The Efficacy of Neoadjuvant Gemcitabine and Cisplatin Chemotherapy for cT3N0M0 Upper Tract Urothelial Carcinoma: The Impact of Tumor Location

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Purpose: Upper tract urothelial carcinoma (UTUC) can be divided into renal pelvis tumor (RPT) and ureteral tumor (UT) based on the tumor origin. This study aimed to evaluate the efficacy of neoadjuvant chemotherapy with gemcitabine and cisplatin (NAC-GC) in terms of the pathological outcomes and oncological prognoses in patients with UTUC. We also compared its efficacy between RPT and UT.

Materials and Methods: Patients who underwent radical nephroureterectomy for clinical T (cT)3N0M0 UTUC between 1999 and 2021 were included. Patients who underwent NAC-GC and those who did not were included in the NAC-GC and non-NAC-GC groups, respectively. Based on the tumor origin, we divided patients with UTUC into RPT and UT groups. Oncological prognosis was assessed using progression-free survival (PFS) and overall survival.

Results: Of 44 patients, 20 (45.5%) and 24 (54.5%) patients were in the NAC-GC and non-NAC-GC groups, respectively. The NAC-GC group had significantly lower pathological T stage and negative lymphovascular invasion (LVI), and a better PFS ($p < .05$) compared to those in the non-NAC-GC group. Among patients with RPT, the NAC-GC group had significantly negative LVI and better PFS than the non-NAC-GC group ($p < .05$). In contrast, in patients with UT, the NAC-GC group had no significant difference in pathological outcomes, and no significant difference in oncological prognosis was observed between the NAC-GC and non-NAC-GC groups.

Conclusion: NAC-GC improves both pathological outcomes and oncological prognosis in patients with cT3N0M0 UTUC. With regard to tumor location, RPT has better pathological outcomes and oncological prognoses than UT.

Keywords: Upper tract urothelial carcinoma; neoadjuvant chemotherapy; gemcitabine and cisplatin; downstage; prognosis

INTRODUCTION

Urothelial carcinoma (UC) is the most common malignant tumor of the urinary system and is classified as bladder carcinoma (BC) or upper tract urothelial carcinoma (UTUC) depending on its origin. BC is responsible for 90–95% of UC cases, is the fourth most common malignancy in men, and is the seventh most common cause for cancer-related death in men in the United States.[1] In contrast, UTUC, arising from the renal pelvis and ureters, is responsible for 5–10% of all UCs in the urinary system.[2] For both muscle-invasive BC (MIBC) and UTUC, the standard treatment is surgical resection.[3,4] Among cases of MIBC, cisplatin-based neoadjuvant chemotherapy (NAC) has been shown to improve pathological outcomes and oncological prognoses.[5,6] However, evidence for the role of NAC in improving clinical and prognoses in patients with UTUC has not yet been established.

There are some limitations for evaluating the efficacy of NAC in patients with UTUC. First, efficacy evaluation in prospective clinical trials is difficult owing to its rarity. Second, although the established evidence of NAC in UCs consists of cisplatin-based chemotherapy, many previous studies have assessed the efficacy of NAC for UTUC using gemcitabine and carboplatin regimens.[7-11] As gemcitabine and carboplatin for UTUC treatment are only recommended in cisplatin-unfit patients,[3] the utility of cisplatin-based NAC for UTUC should be verified prior to a carboplatin regimen.

Furthermore, to select the best adaptation of NAC for UTUC, tumor location should be considered. UTUC is separated into renal pelvis tumor (RPT) and ureteral tumor (UT) according to its origin, and the anatomical structure and oncological prognosis may differ between RPT and UT.(12, 13) Thus, the efficacy of NAC may differ between RPT and UT.

In this study, we evaluated the efficacy of NAC with gemcitabine and cisplatin (NAC-GC) in terms of pathological and oncological outcomes in patients who underwent radical nephroureterectomy (RNU) for clinical T (cT)3N0M0 UTUC. Furthermore, we compared the efficacy of NAC-GC between patients with RPT and UT.

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Table 1. Baseline characteristics.

Variables	All cases n = 44	NAC-GC group n = 20	Non-NAC-GC group n = 24	*p*-value
Age: median (IQR)	70 (65-76)	69.5 (67-74.5)	72.5 (62.3-77.8)	.152
Gender: n (%)				
□ Male	32 (72.7)	16 (80.0)	16 (66.7)	.319
Location: n (%)				.580
□ Renal pelvis	20 (45.5)	10 (50.0)	10 (41.7)	
□ Ureter	24 (55.5)	10 (50.0)	14 (58.3)	
Past/concomitant bladder tumor: n (%)	5 (11.4)	3 (15.0)	2 (8.3)	.488
White blood cells (/μL): median (IQR)	5825 (4695-6518)	6045 (4705-6545)	5345 (4575-6440)	.680
Hemoglobin (g/dL): median (IQR)	13.2 (11.9-14.1)	12.9 (11.2-14.6)	13.4 (12.1-13.8)	.953
Serum albumin (g/dL): median (IQR)	4.2 (3.9-4.5)	4.2 (3.9-4.6)	4.3 (3.9-4.5)	.818
eGFR (mL/min/1.73 m^2): n (%)	60.7 (50.3-70.0)	60.0 (50.8-69.8)	61.5 (49.6-73.0)	1.000
CRP (mg/dL): n (%)				
□ ≥ 0.30	9 (20.5)	4 (20.0)	5 (20.8)	.946
Hydronephrosis: n (%)	28 (63.6)	12 (60.0)	16 (66.7)	.647
Lymph node dissemination: n (%)	33 (75.0)	17 (85.0)	16 (60.5)	.155
Adjuvant chemotherapy	3 (6.8)	0 (0.0)	3 (12.5)	.051

IQR: interquartile range, NAC-GC: neoadjuvant gemcitabine and cisplatin chemotherapy, eGFR: estimated glomerular filtration rate, CRP: c-reactive protein

MATERIALS AND METHODS

Patient population

In this retrospective single center study, a total of 273 patients who underwent RNU for UTUC at Hiroshima University between April 1999 and April 2022 were included. This study was approved by the Ethics Committee of Hiroshima University, Japan (E2016-0589). Patients who were preoperatively diagnosed with cT-3N0M0 UTUC were included, and those with other variations, namely ≤ cT2 and cT4, were excluded. To diagnose cT stage, un-enhanced and contrast-enhanced CT images were obtained. These images were reviewed by radiologists for clinical staging based on the CT grading system that we previously reported.[14] The preoperative pathological diagnosis of UTUC was confirmed by either urinary cytology of upper tract collected by retrograde urography or tumor biopsy by ureteroscopy. RNU was performed using either an open or a laparoscopic approach, with open distal ureteric excision in all cases. Lymph node dissemination (LND) was performed by Kondo et al.[15]

The decision to opt for NAC was made at the discretion of the attending physician. We measured 24-hour creatinine clearance for all patients who had NAC administrated to them and confirmed that their creatinine clearance was ≥ 60 ml/min. All NAC regimens were performed as follows: gemcitabine (1000 mg/m2 on days 1, 8, and 15) and cisplatin (70 mg/m2 on day 2) were administered in two cycles. Patients who underwent NAC-GC were defined as the NAC-GC group and those who did not were defined as the non-NAC-GC group.

To evaluate the effect of UTUC tumor location on NAC-GC, we further divided patients into RPT and UT groups according to their tumor location. In cases of multiple tumors, the tumor location was defined as the location of the main tumor, which was the one with the largest diameter.

Clinical data collection

Clinicopathological data were retrospectively collected from medical records. The variables included age; sex; tumor location; past/concomitant bladder tumors; hydronephrosis; LND; adjuvant chemotherapy (AC), and serum biomarkers such as white blood cells, hemoglobin, serum albumin, estimated glomerular filtration rate (eGFR), and C-reactive protein. Serum biomarkers were collected prior to 1st-line NAC-GC in the NAC-GC group and preoperatively in the non-NAC-GC

Table 2. All cases pathological outcome.

Variables	*NAC-GC group* n = 20	*Non-NAC-GC group* n = 24	*p*-value
Pathological T stage: n (%)			.012[a]
≥T3	5 (25.0)	15 (62.5)	
≤T2	15 (75.0)	9 (37.5)	
Pathological grade: n (%)			.679
≥Grade 3	15 (66.7)	17 (70.8)	
≤Grade 2	5 (33.3)	7 (29.2)	
Lymphovascular invasion: n (%)			.012[a]
Positive	3 (15.0)	12 (50.0)	
Negative	17 (85.0)	12 (50.0)	
Concomitant CIS: n (%)			.086
Positive	5 (25.0)	12 (50.0)	
Negative	15 (75.0)	12 (50.0)	
Resection margin: n (%)			.114
Positive	0 (0.0)	2 (8.3)	
Negative	20 (100)	22 (91.7)	
Pathological N stage: n (%)b			.082
Positive	0 (0.0)	2 (12.5)	
Negative	17 (100)	14 (87.5)	

NAC-GC: neoadjuvant gemcitabine and cisplatin chemotherapy, CIS: carcinoma in situ, [a] $P < .05$, [b] Pathological N stage was evaluated for patients who underwent Lymph node dissection

Table 3. Univariate and multivariate analysis that assess the association between clinicopathological factors and PFS in patients who underwent radical nephroureterectomy.

	Progression-free survival	
Clinicopathological factors	Univariate analysis	Multivariate analysis
Tumor location (renal pelvis vs. ureter)		
HR (95%CI)	0.56 (0.19–1.64)	
p-value	.288	
Pathological T stage (≥T3 vs. ≤T2)		
HR (95%CI)	4.77 (1.53–14.87)	
p-value	.007[a]	
Pathological grade (≥3 vs. ≤2)		
HR (95%CI)	1.92 (0.62–5.97)	
p-value	.262	
Lymphovascular invasion (positive vs. negative)		
HR (95%CI)	5.70 (1.93-16.83)	4.57 (1.52-13.70)
p-value	.002a	.007[a]
Resection margin (positive vs. negative)		
HR (95%CI)	2.03 (0.27–15.47)	
p-value	.496	
Concomitant CIS (positive vs. negative)		
HR (95%CI)	2.09 (0.76–5.77)	
p-value	.155	
Lymph node dissection (yes vs. no)		
HR (95%CI)	0.43 (0.15–1.20)	
p-value	.107	
Hydronephrosis (present vs. absent)		
HR (95%CI)	1.81 (0.57-5.73)	
p-value .310		
NAC-GC (yes vs. no)		
HR (95%CI)	0.15 (0.03-0.66)	0.22 (0.05-0.99)
p-value	.012[a]	.049[a]

PFS: progression-free survival, HR: hazard ratio, CI: confidence interval, CIS: carcinoma in situ, NAC-GC: neoadjuvant gemcitabine and cisplatin chemotherapy, a $P < .05$

group. Ipsilateral hydronephrosis was graded from 0 to 4 according to the classification by Cho et al., and all the images were re-reviewed, considering the presence of hydronephrosis when the grade was higher than grade 2 according to this classification.[16]

Outcome

Pathological factors, such as pathological T (pT) stage, lymphovascular invasion (LVI), concomitant carcinoma in situ (CIS), resection margin (RM), and pathological N (pN) stage, were assessed for evaluating patho-

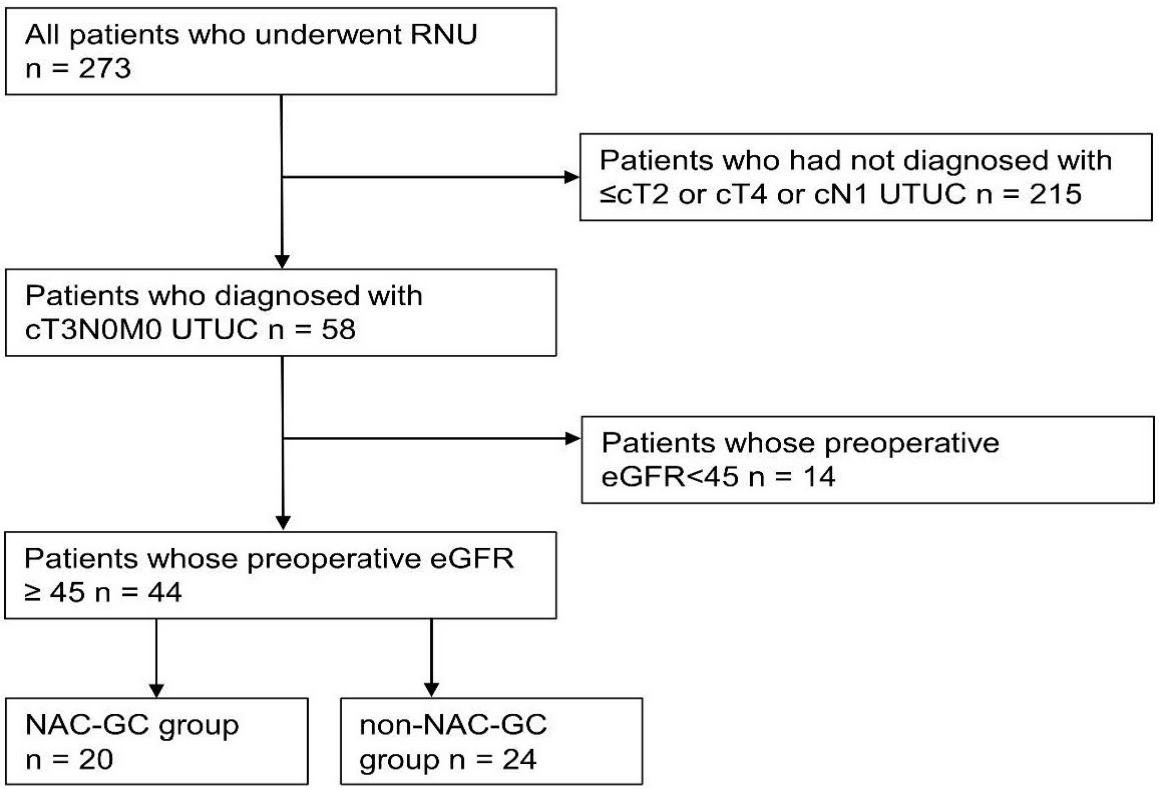

Figure 1. Flow chart of patient selection in this study.

Table 4. Adverse events of NAC-GC.

Adverse events	Grade 3	Grade 4	Total
Platelet count decreased	8 (40.0%)	0 (0.0%)	8 (40.0%)
Neutrophil count decreased	2 (10.0%)	1 (5.0%)	3 (15.0%)
Urinary tract infection	1 (5.0%)	0 (0.0%)	1 (5.0%)
Total events	10 (50.0%)	1 (5.0%)	11 (55.0%)

NAC-GC: neoadjuvant gemcitabine and cisplatin chemotherapy

logical outcomes. To evaluate tumor grading, we used the WHO International Society of Urological Pathology consensus classification.[17] According to the 2002 American Joint Committee of Cancer/Union for International Cancer Control (AJCC/UICC) TNM classification,[18] pathological specimens were examined and re-reviewed for staging.

We assessed adverse events (AE) during NAC-GC and the safety of NAC-GC preoperatively in patients with UTUC. AEs were evaluated based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5, and grades 3 or 4 were defined as severe AE. To assess the influence of NAC-GC on renal function, we also compared the longitudinal changes in renal function between the NAC-GC and non-NAC-GC groups.

Progression-free survival (PFS) and overall survival (OS) were assessed to determine oncological prognosis. Progression was defined as a local failure at the operative and regional lymph nodes or distant metastasis, whereas bladder cancer recurrence or contralateral UTUC was not considered as progression. The start date for survival analysis was the date of RNU, the end time for PFS was the date of progression or that of the last observation, and the end time for OS was the date of death. Our follow-up protocol consisted of complete blood counts, serum chemistry tests, urine analysis, cystoscopy, and chest/abdo/pelvic CT scan with or without contrast every three months for two years, and every six months thereafter until five years, and then yearly.

Statistical Analysis

Pearson's chi-square test was used to compare the distributions of categorical variables. Differences in variables with a continuous distribution across dichotomous categories were assessed using the Wilcoxon rank-sum test. Associations between clinicopathological parameters and prognosis were assessed using univariate and multivariate Cox proportional hazards regression models. Hypothesis tests for the proportional hazard assumption were performed and confirmed that there were no significant differences in the parameters. The Kaplan–Meier method was employed to evaluate the survival outcomes, and the log-rank test was used to assess the differences. All statistical analyses were conducted using JMP Pro 16.0.0 (SAS Institute Inc., Cary, NC, USA), with $P < .05$ indicating statistical significance.

Table 5. Comparison of pathological outcomes in RPT and UT.

Variables	NAC-GC group	Non-NAC-GC group	*p*-value
RPT	**n = 10**	**n = 10**	
Pathological T stage: n (%)			.063
≥T3	2 (20.0)	6 (60.0)	
≤T2	8 (80.0)	4 (40.0)	
Pathological grade: n (%)			1.000
≥Grade 3	7 (70.0)	7 (70.0)	
≤Grade 2	3 (30.0)	3 (30.0)	
Lymphovascular invasion: n (%)			.021[a]
positive	2 (20.0)	7 (70.0)	
negative	8 (80.0)	3 (30.0)	
Concomitant CIS: n (%)			.155
positive	2 (20.0)	5 (50.0)	
negative	8 (80.0)	5 (50.0)	
Resected margin: n (%)			1.000
positive	0 (0.0)	0 (0.0)	
negative	10 (100)	10 (100)	
Pathological N stage: n (%)[b]			.065
positive	0 (0.0)	2 (28.6)	
negative	8 (100)	5 (71.4)	
UT	n = 10	n = 14	
Pathological T stage: n (%)			.094
≥T3	3 (30.0)	9 (64.3)	
≤T2	7 (70.0)	5 (35.7)	
Pathological grade: n (%)			.559
≥Grade 3	8 (80.0)	10 (71.4)	
≤Grade 2	2 (20.0)	4 (28.6)	
Lymphovascular invasion: n (%)			.134
positive	1 (10.0)	5 (35.7)	
negative	9 (90.0)	9 (64.3)	
Concomitant CIS: n (%)			.323
positive	3 (30.0)	7 (50.0)	
negative	7 (70.0)	7 (50.0)	
Resected margin: n (%)			.131
positive	0 (0.0)	2 (14.3)	
negative	10 (100)	12 (85.7)	
Pathological N stage: n (%)[b]			1.000
positive	0 (0.0)	0 (0.0)	
negative	9 (100)	9 (100)	

NAC-GC: neoadjuvant gemcitabine and cisplatin chemotherapy, RPT: renal pelvis tumor, UT: ureteral tumor, CIS: carcinoma in situ, a P < .05, b Pathological N stage was evaluated for patients who underwent Lymph node dissection

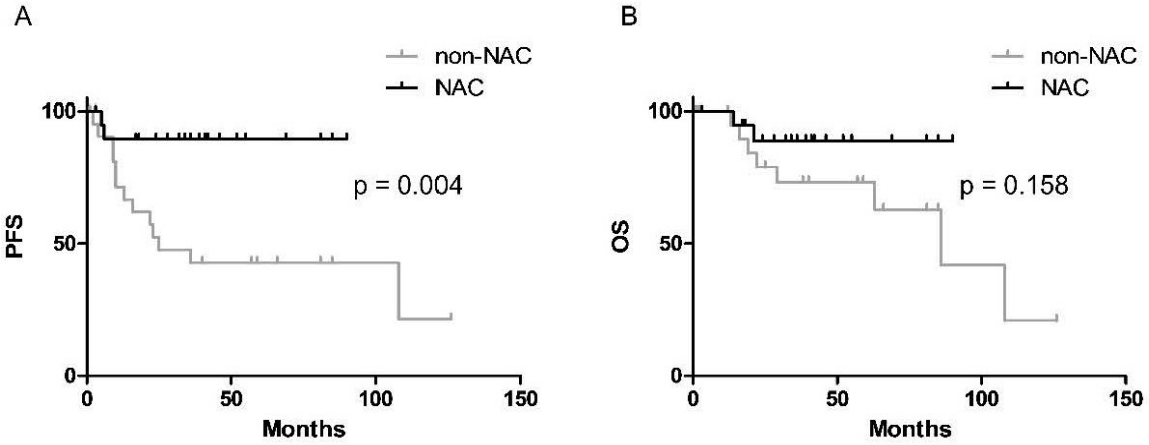

Figure 2. PFS (A), and OS (B) after radical nephroureterectomy for the NAC-GC and non-NAC-GC groups.
PFS: progression-free survival, OS: overall survival, NAC-GC: neoadjuvant gemcitabine and cisplatin chemotherapy.

RESULTS

Characteristics of patients in the UTUC cohort

A total of 273 patients underwent RNU for UTUC at our institution, 58 (21.2%) of whom were diagnosed with cT3N0M0. Of these, 44 patients (16.1%) whose preoperative eGFR was ≥ 45 were included in this study. Of these patients, 20 (45.5%) were in the NAC-GC group, and 24 (54.5%) were in the non-NAC-GC group (**Figure 1**). The median follow-up period was 37 months (range, 3–126 months) for patients in this cohort, and the respective clinicopathological characteristics of these patients are listed in Table 1. There were no significant differences between the NAC-GC and non-NAC-GC groups. In the NAC-GC group, ten patients with RPT and four patients with UT had experience for complete or partial response evaluated by preoperative CT, and two patients with RPT and one patient with UT had experience for complete response with T0 lesion on final pathology.

NAC-GC improves both pathological outcomes and PFS for patients with UTUC

To assess the efficacy of NAC-GC for pathological outcomes in patients with UTUC, we compared the pathological factors between the NAC-GC and non-NAC-GC

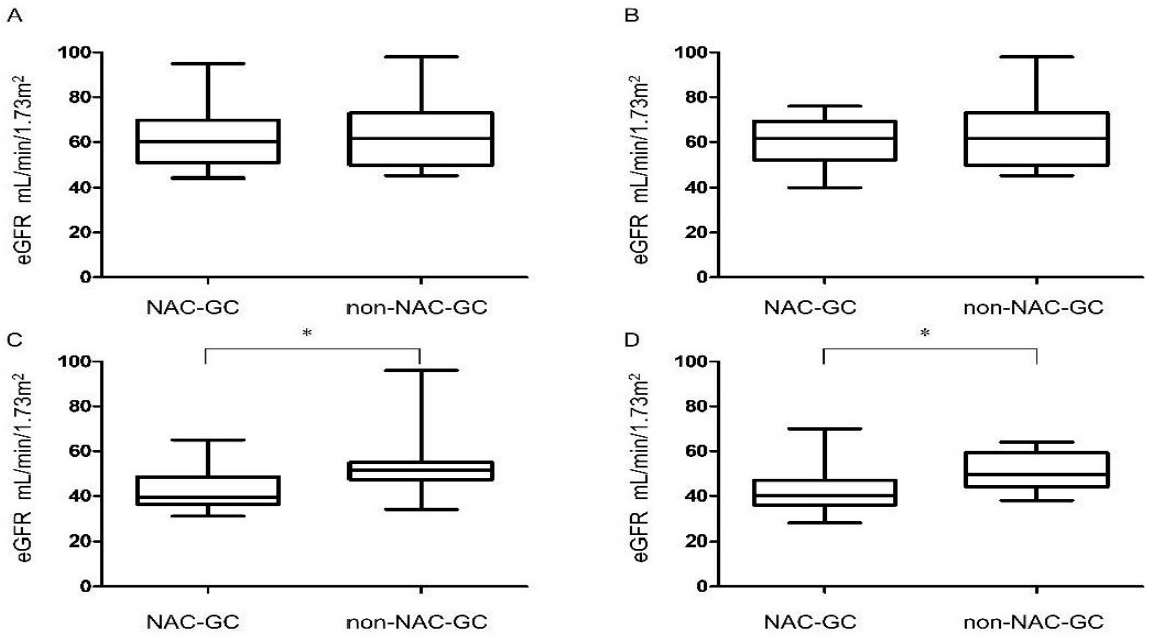

Figure 3. Longitudinal change of renal function in the NAC-GC and non-NAC-GC groups. **A:** Comparison of the renal function before NAC between the NAC-GC (median eGFR; 60.0, range 45.0–95.0) and non-NAC-GC group (median eGFR; 61.5, range 45.0–98.0; *P* = 1.000), **B:** Comparison of the renal function after NAC between the NAC-GC (median eGFR; 61.5, range 40–76) and non-NAC-GC group (median eGFR; 61.5, range 45.0–98.0; *P* = .832), **C:** Comparison of the renal function at 1 month after RNU between the NAC-GC (median eGFR; 39.5, range 31.0-65.0) and non-NAC-GC group (median eGFR; 51.5, range 34.0–96.0; *P* = .001), **D:** Comparison of the renal function at 1 year after RNU between the NAC-GC (median eGFR; 40.0, range 28.0–70.0) and non-NAC-GC group (median eGFR; 49.5, range 38.0–64.0; *P* = .005)
NAC-GC: neoadjuvant gemcitabine and cisplatin chemotherapy, eGFR: estimated glomerular filtration rat e, RNU: Radical Nephroureterectomy. **P* < .05

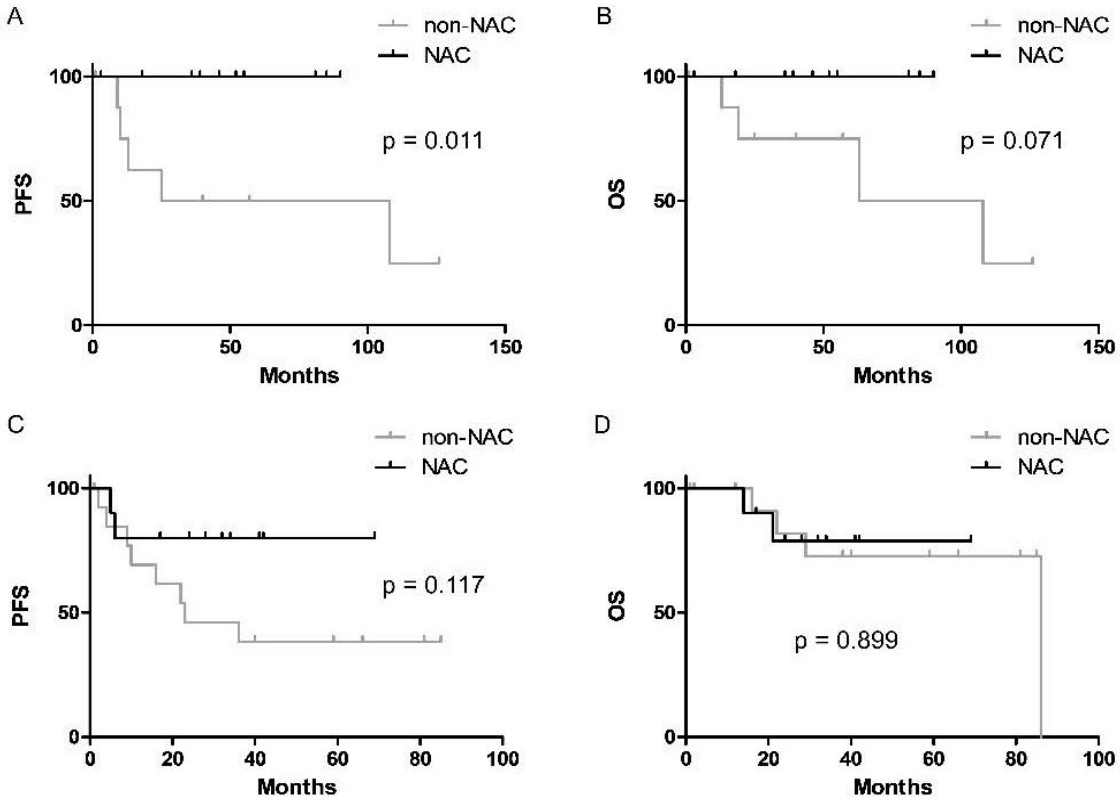

Figure 4. PFS and OS after radical nephroureterectomy for the NAC-GC and non-NAC-GC groups in patients with RPT and UT. A: PFS for RPT, B: OS for RPT, C: PFS for UT, D: OS for UT.
PFS: progression-free survival, OS: overall survival, NAC-GC: neoadjuvant gemcitabine and cisplatin chemotherapy, RPT: renal pelvis tumor, UT: ureteral tumor.

groups. The patients in the NAC-GC group had a significantly lower pT stage (≤ 2; $P = .012$) and negative LVI ($P = .012$) compared with those of the non-NAC-GC group (**Table 2**), suggesting that NAC-GC improves the pathological outcomes of patients who underwent RNU for UTUC.

We also assessed the efficacy of NAC-GC for the oncological prognosis of patients with UTUC. To address the clinical significance of NAC-GC in patients with UTUC, we performed Kaplan–Meier analysis. **Figure 2** shows that the NAC-GC group had significantly better PFS ($P = .004$) than the non-NAC-GC group, but the difference in OS was not significant between the groups ($P = .158$). The median PFS values of the NAC-GC and non-NAC-GC groups were "not reached" and 25 months, respectively, and the median OS values of the NAC-GC and non-NAC-GC groups were "not reached" and 86 months, respectively.

We also assessed the efficacy of NAC-GC for the PFS of patients with UTUC. Univariate analysis revealed that NAC-GC ($P = .012$; hazard ratio (HR), 0.15) was significantly associated with PFS in patients with UTUC, as well as pathological T stage ($P = .007$; HR, 4.77), and LVI ($P = .002$; HR, 5.70) (**Table 3**). Multivariate analysis of LVI, which is an established prognosis factor for UTUC, and NAC-GC showed that NAC-GC was significantly associated with PFS ($P = .049$; HR, 0.22), as well as LVI ($P = .007$; HR, 4.57). These results suggest that NAC-GC also improves the PFS in patients who underwent RNU for UTUC.

NAC-GC may be safely administered in patients with UTUC

Next, we assessed the AE of NAC-GC in patients with UTUC. In the NAC-GC group, severe AE developed in 11 patients (55%) during the therapy, but none of the patients were unable to undergo RNU (Table 4). Moreover, there were no patients who had severe AE perioperatively (0%) in the NAC-GC group, while two patients had severe AE in the non-NAC-GC group (5.3%; intestinal perforation and acute renal failure). We also assessed the longitudinal changes in eGFR (**Figure 3**). There was no significant difference in eGFR between the NAC-GC and non-NAC-GC groups before and after NAC (which was only administered to the former, Figure 3 A and B), whereas at 1 month (P = .001) and 12 months ($P = .005$) after RNU, the NAC-GC group had significantly lower eGFR than the non-NAC-GC group (Figure 3C and 3D). These results suggest that NAC-GC could be performed safely in patients with UTUC, while it could influence renal function after RNU.

The efficacy of NAC-GC for pathological outcomes and oncological prognosis differs for patients with RPT and UT

To assess the influence of tumor location on the efficacy of NAC-GC for UTUC, we compared the pathological outcomes and oncological prognoses of patients with RPT and UT. This cohort included 20 patients with RPT (NAC-GC group, n = 10; non-NAC-GC group, n = 10) and 24 patients with UT (NAC-GC group, n = 10; non-NAC-GC group, n = 14). Table 5 shows a com-

parison of pathological outcomes after RNU between the RPT and UT groups. Among patients with RPT, the NAC-GC group had a significantly negative LVI (P = .021) than the non-NAC-GC group, while there was no significant difference in pathological outcomes between the NAC-GC and non-NAC GC groups in patients with UT.

We subsequently compared the oncological outcomes between RPT and UT groups. Kaplan–Meier analyses showed that in patients with RPT, the NAC-GC group had significantly better PFS (P = .011) than the non-NAC-GC group. No significant difference was observed in OS, but there was a trend for the NAC-GC group to have better OS than the non-NAC-GC group (P = .071) (**Figure 4**). In contrast, there were no significant differences in PFS and OS between the NAC-GC and non-NAC-GC groups in patients with UT. These results suggest that NAC-GC improves both the pathological outcome and oncological prognosis in patients with RPT, but not in patients with UT.

DISCUSSION

Herein, we showed that NAC-GC is safe and improved both the pathological outcomes and PFS of patients who underwent RNU for cT3N0M0 UTUC. We also demonstrated that NAC-GC improved pathological outcomes and PFS in patients with RPT and not in those with UT. To the best of our knowledge, there are no previous studies that have evaluated the efficacy of NAC-GC for cT3N0M0 UTUC as per the tumor original.

Among UC, NAC-GC is recommended in patients with MIBC based on survival benefits, as shown in previous studies.[5,19] However, in patients with UTUC, the efficacy of NAC in terms of the pathological outcomes and oncological prognoses remains controversial, although several studies showed that cisplatin- or carboplatin-based NAC induced pathological downstaging and increased survival outcomes of locally advanced UTUC.[7,20,21] Because cisplatin-based chemotherapy has been reported to improve the oncological prognoses of patients with metastatic UTUC compared with carboplatin-based chemotherapy,[22,23] the evaluation of NAC-GC without a carboplatin regimen is necessary to assess the efficacy of NAC. The strength of our study is that we only included patients who underwent NAC-GC. Moreover, there was no significant difference in patients' characteristics with regard to risk factors, such as tumor site,[13] hydronephrosis,[24] and inflammatory index,[25] between the NAC-GC and non-NAC-GC groups.

We also demonstrated the safety of NAC-GC in patients with UTUC. Previous studies on NAC only assessed the efficacy of NAC, and there are no studies that have evaluated the AE of NAC.[7,20,21] We verified the safety of NAC-GC for patients with UTUC by proving that it did not cause perioperative AE. We also confirmed that the NAC-GC group had lower renal function after RNU compared to the non-NAC-GC group, suggesting that NAC-GC influences renal function. However, there were no patients who developed severe renal dysfunction that required hemodialysis. Therefore, we believe that the reduction of renal function caused by NAC-GC is acceptable. These results suggest that patients with UTUC can benefit from the anti-tumor effects of NAC-GC without the unfavorable AE.

Interestingly, NAC-GC showed improved pathological and oncological outcomes in patients with RPT, while it did not for UT (**Table 5 and Figure 4**). The correlation between tumor location and the prognosis of UTUC remains controversial. In this study, we could not determine why NAC-GC was more effective in RPT than UT. Therefore, further studies that compare pathological or molecular mechanisms for NAC-GC between RPT and UT are needed.

Recently, a randomized controlled phase 3 trial showed that adjuvant gemcitabine-platinum combination chemotherapy significantly improved disease-free survival in patients with locally advanced UTUC.[26] Although AC is advantageous for selecting patients with pathologically confirmed invasive UTUC, AC is inferior to NAC in that a large number of patients who underwent RNU cannot maintain renal function, and only a limited number of patients can undergo adjuvant GC therapy, which was also shown in our cohort (**Figure 3**). NAC and AC should be compared in future prospective randomized trials to achieve a standardized treatment.

Evidence of sequential therapy after NAC in patients with UTUC is increasing. Immune checkpoint inhibitors (ICIs) are considered a part of adjuvant therapy for patients with advanced UTUC who undergo platinum-based NAC. A randomized controlled phase 3 trial on ICI (CheckMate 274 clinical trials) showed that the use of adjuvant nivolumab as an adjuvant prolonged disease-free survival in high-risk muscle-invasive UC.[27] The combination of NAC-GC and adjuvant ICI may be beneficial for UTUC.

Our study has several limitations. First, this study was performed at a single center and included a relatively small number of patients; therefore, further studies are needed to confirm the difference in efficacy of NAC-GC depending on tumor location in UTUC. Second, we did not perform a long-term follow-up. Third, this study was retrospectively analyzed. Despite these limitations, we believe that our study provides important evidence for the effects of NAC-GC in patients with UTUC. Due to the low incidence of UTUC within UC, it is difficult to construct a large cohort to assess the efficacy of NAC specific to UTUC. To verify the results of our study, we will attempt to assess the efficacy of NAC-GC for UTUC in a prospective study, with a larger cohort and long-term follow-up.

CONCLUSIONS

NAC-GC could be performed safely for patients with cT3N0M0 UTUC, and it improved both pathological and oncological outcomes, especially in patients with RPT. Our study is important for supporting the efficacy of NAC-GC for UTUC. Thus, NAC-GC may be administered to patients with cT3N0M0 UTUC, after assessing their renal function.

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CONFLICT ON INTEREST

The authors have no conflict of interest.

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