A Role for Preoperative Systemic Chemotherapy in Node-positive Upper Tract Urothelial Carcinoma Treated with Radical Nephroureterectomy

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Objective: There are few reports investigating the potential benefits of preoperative systemic chemotherapy for patients with node-positive upper tract urothelial carcinoma. The purpose of this study was to examine the impact of preoperative systemic chemotherapy on the clinical outcomes of patients with node-positive upper tract urothelial carcinoma treated by radical nephroureterectomy.

Methods: Data were collected on 195 consecutive patients with upper tract urothelial carcinoma treated by radical nephroureterectomy between 1995 and 2010 at a single institute. Of these, 29 patients with node-positive disease but no visceral metastasis were retrospectively evaluated. In patients who underwent preoperative systemic chemotherapy, tumor response, post-therapy pathological downstaging to either residual disease at radical nephroureterectomy or no residual lymph node metastasis (pN0) and toxicity were the endpoints of interest. Overall survival was compared between two groups: those with and without preoperative chemotherapy.

Results: All patients underwent regional lymphadenectomy. Overall, 15 patients (52%) underwent preoperative systemic chemotherapy. Pathological downstaging was achieved in 47%, including pN0, but there was no pathological complete response. Eighty-six percent of the patients with pathological downstaging had no evidence of recurrence. The median overall survivals were 38 and 9 months for patients with and without preoperative systemic chemotherapy, respectively (hazard ratio: 0.26, $P = 0.015$, log-rank test). There was no significant difference in operative morbidity between the two groups, and no operations were delayed because of preoperative chemotherapy.

Conclusions: The survival of patients who undergo preoperative systemic chemotherapy following radical nephroureterectomy seems to be superior to that of those undergoing radical nephroureterectomy alone. However, to confirm this, prospective randomized studies are needed.

Key words: nephroureterectomy – chemotherapy – upper urinary tract – urothelial carcinoma – lymph node metastasis

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INTRODUCTION
Radical nephroureterectomy (RNU) is the mainstay of treatment for upper urinary tract urothelial cell carcinoma (UTUC). In patients with regional node-positive UTUC, however, the prognosis after RNU is significantly worse than in those with node-negative disease (1,2) and lymph node status is one of the most important predictors of survival in patients with UTUC (3). Although platinum-based chemotherapy is expected to produce results similar to those seen in bladder cancer (4,5), only a few retrospective studies (6–8) have reported the effect of neoadjuvant or preoperative chemotherapy. Of them, only one study (8) concluded that preoperative chemotherapy followed by RNU for node-positive UTUC might afford favorable oncological outcomes. However, no benefit in cancer-specific survival was demonstrated in that study. Thus, the efficacy of neoadjuvant chemotherapy or preoperative chemotherapy for advanced UTUC is still controversial.

To better understand the efficacy of preoperative systemic chemotherapy for node-positive UTUC, we conducted a critical retrospective review of patients with UTUC who underwent RNU over a 15-year inclusion interval. The objective of this study was to examine the impact of preoperative chemotherapy on the clinical outcomes of patients with node-positive UTUC treated by RNU.

PATIENTS AND METHODS
We retrospectively analyzed the clinical and demographic information of 195 consecutive patients with histopathologically confirmed UTUC treated by RNU between 1995 and 2010 at our institute. Of them, 29 patients with locoregional node-positive disease but no visceral metastasis, diagnosed by two independent expert radiologists on enhanced computed tomography (CT), were selected as the study group. Nodes with a short axis of ≥10 mm were considered node positive. Clinical information and follow-up data for patients were obtained from the UTUC database after receiving the patients’ consent. This study was approved by the institutional review board.

All the patients underwent RNU with the extrafascial dissection of the kidney and the complete resection of the distal ureter and bladder cuff. Open RNU was performed for 25 patients and laparoscopic RNU, in conjunction with the open distal ureter and bladder cuff removal, was carried out for 4 patients with lower ureteral cancer. In 24 of the 29 patients, all regional nodes were dissected by open surgery as described previously (9). In 2 (13%) patients of the preoperative chemotherapy group and 3 (21%) of the no-preoperative-chemotherapy group, the extent of the lymph node dissection did not include all regional sites.

CT (chest to pelvis), cystoscopy and urinary cytology were performed every 3 months in the first 5 years after RNU, and semi-annually or annually thereafter for patients without the evidence of recurrent disease. Additional radiographic and diagnostic tests were performed when clinically indicated. At the time of the retrospective analysis, the median follow-up time was 81 months (range: 19–201).

The primary endpoints analyzed were overall survival (OS) and disease-specific survival (DSS). The cause of death was investigator defined and reported in the follow-up case report forms. However, DSS was not calculated because all the deaths were caused by cancer. The secondary endpoint was operative morbidity, which was evaluated using the National Cancer Institute Common Terminology Criteria (NCI-CTC), version 4.0.

In patients who underwent preoperative systemic chemotherapy, tumor response, post-therapy pathological downstaging to either residual disease at RNU or no residual lymph node metastasis (pN0) and toxicity were the endpoints of interest. Tumor responses were evaluated using the Response Evaluation Criteria in Solid Tumours, version 1.0 (10). The qualitative and quantitative toxic effects were graded in agreement with NCI-CTC, version 4.0.

The Kaplan–Meier method was used to calculate the OS. The differences were tested with the log-rank test. All tests were two-sided with the significance level set at 0.05 and statistical tests were performed using GraphPad Prism®, version 5.0 (GraphPad Software Inc., La Jolla, CA).

RESULTS
Fifteen (52%) of the 29 patients received preoperative systemic chemotherapy. The patients’ characteristics at presentation are provided in Table 1. The clinical stages of the preoperative chemotherapy and no-preoperative-chemotherapy groups were similar, but there were two patients with T4 disease in the no-preoperative-chemotherapy group. Adjuvant therapy was performed for 5 of the 14 patients in the no-preoperative-chemotherapy group. Of the other nine patients, three and six did not receive adjuvant chemotherapy because of renal insufficiency and the patients’ refusal, respectively.

All 15 patients received cisplatin-based preoperative chemotherapy: methotrexate/vinblastine/doxorubicin/cisplatin (MVAC) for 14 patients and gemcitabine/cisplatin (GC) on a 28-day schedule for 1. The median number of cycles of preoperative chemotherapy received was 2 (range: 2–3). The median duration between the last day of chemotherapy and that of RNU was 18 days (range: 9–35). Twelve (80%), 3 (20%) and 2 (13%) of the patients had neutropenia, febrile neutropenia and anemia grade 3 or 4, respectively. No patients had a delay in surgery due to these adverse effects.

In the 15 patients, 1 CR and 5 PR were obtained (Table 2) on CT. The overall response rate was 40%. Three (50%) of these six patients died of the disease at 19, 22 and 29 months after the initial therapy. Seven (47%) of the 15 patients achieved downstaging from the clinical to pathological T or N stage by preoperative chemotherapy; from clinical (c) T3 to pathological (p) T2 in 2 patients (13%),
from cT3 to pT1 in 2 (13%), from cN2 to pN0 in 3 (20%) and from cN1 to pN0 in 4 (27%). Of the 7 patients with pathological downstaging, 1 (14%) died of the disease 22 months after the initial therapy. Six (86%) had no evidence of recurrence with a median of 29 months of follow-up (range: 19–86). There was no pathological complete response. One patient had upstaging from cT2N1 to pT3N2, but he had no evidence of recurrence during 22 months of follow-up. Table 3 shows the differences in the stage between clinical and pathological diagnoses. No patients in the no-preoperative-chemotherapy group had downstaging from the clinical to pathological T or N stage, whereas 7 of the 15 patients who received preoperative chemotherapy displayed downstaging (Table 3).

Postoperative adverse events greater than grade 3 were seen in one patient (7%) each in the preoperative chemotherapy (postoperative hemorrhage) and no-preoperative-chemotherapy groups (ileus). There was no surgery-related death in either group.

The median OS of the preoperative chemotherapy and no-preoperative-chemotherapy groups were 38 and 9 months, respectively. Their 5-year OS rates were 48 and 10%, respectively. There was a significant difference in the OS between the two groups [hazard ratio (HR), 0.26; 95% confidence interval (CI): 0.09–0.77; P = 0.015] (Fig. 1). In the 15 patients who underwent preoperative chemotherapy, the 3-year OS rates of patients with downstaging and those without downstaging by preoperative chemotherapy were 83 and 33%, respectively. There was a significant difference in OS between them (HR, 0.22; 95% CI: 0.05–0.94; P = 0.041) (Fig. 2).

**DISCUSSION**

Despite significant improvements in the efficacy of cisplatin-based systemic chemotherapy for urothelial cancer, the best strategy for multidisciplinary treatment of advanced UTUC, including node-positive disease, remains a matter of debate. Previous studies showed a diminished renal function after RNU (11,12) and a minimal impact of adjuvant or postoperative chemotherapy on survival for patients with high-risk UTUC (13). Although several retrospective studies suggested
that neoadjuvant or preoperative chemotherapy might yield favorable outcomes for such patients (6–8), the survival benefits have not been clearly elucidated.

We found that approximately half of the patients achieved downstaging by preoperative chemotherapy and that most of these obtained long-term survival without recurrence, whereas the objective response on CT did not seem to be related to the survival. Furthermore, there was a significant difference in OS between the preoperative chemotherapy and no-preoperative-chemotherapy groups. These data suggested that cisplatin-based preoperative systemic chemotherapy followed by RNU might provide a survival benefit for patients with regional node-positive UTUC. To our knowledge, we are the first to report the relationship between pathological downstaging and survival in patients with node-positive UTUC undergoing preoperative chemotherapy.

There has been only one study, by Matin et al. (7), evaluating the incidence of pathological downstaging after neoadjuvant chemotherapy for UTUC. Of the 43 patients who underwent a median of 4 courses of neoadjuvant chemotherapy for high-risk UTUC, 6 (14%) patients had a pathological CR. The overall incidence of patients who had \( \geq pT2 \) or \( \geq pT3 \) disease was lower in the neoadjuvant chemotherapy group than that in the control. The pathological CR rate was higher than that in our study. One of the reasons explaining this is a difference in the patients’ characteristics. Their study included only eight patients having node-positive disease. Another possibility is a difference in the number of courses of systemic chemotherapy. Unfortunately, the survival benefit of neoadjuvant chemotherapy was not demonstrated in their non-randomized retrospective study (7) because of a lack of survival data.

More recently, the survival data for UTUC with locoregional nodal metastases were retrospectively reviewed in a multi-institutional study (8). The study included 18 patients who underwent a median of six cycles of GC or MVAC before RNU and 120 patients who underwent only RNU. The no-preoperative-chemotherapy group had a significantly lower disease-free survival rate than the preoperative chemotherapy group. However, the study demonstrated no statistically significant difference in cancer-specific survival between the preoperative chemotherapy and no-preoperative-chemotherapy groups. In that study, 5 (28%) patients achieved pathological CR. Nine (50%) and 6 (33%) patients were pN0 and pT0, respectively. The pN0 rate was the same as in our study. Unfortunately, data about the relationship between the pathological downstaging and survival were not provided (8). The 5-year cancer-specific survival rate in patients who received preoperative chemotheraphy was 44%, which is similar to our data.

Although the theoretical advantages of neoadjuvant chemotherapy for non-metastatic UTUC include the eradication of subclinical metastatic disease, improved patient tolerability prior to surgical extirpation, and the ability to deliver higher chemotherapy doses due to the loss of renal function after RNU (4), a delay in the interval from diagnosis to RNU is associated with more advanced disease stage (14). In other words, patients without chemosensitive tumors may suffer a delay in RNU for a few months during the chemotherapy. Thus, neoadjuvant chemotherapy for non-metastatic UTUC is still controversial. Meanwhile, the surgical approach alone, i.e. RNU with lymphadenectomy, is not sufficient to provide favorable oncological outcomes in patients with locoregional nodal metastasis (15,16), which can be considered to be a systemic disease. In this study, there was no significant difference in the number of lymph nodes removed between patients who received preoperative chemotherapy and those without preoperative chemotherapy. Our results suggest that the patients who benefit from preoperative chemotherapy appear to be those with locoregional node-positive disease.

Although 80% of the patients who underwent preoperative chemotherapy in this study displayed hematological toxicity, including neutropenia and anemia, these adverse effects were manageable, and no delay in the RNU was required. No patient discontinued preoperative chemotherapy due to
toxic effects. Preoperative chemotherapy was well tolerated with hematological toxicity being the most significant side effect. Furthermore, there was no difference in the perioperative morbidity rate between the preoperative chemotherapy (7%) and no-preoperative-chemotherapy groups (7%). A population-based assessment of perioperative mortality after RNU reported that the mortality rate at 90 days was 4.4% (17). Rajput et al. (18) showed that the perioperative complication rates after neoadjuvant chemotherapy following laparoscopic RNU were 31% for both Clavien grades 2 and 3/4. These rates were similar to those after laparoscopic RNU without chemotherapy. Thus, it is suggested that preoperative chemotherapy does not affect surgery-related complications after RNU.

There are several limitations to our study. First, this was a retrospective study with selection biases and a small number of patients at a single institute. Secondly, the lymph node metastases were diagnosed not histologically by biopsy but radiographically on enhanced CT, although two independent radiologists diagnosed the node status. Thirdly, RNU with lymphadenectomy was performed by various surgeons over a long time period. Finally, node-positive UTUC patients who received cisplatin-based chemotherapy but did not undergo RNU were not evaluated. This may have led to bias in which survival of patients receiving preoperative chemotherapy seemed to be superior to that of patients without chemotherapy, although there must be patients who did not undergo RNU in the latter group.

In this retrospective analysis of a series of locoregional node-positive UTUC, we observed that survival of patients receiving preoperative systemic chemotherapy following RNU seemed to be superior to that of those undergoing RNU alone. Furthermore, patients who achieved pathological downstaging tended to have favorable oncological outcomes. Prospective randomized studies are required to confirm these results.

Conflict of interest statement
None declared.

References