chemotherapy following surgery, which may impair the achievement of an adequate dose-intensity of cisplatin-based chemotherapy to successfully eradicate micrometastasis. The majority of the patients enrolled in the present study were able to complete >4 cycles of full-dose chemotherapy, which may explain the markedly decreased rate of distant metastasis compared with those who cannot tolerate chemotherapy (26-28).

Owing to the relatively low frequency of UTUC, thus far, no randomized trial has been conducted to evaluate the impact of chemotherapy on patients with UTUC. However, a number of retrospective studies have been published (Table V). In 2011, Vassilakopoulou *et al* (26) conducted the largest retrospective study, which included 140 patients with UTUC who had received diverse adjuvant chemotherapy regimens based on what they were predicted to be able to tolerate according to their renal function. Univariate and multivariate analyses revealed that adjuvant chemotherapy significantly improved metastasis-free survival. In a previous retrospective study (26), overall survival was not improved following adjuvant chemotherapy as nearly 25% of all patients had metastatic disease, and 15% of the patients had positive surgical margins. These patients, who had potential metastasis and received chemotherapy following surgery, may consider a palliative chemotherapy, inhibiting the cancer progression and easing symptoms without, however, the possibility of a cure. As the previous investigation was not conducted in a completely 'adjuvant' setting, the ability of chemotherapy to eradicate micrometastasis was underestimated. This may have additionally resulted in an underestimation of the OS benefit. In addition, considering the diversity of chemotherapy regimens, including single-agent chemotherapy and administration of fluorouracil, which has weak cytotoxicity for transitional cell carcinoma, a number of patients in the adjuvant group may have been in a relatively poor condition and therefore not apt candidates for adjuvant chemotherapy.

In 2009, Hellenthal *et al* (27) compared 121 patients with UTUC who received adjuvant chemotherapy with 421 patients who did not receive adjuvant chemotherapy, and revealed that chemotherapy did not result in any significant differences in OS. Platinum-based chemotherapy was used in 97% of patients and primarily comprised MVAC. Furthermore, there were a number of notable limitations: Data on the surgical margin and cycles of adjuvant chemotherapy were unavailable and data were incomplete in ~10% of the cases (27). In 2009, Soga *et al* (28 conducted a case-control study including patients with good renal function and of a young age (<80 years old) in order to avoid severe adverse side effects induced by MVAC; a majority of patients had received >2 cycles of chemotherapy. The authors reported decreased bladder cancer recurrence and improved survival outcomes in patients treated with adjuvant chemotherapy (28). In 2006, Kwak *et al* (16) demonstrated the therapeutic benefit of adjuvant chemotherapy in a cohort of 43 patients with invasive but non-metastatic UTUC. In this previous study, all patients received >4 cycles of cisplatin-based chemotherapy.

In contrast to the studies of adjuvant chemotherapy by Vassilakopoulou *et al*, Kwak *et al*, and Soga *et al* (16,26,28),

Table V. Outcomes of adjuvant chemotherapy for patients with locally advanced UTUC.

First author, year	Number of patients		UTUC stage	Chemotherapy regimen (%)	Survival outcomes (with vs. without chemotherapy)	(Refs.)
	With adjuvant chemotherapy	Without adjuvant chemotherapy				
Vassilakopoulou *et al*, 2011	140	487	T3N0, T4N0 and/or N+ and/or M+	Cisplatin-based (52.8%); carboplatin-based (39.4%)	HR (95% CI) for cancer-specific survival: 4.63 (0.16-128.69)	(26)
Hellenthal *et al*, 2009	121	421	T3N0M0, T4N0M0 and/or N+	Cisplatin-based (89%); methotrexate + vinblastine + doxorubicin + cisplatin (59%)	HR (95% CI) for OS: 1.06 (0.80-1.40)	(27)
Kwak *et al*, 2006	32	11	T2N0M0 and T3N0M0	Cisplatin-based	5-year OS rate: 78.1 vs. 36.4%	(16)
Soga *et al*, 2008	24	22	T2N0M0 and T3N0M0	Methotrexate + vinblastine + doxorubicin + cisplatin	5-year OS rate: 95.8 vs. 86.5%	(28)
Chang *et al* (the present study)	38	50	T3N0, T4N0 and/or N+	Gemcitabine + carboplatin; or carboplatin + methotrexate + vinblastine	5-year OS rate: 67.1 vs. 33.7%	-

UTUC, upper-tract urothelial carcinoma; T, tumor; N, node; M, metastasis; HR, hazard ratio; CI, confidence interval; OS, overall survival.

in the present study, locally advanced, lymph node-positive and non-metastatic patients with UTUC were enrolled. In our locally advanced group, the 5-year OS rate of patients who did not receive adjuvant chemotherapy was 33.7%, which was similar to that reported by Hellenthal *et al* (27). Taking into consideration the renal toxicity of cisplatin, the advanced age of the patients, and the comorbidities following nephroureterectomy, a carboplatin-based combination chemotherapy was used, and the majority of the patients in the cohort of the present study completed >4 cycles of chemotherapy. Although there is a lack of studies comparing cisplatin and carboplatin in patients with UTUC, a number of studies on transitional cell carcinoma of the bladder have revealed that carboplatin-based chemotherapy yields pathological and survival outcomes similar to those of cisplatin-based combination chemotherapy (29,30). Therefore, consistent with the findings of Soga *et al* and Kwak *et al* (16,28), either by administering less toxic regimens (as was performed in the present study) or by selecting patients with a greater capacity to tolerate chemotherapy [as was performed by Soga *et al* (28)], it is possible to achieve optimal dosing of adjuvant chemotherapy in patients with locally advanced UTUC and improve survival outcomes.

In the present study, distant metastasis in patients with locally advanced UTUC was the most probable cause of mortality. The implementation of adjuvant chemotherapy significantly improved DMFS but not LRFS rates, resulting in improved OS rates in patients with locally advanced UTUC. Similar results were observed in the study by Vassilakopoulou *et al* (26). Locoregional recurrence may usually be treated by surgical intervention; however, if distant metastasis occurs, curative treatment is not possible.

There were a number of limitations to the present study. First, this was a retrospective study, and therefore it was not possible to determine the rationale behind administering or not administering chemotherapy to these patients. Second, the sample size was relatively small, and the treatments were not uniform. Third, a number of patient demographics, including performance status and comorbidities, were not recorded in the present study, and thus there may have been a selection bias in the study cohort. Therefore, the results of the present study should be considered as hypothesis-forming.

In summary, survival rates were higher in patients with localized UTUC compared with locally advanced patients who did not receive adjuvant chemotherapy. The present study supports the hypothesis that adjuvant chemotherapy may improve outcomes in patients with locally advanced UTUC. Further large-scale, prospective, randomized studies are required in order to verify the results of the present study and determine the precise effectiveness of adjuvant chemotherapy in patients with UTUC.

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