Oncologic Outcomes of Salvage Chemotherapy in Patients with Recurrent or Metastatic Lesions after Radical Nephroureterectomy: A Multi-Institutional Retrospective Study

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Keywords

Liver metastasis · pT stage · Short time to recurrence · Salvage chemotherapy · Radical nephroureterectomy

Abstract

Background: Radical nephroureterectomy (RNU) is the standard treatment for patients with upper tract urothelial carcinoma (UTUC). However, approximately 25% of patients experience recurrence or metastasis after RNU. This study evaluated the clinical outcome and efficacy of salvage chemotherapy (SC) after recurrence or metastasis. **Patients and Methods:** Of the 441 nonmetastatic UTUC patients who underwent RNU, 147 patients with recurrent or metastatic lesions were analyzed; patients with bladder cancer recurrence were excluded. Time from disease recurrence or metastasis to cancer-specific survival (CSS) was estimated by the Kaplan-Meier method. Multivariate analyses were performed with the Cox proportional hazards regression model,

controlling for the effects of clinicopathological factors.

Results: The median time from RNU to disease recurrence or metastasis was 13.2 months. In the recurrent or metastatic sites, 31 cases (21%) were liver. In multivariate analyses, pT stage ($\geq$ pT3), time to recurrence ($<$ 12 months), and liver metastasis were independently predictive factors. In the risk stratification model for CSS after recurrence, patients were categorized into 2 groups based on pT stage, time to recurrence, and liver metastasis. The low-risk group (0–1 risk factors) included 87 patients, and the high-risk group (2–3 risk factors) included 60 patients. In the high-risk group, 27 patients received SC. The probability of CSS after recurrence or metastasis was higher in patients in the SC group compared to the non-SC group (9.5 vs. 3.7 months; $p < 0.001$). **Conclusion:** Two or more risk factors defined the high-risk group for patients with recurrence or metastasis after RNU. SC was associated with improved survival in patients with high-risk UTUC.

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Introduction

Upper tract urothelial carcinoma (UTUC) is a rare disease, accounting for only 5–10% of all urothelial malignancies [1, 2]. Radical nephroureterectomy (RNU) with excision of the bladder cuff is considered to be the standard surgical treatment for patients with nonmetastatic UTUC and offers adequate local tumor control and long-term survival. However, approximately 25% patients experience recurrence or metastasis after RNU, and cancer-specific mortality after recurrence or metastasis remains poor [3, 4].

Urologists may administer perioperative chemotherapy, such as neoadjuvant or adjuvant chemotherapy (AC), to improve prognosis even slightly. Although there were no randomized trials and no prospective studies, available studies suggest that neoadjuvant and AC are associated with improved survival in patients with UTUC [5–7]. Recently, AC after RNU was reported to have significantly improved disease-free survival in patients with locally advanced UTUC in the POUT trial, a phase 3 randomized controlled trial [8]. Salvage chemotherapy (SC) is considered when there is recurrence or metastasis after RNU.

The natural progression of UTUC from RNU to disease recurrence or metastasis has been intensively investigated [9–12]. However, few studies have focused on the clinical outcomes of patients who experienced disease recurrence or metastasis after RNU, and the details are still poorly understood. This study evaluated whether clinicopathological factors at time of disease recurrence or metastasis were associated with cancer-specific outcomes in these patients and whether SC was effective. In addition, for a multi-institutional cohort of patients who experienced disease recurrence or metastasis after RNU for UTUC, we determined which patients qualified for SC.

Patients and Methods

Patient Selection

We retrospectively reviewed clinical data for 441 nonmetastatic UTUC patients who underwent RNU between 1990 and 2015, excluding 8 patients who received neoadjuvant chemotherapy. Of the 441 patients who underwent RNU, 147 patients (33%) experienced recurrence or metastasis; patients with bladder cancer recurrence were excluded. Among them, 74 (50%) patients received SC, and the remaining 73 (50%) received best supportive care (BSC). Although this study has a nonrandomized retrospective design, all recurrent or metastatic patients who were usually recommended for additional therapy after RNU received informed consent for SC. Ultimately, the administration of SC was determined

by consultation with the urologist in charge and in accordance with the patients on the basis of their performance status, desire for treatment, and renal function.

Clinicopathological Evaluation

The following data on patient characteristics were collected: age at recurrence or metastasis, sex, surgery approach, change rate of postoperative estimated glomerular filtration rate (eGFR), history of AC, mortality, and pathological status (including histology, primary organ, pT stage, pN stage, tumor grade, concomitant carcinoma in situ, tumor architecture, lymphovascular invasion, and soft tissue surgical margin). Patients were stratified into 3 groups based on the change in rate between pre- and postoperative eGFR: normal change (increased or <10% decrease), moderate change (10–30% decrease), and severe change (>30% decrease) [13]. Tumor grade was assessed according to the 1998 World Health Organization/International Society of Urologic Pathology consensus [14]. The 2002 TNM Classification of the International Union for Cancer Control and American Joint Committee on Cancer Guidelines was used to determine cancer stage [15]. Surgical specimens were processed according to standard pathological procedures at each institution. Tumor location was divided into 2 areas (renal pelvis and ureter) based on the site of the dominant lesion [16].

Follow-Up of Patients

Patients were generally followed every 3 months for the first 2 years after RNU, then every 6 months for the next 3 years, and annually thereafter. Follow-up consisted of physical examinations, routine blood tests, urinary cytology, and cystoscopic evaluation. Computed tomography evaluations of local recurrence and metastatic lesions, as well as chest X-rays, were performed every 6 months for the first 2 years and annually thereafter. Bone scans were performed when disease progression was clinically indicated. On the basis of patients' medical records, the time from recurrence or metastasis to cancer-specific survival (CSS) was calculated. Disease recurrence was defined as failure in nonbladder lesions, such as local recurrence at the surgery site, in regional lymph nodes, and (or) distant metastasis. Sites of distant metastases were defined as the liver, lung, bone, distant lymph nodes, brain, and others (including the peritoneum, skin, contralateral upper tract, and other organs).

Statistical Analysis

The clinicopathological variables in each group were compared using the Kruskal-Wallis test, the χ^2 test, and the Fisher's exact test. CSS probabilities after recurrence or metastasis were estimated by the Kaplan-Meier method and compared among groups with the log-rank test. Multivariate analyses were performed with the Cox proportional hazards regression model, controlling for age at recurrence or metastasis (<70 vs. $\geq$ 70 years), sex (male vs. female), eGFR change (normal change vs. moderate change vs. severe change), pT stage (pT2 or lower vs. pT3 or higher), time from RNU to recurrence or metastasis (time to recurrence [TTR]) (<12 vs. $\geq$ 12 months), lung metastasis (yes vs. no), liver metastasis (yes vs. no), bone metastasis (yes vs. no), lymph node metastasis (yes vs. no), AC status (yes vs. no), and SC status (yes vs. no) with CSS after recurrence or metastasis. Statistical analyses were performed with Stata version 13 for Windows (Stata, Chicago, IL, USA). All *p* values were 2-sided, and *p* < 0.05 was considered statistically significant.

Table 1. Clinicopathological characteristics of 147 recurrence or metastasis patients after RNU according to SC status

Characteristics	Patients administered SC, <i>n</i> = 74	Patients not administered SC, <i>n</i> = 73	<i>p</i> value
Age at recurrence, years			
Median, IQR	68 (62–74)	73 (65–78)	0.009
Sex, <i>n</i> (%)			
Male	57 (77.0)	47 (64.4)	0.092
Female	17 (23.0)	26 (35.6)	
Surgery approach, <i>n</i> (%)			
Open	45 (60.8)	49 (67.1)	0.425
Laparoscopic	29 (39.2)	24 (32.9)	
Primary organ, <i>n</i> (%)			
Renal pelvis	31 (41.9)	39 (53.4)	0.162
Ureter	43 (58.1)	34 (46.6)	
Change rate of eGFR, <i>n</i> (%)			
Normal (increase or <10%)	31 (41.9)	31 (42.5)	0.931
Moderate (10–30%)	27 (36.5)	25 (34.2)	
Severe (>30%)	16 (21.6)	17 (23.3)	
Histopathology type, <i>n</i> (%)			
UC	64 (86.5)	63 (86.3)	0.974
Nonpure UC	10 (13.5)	10 (13.7)	
Pathological T stage, <i>n</i> (%)			
≤pT2	27 (36.5)	24 (32.9)	0.646
≥pT3	47 (63.5)	49 (67.1)	
Lymph node status, <i>n</i> (%)			
pN0/Nx	61 (82.4)	66 (90.4)	0.158
pN+	13 (17.6)	7 (9.6)	
Tumor grade, <i>n</i> (%) ^a			
G1/G2	39 (53.4)	34 (47.2)	0.455
G3	34 (46.6)	38 (52.8)	
Concomitant CIS, <i>n</i> (%) ^b			
Absent	61 (82.4)	58 (81.7)	0.907
Present	13 (17.6)	13 (18.3)	
Tumor architecture, <i>n</i> (%) ^c			
Papillary	38 (55.9)	41 (61.2)	0.531
Sessile	30 (44.1)	26 (38.8)	
Lymphovascular invasion, <i>n</i> (%) ^d			
Absent	26 (40.0)	20 (29.0)	0.180
Present	39 (60.0)	49 (71.0)	
Soft tissue surgical margin, <i>n</i> (%)			
Negative	63 (85.1)	55 (75.3)	0.136
Positive	11 (14.9)	18 (24.7)	
AC, <i>n</i> (%)			
No	48 (64.9)	47 (64.4)	0.951
Yes	26 (35.1)	26 (35.6)	
Follow-up, months			
Median, IQR	28.3 (18.7–50.2)	21.6 (8.7–45.2)	0.027

IQR, interquartile range; eGFR, estimated glomerular filtration rate; UC, urothelial carcinoma; CIS, carcinoma in situ; AC, adjuvant chemotherapy; RNU, radical nephroureterectomy; SC, salvage chemotherapy. ^a Two patients with unknown tumor grade. ^b Two patients with unknown CIS. ^c Twelve patients with unknown tumor architecture. ^d Thirteen patients had no lymphovascular invasion status.

Table 2. Sites of recurrence or metastasis in 147 patients

Region	Patients, <i>n</i> (%)
Lymph node	57 (39)
Lung	43 (29)
Bone	41 (28)
Liver	31 (21)
Local	21 (14)
Peritoneal dissemination	9 (6)
Lateral upper tract	8 (5)
Brain	4 (3)
Other	12 (8)

Results

Demographic and clinicopathological characteristics of 147 recurrence or metastasis patients are summarized in Table 1. The median age at recurrence or metastasis of all cohorts was 69 years (interquartile range [IQR], 63–77 years), and the median TTR was 13.2 months (IQR, 5.7–28.7 months). For 68 patients (46%), the TTR was <12 months. During follow-up, 100 (68%) of 147 patients died due to UTUC, and the median survival time from recurrence or metastasis to cancer death was 9.9 months. In the recurrent or metastatic sites, 57 (39%) cases were lymph node, 43 (29%) were lung, 41 (28%) were bone, and 31 (21%) were liver (Table 2).

Of the 147 patients with recurrence or metastasis disease after RNU, 74 (50%) received SC, and the remaining 73 (50%) received BSC. Among the patients who received SC, 36 received the methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) regimens, 34 received the gemcitabine and cisplatin (GC) regimens, 11 received the gemcitabine and paclitaxel regimens, 1 received the pembrolizumab regimen, and 7 received other regimens. The number of SC regimens was 1 regimen in 60 cases (81%), 2 regimens in 13 cases (18%), and 3 regimens in only one case (1%). Patients received a median 3 courses (IQR, 2–4 courses) of SC. The majority of patients received platinum-based SC, but cisplatin was reduced by 20–50% in cases of impaired renal function. The median survival time was 12.4 months in the SC group and 6.9 months in the BSC group, respectively. The group who received SC had approximately twice the longer survival time, but there was no statistically significant difference ($p = 0.179$). In the SC group, the median survival times of patients who received AC and patients who did not receive AC were 13.9 and 11.3 months, respectively ($p = 0.237$).

Table 3 shows a summary of the univariate and multivariate analyses for CSS. In multivariate analyses, pT

Table 3. Univariate and multivariate Cox proportional hazards analysis for the prediction of CSS in 147 patients with recurrence or metastasis after RNU

Factor	Univariate	Multivariate	
	<i>p</i> value	HR (95% CI)	<i>p</i> value
Age <70 years (reference: ≥70 years)	0.050	1.50 (0.999–2.260)	0.050
Female (reference: male)	0.717	–	–
eGFR severe change (reference: normal)	0.118	–	–
eGFR moderate change (reference: normal)	0.973	–	–
≥pT3 (reference: ≤pT2)	0.003	1.72 (1.083–2.722)	0.021
<12 months (reference: ≥12 months)	0.018	1.54 (1.033–2.290)	0.034
Lung metastasis (reference: no)	0.081	–	–
Liver metastasis (reference: no)	<0.001	2.27 (1.419–3.628)	0.001
Lymph node metastasis (reference: no)	0.688	–	–
Bone metastasis (reference: no)	0.187	–	–
AC (reference: no)	0.350	–	–
SC (reference: no)	0.181	–	–

CI, confidence interval; HR, hazard ratio; eGFR, estimated glomerular filtration rate; RNU, radical nephroureterectomy; SC, salvage chemotherapy; CSS, cancer-specific survival; AC, adjuvant chemotherapy.

Fig. 1. Kaplan-Meier curves for CSS in the 147 recurrence or metastasis patients after RNU for UTUC, stratified by risk group. RNU, radical nephroureterectomy; UTUC, upper tract urothelial carcinoma; CSS, cancer-specific survival.

stage (≥pT3), TTR <12 months, and presence of liver metastasis were independently predictive factors. For the risk stratification model, patients were categorized into 2 groups based on pT stage, TTR, and liver metastasis (Fig. 1). The low-risk group (0–1 risk factors) included 87 patients, and the high-risk group (2–3 risk factors) included 60 patients. The median survival time in the low-risk groups and high-risk groups was 15.6 and 5.4 months, respectively ($p < 0.001$). Fifty-two patients had disease re-

currence or metastasis after AC, and 26 (50%) were high-risk cases. These patients were more frequent than high-risk cases who relapsed without AC (34 of 95, 36%) but were not significantly different. Figure 2 shows the Kaplan-Meier curves for CSS according to the SC treatment strategy in each group. In the low-risk group, 47 patients (54%) received SC; in the high-risk group, 27 patients (45%) were treated with SC. In the low-risk group, no statistically significant differences were seen between the SC

Fig. 2. Kaplan-Meier curves for CSS in low-risk group **(a)** and high-risk group **(b)** patients, stratified by SC status. SC, salvage chemotherapy; CSS, cancer-specific survival.

treatment strategies regarding median survival time (15.6 vs. 18.1 month; $p = 0.535$; Fig. 2a). However, the median survival time was longer in patients in the SC group compared to the non-SC group in high-risk group (9.5 vs. 3.7 months; $p < 0.001$; Fig. 2b).

Discussion

The survival of patients with UTUC who experienced disease recurrence or metastasis after RNU was poor. Most of these patients died due to UTUC within 1 year after recurrence or metastasis, and only few patients (19%) survived beyond 2 years [3]. Indeed, the median

survival time from recurrence or metastasis to cancer death was 9.9 months in our study. The 2- and 3-year CSS rates after recurrence or metastasis were 24 and 16%, respectively.

A few studies have focused on the predictive factors of patients who experienced recurrence or metastasis after RNU. In the present study, we found that pT stage ($\geq pT3$), TTR < 12 months, and the presence of liver metastasis were significant predictors of post-recurrence cancer-specific mortality according to a multivariate analysis. Generically, nonorgan-confined pathological stage ($\geq pT3$) is an established predictive factor for outcomes prognostication after RNU [4, 11, 17, 18]. Even after recurrence or metastasis, patients with nonorgan-

confined UTUC have a worse survival rate than those with organ-confined UTUC. The low survival rate is possibly attributable to a higher burden of disease that cannot be easily identified, such as micrometastatic cancer [3, 19].

A TTR of <12 months and the presence of liver metastasis are also very important factors. Rink et al. [3] reported the risk of cancer-specific mortality following recurrence after RNU. Of 2,494 UTUC patients treated with RNU without neoadjuvant chemotherapy, 597 patients who experienced disease recurrence were analyzed. They found that a shorter time (<12 months) from RNU to disease recurrence is associated with poorer survival after disease recurrence, results which were similar to those in our study. In a study of urothelial carcinoma of the bladder, Mitra et al. [20] also reported similar results.

The liver is the main site of metastatic disease, and liver metastases remain a major barrier in the treatment of many malignancies [21]. For the importance of liver metastasis, prognostic risk factors (sometimes called Bajorin risk factors) model and a report by Bellmunt et al. [22] may be helpful [22, 23]. Bajorin et al. [23] reported that a Karnofsky performance status less than 80% and the presence of visceral metastasis (lung, liver, and [or] bone) were independent prognostic factors of poor survival after MVAC chemotherapy. Bellmunt et al. [22] reported that the same Bajorin risk factors have a poor survival even after treatment with paclitaxel, cisplatin, and gemcitabine regimen. It should be noted that these studies included a very heterogeneous patient cohort with unresectable and (or) metastatic urothelial cancer of any type (bladder, ureter, and pelvis) compared to our study of recurrence or metastasis after treatment with RNU for UTUC. Although there are differences in patient backgrounds, the presence of liver metastasis is one of the key prognostic factors. However, it is unknown whether the mechanism that affects the prognosis of liver metastasis is direct or indirect. In fact, once a liver recurrence has developed, patients will have a poor prognosis regardless of primary tumor characteristics [24]. Although the resection of isolated liver metastasis provides a good long-term CSS benefit when treating selected patients with colorectal cancer, its role in patients with liver metastasis is not well defined in patients with other types of cancer [24, 25]. Albumin, which is produced in the liver, reflects nutritional status and inflammatory processes and has been demonstrated to be prognostic factor in a number of malignancies [26, 27]. Thus, hypoalbuminemia may be associated with prognosis as an indirect mechanism of liver metastasis.

Finally, we found that SC was associated with improved survival in the multivariate analyses, especially in the high-risk group. However, the benefit of SC was biased by the fact that it was the younger and healthier patients who received SC, and it may be that the apparent survival time was prolonged. In general, elderly patients tended to lose the opportunity for the therapeutic intervention (such as SC) compared with younger patients. Although an accurate prediction of clinical outcomes after disease recurrence or metastasis can help therapeutic intervention, it is more important to select the patients who may benefit from SC on the basis of the ability to preserve their quality of life.

The present study has several limitations. One major limitation is that this is a retrospective study without randomization, which may have introduced bias in the patient selection process. Second, all cohort and high-risk groups were relatively small. Third, pembrolizumab was used in only one case during the observation period in this study, which may be insufficient for evaluation in the immunotherapy era. However, pembrolizumab is positioned as a second-line treatment, and although the effectiveness of AC is being shown recently [8], the majority of recurrence or metastasis after RNU still require first-line chemotherapy. Selecting the patients who should receive SC is an important role. Finally, because our cohort included patients from several different institutions, RNU was performed by multiple surgeons, and the present study lacks a central pathological review. Nevertheless, clinicopathological factors were almost nonbiased, and we found that pT stage ($\geq$ pT3), TTR <12 months, and the presence of liver metastasis were important predictors of post-recurrence CSS. Using these factors for risk classification may help to properly screen the patients who should receive SC.

Conclusion

In this multi-institutional retrospective study, we found that 2 or more risk factors ($\geq$ pT3, TTR <12 months, and presence of liver metastasis) defined the high-risk group for patients with recurrence or metastasis after RNU. SC was associated with improved survival in patients with high-risk UTUC.

Statement of Ethics

This study was approved by the institutional review board at 6 Kitasato university-affiliated hospitals (B15-25) and was conducted in accordance with the Declaration of Helsinki and its later amendments.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.I. (First author): project development, data collection, data analysis, manuscript writing, and submission. K.M.: project development, data analysis, and manuscript writing and editing. T.H., D.K., Y.M., Y.T., and A.I.: data collection and project development. D.M., N.O., and T.U.: data collection. M.I.: project development and manuscript editing.