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Longitudinal Change in Renal Function During and After Perioperative Chemotherapy of Nephroureterectomy in Patients With Upper Tract Urothelial Carcinoma

MOTOHIRO FUJIWARA, SATOSHI SHISHIDO, AYAKA ONUKI, YUICHIRO KATO, AKIHIRO KOJIMA, DAISUKE KATO, TAKUMASA AMEMIYA, TSUNEHIRO NENOHI, YUKI MATSUMOTO, MASAYASU URUSHIBARA, KAZUHIRO ISHIZAKA and MINATO YOKOYAMA

Department of Urology, Teikyo University Hospital, Kanagawa, Japan

Abstract

Background/Aim: Platinum-based adjuvant chemotherapy (AC) is recommended for invasive upper tract urothelial carcinoma (UTUC); however, many patients are ineligible for cisplatin due to renal impairment following radical nephroureterectomy (RNU). The optimal perioperative chemotherapy (PC) strategy for RNU remains unclear. This study focused on the impact of PC on renal function.

Patients and Methods: We retrospectively evaluated patients with clinical T2-4N0M0 UTUC who underwent RNU at our institution between 2018 and 2024. Patients were stratified into three groups: AC, neoadjuvant chemotherapy (NAC), and no-PC. New baseline estimated glomerular filtration rate (NB-eGFR) was defined as the eGFR at one-month post-treatment. Longitudinal eGFR changes from NB-eGFR were assessed, and the incidence of a 20% decline in eGFR from NB-eGFR was examined.

Results: A total of 27 patients were included: eight (30%) received NAC, five (19%) received AC, and 14 (51%) received no-PC. No patient received both NAC and AC. The mean NB-eGFR for the AC, NAC, and no-PC groups was 47.7, 42.3, and 40.7 ml/min/1.73 m^2, respectively. Over a median follow-up of 29 months, three patients (two in the NAC group and one in the no-PC group) developed a 20% decline in eGFR from NB-eGFR. Annual changes in eGFR were +1.0, –1.5, and –0.8 ml/min/1.73 m^2/year, with no significant differences among groups.

Conclusion: Although the sample size was limited, this study suggests that PC does not significantly impair long-term renal function. Both AC and NAC appear to be viable treatment options for patients with invasive UTUC.

Keywords: Urologic neoplasms/surgery, prognosis, urothelial carcinoma/drug therapy, retrospective studies.

Motohiro Fujiwara, MD, Ph.D., Department of Urology, Teikyo University Hospital, Mizonokuchi, 5-1-1, Futago, Takatsu-ku, Kawasaki, Kanagawa, 213-8507, Japan. Tel: +81 448443333, e-mail: motohiro.fujiwara@gmail.com

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Introduction

Upper tract urothelial carcinoma (UTUC) accounts for approximately 5 to 10% of all urothelial malignancies, with approximately 60% of cases being invasive (1). The standard treatment for high-grade or invasive UTUC has been radical nephroureterectomy (RNU) with bladder cuff resection. Recently, evidence supporting the use of perioperative chemotherapy (PC) in conjunction with RNU has been growing.

Historically, the phase III BA06 30894 trial in patients with muscle-invasive bladder cancer (MIBC) demonstrated a survival benefit from neoadjuvant cisplatin-based chemotherapy (cisplatin, methotrexate, and vinblastine) followed by surgery, compared to surgery alone (2). More recently, the POUT trial, a phase III, randomized controlled trial, demonstrated favorable oncologic outcomes with adjuvant chemotherapy (AC) compared to surveillance (3, 4). Based on these findings, current guidelines recommend a multidisciplinary approach involving platinum-based chemotherapy alongside RNU for the treatment of invasive UTUC (5, 6).

Although the efficacy of AC for invasive UTUC was demonstrated in the POUT trial, approximately half of patients are ineligible for cisplatin-based chemotherapy due to renal impairment (7), and the optimal timing of PC remains unclear. Because cisplatin eligibility hinges on renal function, longitudinal data on renal outcomes in this context are warranted. The purpose of this study was to describe renal function changes over time in patients undergoing RNU with and without PC, to help inform optimal treatment strategies in relation to renal function.

Patients and Methods

Ethical statement. This study protocol was approved by the Ethics Review Boards of our institution (approval number: 24-038). All activities were conducted in accordance with the ethical standards of the Declaration of Helsinki.

Patients. Between 2018 and 2024, 28 consecutive Japanese patients underwent RNU for clinical stage T2-T4N0M0 UTUC at our institution. One patient who received nivolumab as adjuvant treatment was excluded from the analysis, resulting in a final cohort of 27 patients for this retrospective study. Patient and tumor characteristics were obtained from medical records. Cancer staging was determined according to the TNM classification, based on computed tomography of the chest, abdomen, and pelvis, as well as magnetic resonance imaging. Post-treatment renal function was compared among the AC, neoadjuvant chemotherapy (NAC), and no-PC groups.

Treatments. In both the AC and NAC groups, gemcitabine plus cisplatin (GEM/CDDP) was used as the primary regimen, while gemcitabine plus carboplatin (GEM/CBDCA) was administered to patients deemed unfit for cisplatin. The standard full-dose GEM/CDDP regimen consisted of 1,000 mg/m^2 gemcitabine on days 1, 8, and 15, and 70 mg/m^2 cisplatin on day 2, repeated every 28 days. The GEM/CBDCA regimen consisted of 1,000 mg/m^2 gemcitabine on days 1, 8, and 15, with carboplatin dosed at an area under the curve of 5 on day 2, also repeated every 28 days.

The choice of regimen (GEM/CDDP or GEM/CBDCA) and any dose modifications were at the discretion of the attending physician. No patients in this study received immune checkpoint inhibitors or other chemotherapy regimens as part of their perioperative treatment.

Data collection and definition of NB-eGFR. Serum creatinine levels were retrospectively collected for each patient during chemotherapy and at 1, 3, 6 months, 1 year, and annually thereafter following treatment. eGFR was calculated using the Japanese Society of Nephrology equation: eGFR (ml/min/1.73 m^2)=194×serum creatinine (mg/dl)$^{-1.094}$×age (year)$^{-0.287}$×0.739 (if female) (8). The new baseline (NB)-eGFR was defined as the eGFR one month after treatment. For the AC group, NB-eGFR was defined as that one month after completion of AC. For the NAC or no-PC groups, NB-eGFR was defined as that one month after RNU, in accordance with a previous report

Table I. *Patient characteristics.*

Variables	All patients (n=27)	Adjuvant (n=5)	Neoadjuvant (n=8)	No-perioperative (n=14)	*p*-Value
Age, years	72 (41-84)	59 (47-67)	74 (48-83)	76 (41-84)	0.061
Sex: Male	18 (67)	3 (60)	5 (63)	10 (71)	0.858
ECOG performance status					0.199
0	16 (59)	5 (100)	5 (63)	6 (43)	
1	9 (33)	0 (0)	3 (37)	6 (43)	
2-4	2 (8)	0 (0)	0 (0)	2 (14)	
Primary tumor site					0.058
Renal pelvis	18 (67)	5 (100)	3 (37)	10 (71)	
Ureter	9 (33)	0 (0)	5 (63)	4 (29)	
Clinical T stage					0.825
2	18 (67)	3 (60)	6 (75)	9 (64)	
3-4	9 (33)	2 (40)	2 (25)	5 (36)	
Urine cytology: ≥ class III	20 (74)	4 (80)	7 (88)	9 (64)	0.463
Pretreatment eGFR[a]	54.8 (16.5)	62.1 (6.9)	54.9 (14.0)	52.2 (19.8)	0.531
NB-eGFRa	42.5 (10.8)	47.7 (4.9)	42.3 (3.8)	40.7 (2.9)	0.471
Diabetes mellitus	4 (15)	2 (40)	2 (25)	0 (0)	0.061
Hydronephrosis	10 (37)	0 (0)	5 (63)	5 (36)	0.075
Regimen					
GEM/CDDP	11 (41)	4 (80)	7 (88)	–	
GEM/CBDCA	2 (8)	1 (20)	1 (12)	–	
Number of cycles	2 (1-4)	2 (1-3)	2 (1-4)	–	
pT stage					0.056
pT0, a,1	7 (26)	0 (0)	5 (63)	2 (14)	
pT2	5 (19)	0 (0)	1(13)	4 (29)	
pT3	14 (52)	5 (100)	2 (25)	7 (50)	
pT4	1 (4)	0 (0)	0	1 (7)	

eGFR is expressed as the mean (SD), and other values are shown as n (%) or median (range). [a]ml/min/1.73 m^2. ECOG: Eastern Cooperative Oncology Group; NB-eGFR: new baseline estimated glomerular filtration rate; IQR: interquartile range; SD: standard deviation.

(9). Longitudinal eGFR changes from the NB-eGFR were evaluated and compared among the three groups. Data collection was discontinued upon the detection of metastatic recurrence of UTUC.

Statistics analysis. Continuous and categorical variables were compared using the Kruskal-Wallis test, Mann-Whitney *U*-test, and Fisher's exact test, respectively. To evaluate trends in eGFR during chemotherapy, all available eGFR values from laboratory tests were plotted, and locally estimated scatterplot smoothing (LOESS) curves were applied to visualize longitudinal patterns. LOESS, a non-parametric regression method, fits a smooth curve through a scatterplot of data points (10).

The annual change in eGFR was calculated using a linear mixed model. Renal impairment was defined as a ≥20% decline from pretreatment eGFR, in accordance with a previous report (11). Radiological response to chemotherapy was objectively evaluated by computed tomography every two to three months, based on the Response Evaluation Criteria in Solid Tumors guideline version 1.1 (12).

Metastasis-free survival (MFS) and overall survival (OS) were calculated from the date of initial treatment: for NAC cases, from the start of NAC; and for AC and no-PC cases, from the date of RNU. Survival estimates were generated using the Kaplan-Meier method and compared using the log-rank test.

All statistical analyses were performed using the JMP PRO software version 17.0 (SAS Institute Inc., Cary, NC, USA) and R 4.3 software (R Foundation for Statistical Computing, Vienna, Austria). *p*-Values <0.05 were

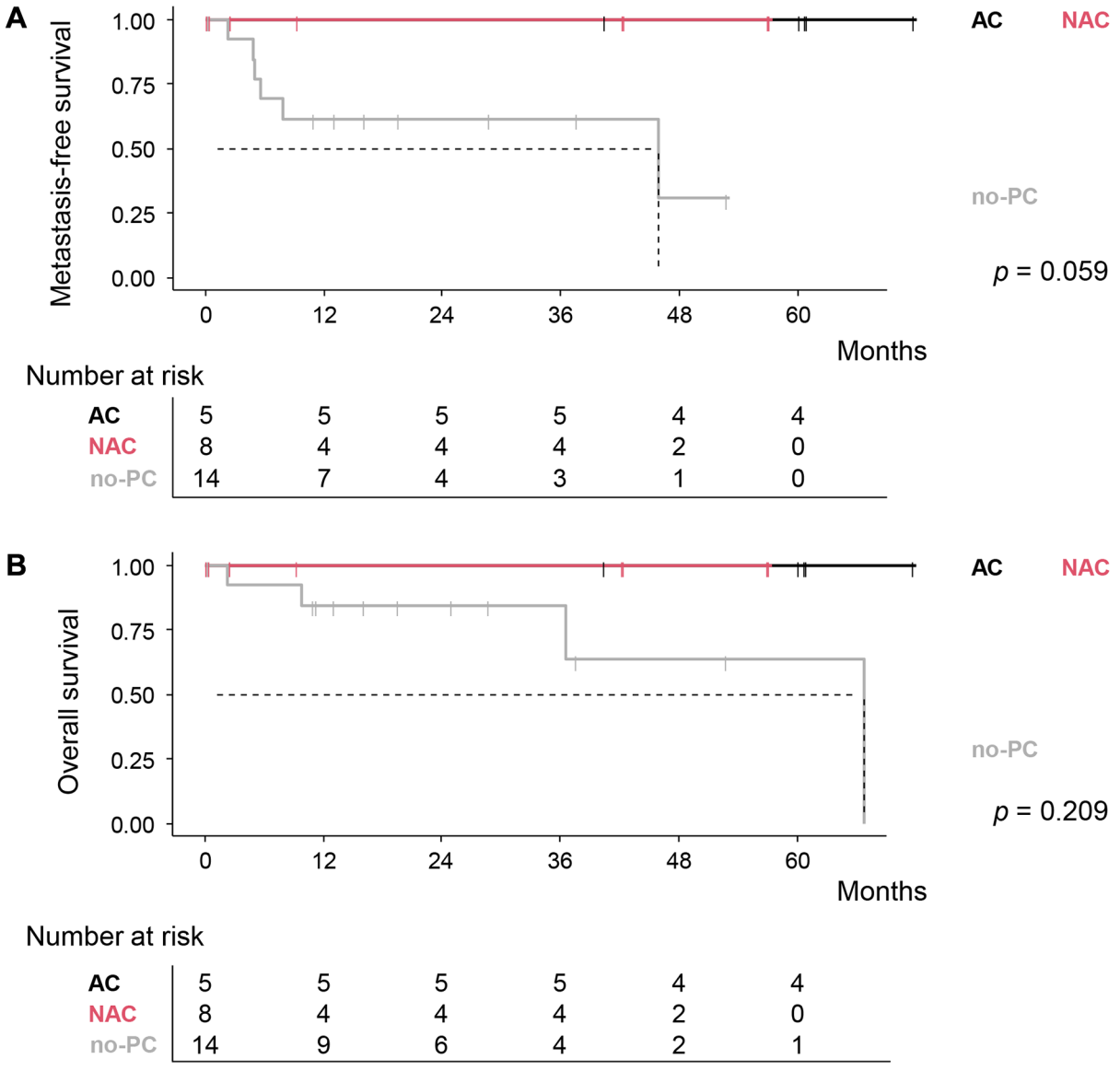

Figure 1. *Kaplan-Meier curves of metastasis-free survival MFS (A) and overall survival (OS) (B) stratified by perioperative chemotherapy type. AC: Adjuvant chemotherapy; NAC: neoadjuvant chemotherapy; no-PC: or none.*

considered statistically significant. All tests were two-tailed.

Results

Patient characteristics. Table I summarizes the baseline characteristics of the 27 patients with clinical T2-4N0M0 UTUC included in this study: eight (30%) were in the NAC group, five (19%) in the AC group, and 14 (51%) in the no-PC group. All patients who received NAC subsequently underwent RNU. The median age was 72 years, and 18 patients (67%) were male. Clinical T stages were T2 and ≥3 in 18 (67%) and nine (33%) patients, respectively. No patients received both AC and NAC. There were no

significant differences in baseline characteristics among the three groups. The AC group tended to be relatively younger, with better performance status and higher pretreatment eGFR. All patients were pathologically diagnosed with urothelial carcinoma (UC).

Oncological survival outcomes. During a median follow-up of 29 months, five patients (19%) developed metastatic recurrence, and four patients (15%) died from any cause. Overall, the 2-year MFS rate and OS rate were 78.4% and 91.3%, respectively. The 2-year MFS rates of the AC, NAC, and no-PC groups were 100%, 100%, and 61.5%, respectively (p=0.059, Figure 1A). Similarly, the 2-year OS rates were 100%, 100%, and 84.6%, respectively (p=0.209, Figure 1B).

Longitudinal changes in eGFR during chemotherapy. Figure 2 shows eGFR trends for each patient during PC. The mean eGFRs before chemotherapy in the AC and NAC groups were 48.9 and 54.9 ml/min/1.73 m^2, respectively (p=0.376). The LOESS curve showed an initial improvement in eGFR at one month in the AC group, but eGFR subsequently declined in both the AC and NAC groups. No patients developed severe renal impairment necessitating discontinuation of chemotherapy during the PC period.

NB-eGFRs and longitudinal changes in eGFR after treatment. The mean NB-eGFRs of the AC, NAC, and no-PC groups were 47.7, 42.3, and 40.7 ml/min/1.73 m^2, respectively (p=0.471). The longitudinal changes in eGFR are shown in Figure 3. No patients progressed to end-stage renal disease. The annual change rates for the AC, NAC, and no-PC groups from NB-eGFR were +1.0 [95% confidence interval (CI)=0.7-1.5] ml/min/1.73 m^2/year, −1.5 (95%CI=−6.9-−2.9) ml/min/1.73 m^2/year, and −0.8 (95%CI=−2.0-0.1) ml/min/1.73 m^2/year, respectively (p=0.092).

Incidence of a 20% decline from NB-eGFR. At two years, the mean eGFRs for the AC, NAC, and no-PC groups were 46.7, 39.5, and 41.1 ml/min/1.73 m^2/year (p=0.635). The corresponding 2-year changes from NB-eGFR were +5.4%, −5.2%, and −7.1% (p=0.249), respectively. During a median follow-up of 29 months, a 20% decline from NB-eGFR was observed in three patients (11.1%): two patients in the NAC group and one in the no-PC group. Time-to-renal impairment analysis showed no significant differences among the groups (p=0.054, Figure 4).

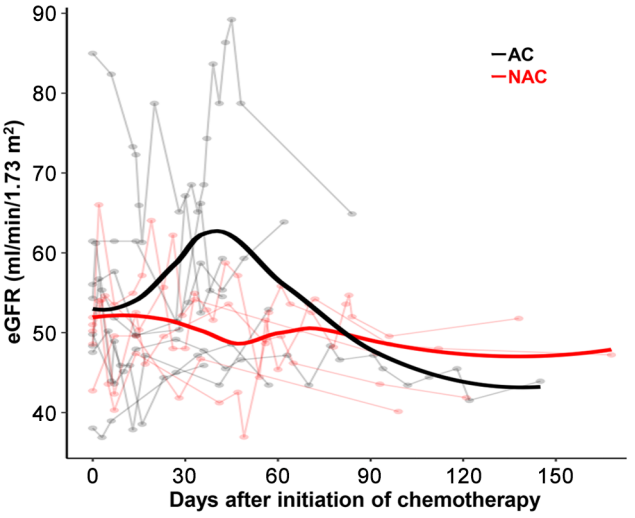

Figure 2. *Estimated glomerular filtration rate (eGFR) trends for each patient during perioperative chemotherapy. Bold lines indicate locally estimated scatterplot (LOESS curves) for the adjuvant chemotherapy (AC) and neoadjuvant chemotherapy (NAC) groups.*

Discussion

This study compared renal functional outcomes in patients with invasive UTUC who received AC, NAC, or no-PC. Analysis of renal function showed no significant differences in eGFR changes or in the incidence of a 20% decline from the NB-eGFR among the three groups. To the best of our knowledge, this is the first study to demonstrate that PC is both effective and safe from a renal function perspective in patients with UTUC.

We evaluated the longitudinal impact of PC on renal function. While several studies have examined perioperative changes in renal function, data following the establishment of NB-eGFR remain limited. Labbate *et al.* reported that in patients undergoing NAC followed by RNU, postoperative renal function was comparable

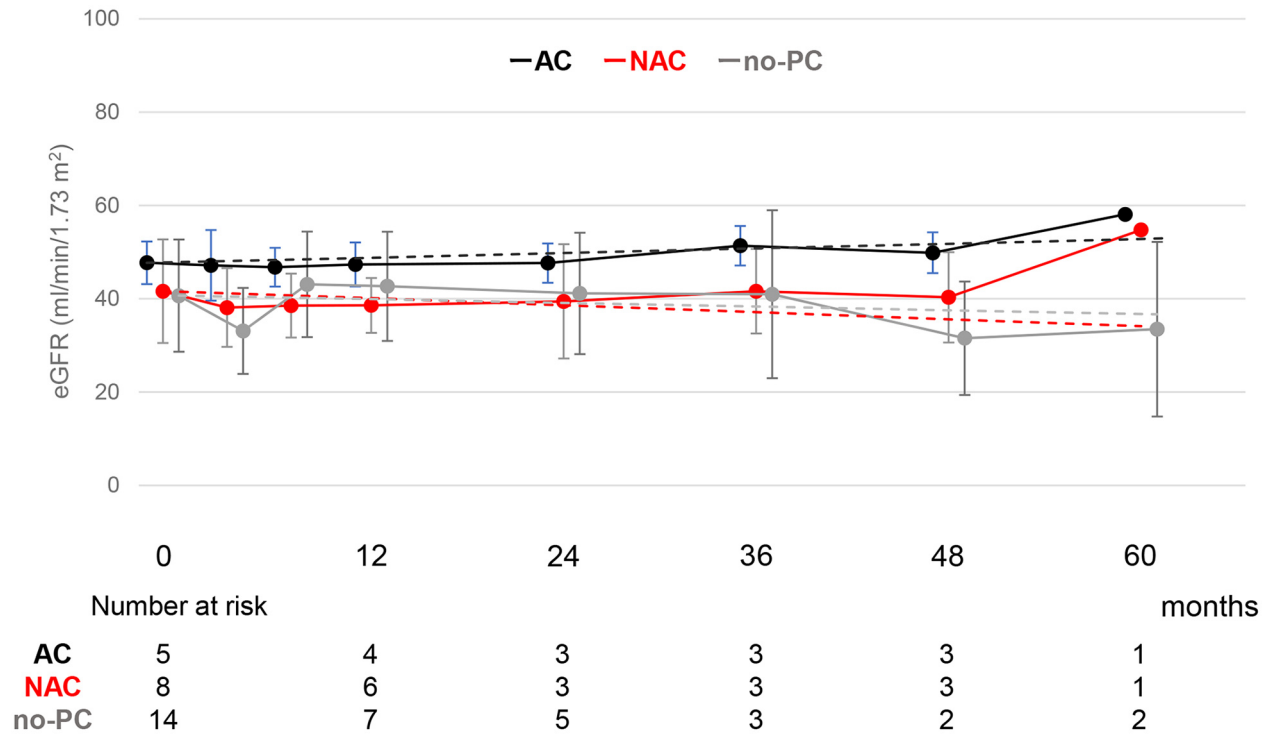

Figure 3. *Estimated glomerular filtration rate (eGFR) change stratified by perioperative chemotherapy type (adjuvant chemotherapy: AC, neoadjuvant chemotherapy: NAC, or none: no-PC). The dotted line represents the ideal line showing eGFR change from the NB-eGFR to the annual rate calculated by the linear mixed model. Data are presented as the mean±standard deviation.*

between those who received cisplatin and those who did not (13). Similarly, in our study, no significant differences in eGFR decline or the rate of ≥20% reduction from NB-eGFR were observed among the three groups.

One potential explanation for the lack of significant renal function decline is the cumulative dose of cisplatin administered. The irreversible nephrotoxicity of cisplatin is known to be dose-dependent, with cumulative toxicity generally occurring at total doses exceeding 400 mg/m^2 (14). In our cohort, the GEM/CDDP regimen included a maximum cisplatin dose of 70 mg/m^2 per cycle, with most patients receiving a median of two cycles. This relatively limited exposure may have mitigated the risk of long-term renal toxicity.

In this study, differences in renal function trends were observed among the AC, NAC, and no-PC groups. The favorable eGFR trend in the AC group remains unclear; however, it is possible that the timing of NB-eGFR measurement contributed to this finding. Specifically, in the AC group, NB-eGFR was set at the shortest interval following cisplatin administration compared to the other groups, potentially affecting residual effects of cisplatin nephrotoxicity. Cisplatin is known to cause acute kidney injury after a single dose of 50 to 100 mg/m^2 (15, 16), and although NB-eGFR was defined as the value one month after treatment, cisplatin-induced nephrotoxicity may not have fully resolved by that time point.

In addition, there was a selection bias in the AC group, as patients with good overall performance status, including better postoperative renal function, were more likely to receive AC. This may have contributed to the temporary improvement in renal function observed in this group. Regarding the NAC group, the annual change rate of eGFR in this study was –1.5 ml/min/1.73 m^2/year. Previous reports have shown annual eGFR declines of –0.8 to –1.5 ml/min/1.73 m^2/year in patients with MIBC

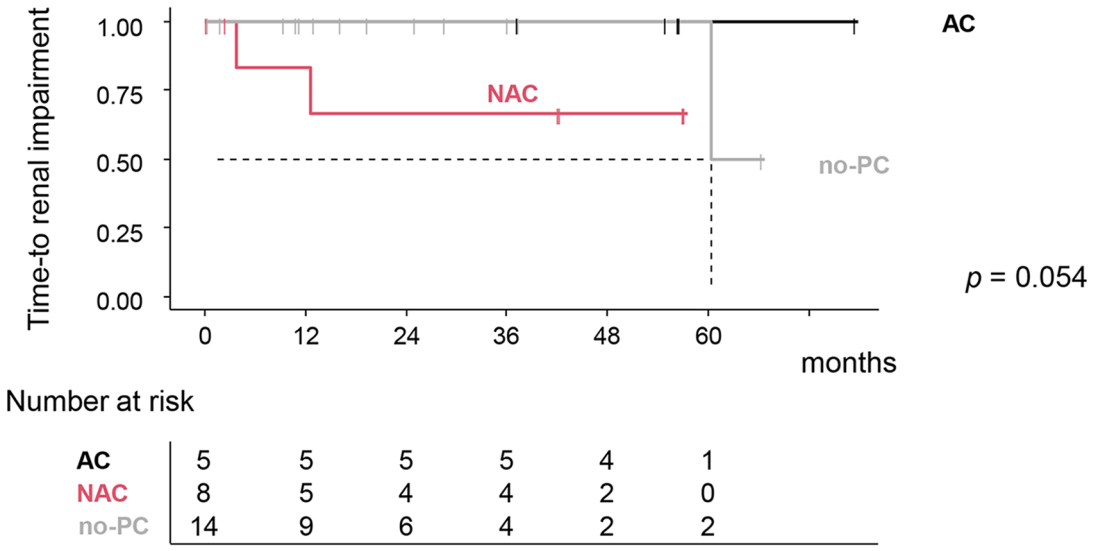

Figure 4. *Time to renal impairment analysis stratified by perioperative chemotherapy type.*

exposed to cisplatin, consistent with our findings (17, 18). It is well known that renal function tends to decline in patients with UC, and exposure to cisplatin appears to further exacerbate this decline.

Regarding the no-PC group, although this group was not exposed to cisplatin, the annual eGFR change rate was –0.8 ml/min/1.73 m^2/year. While the average annual decline in eGFR in the general Japanese population is reported to be –0.36 ml/min/1.73 m^2/year (19), the no-PC group exhibited a more pronounced decline. This trend may reflect the natural progression of renal deterioration in patients with UC, who are predisposed to chronic kidney disease (17, 18). Further large-scale studies are warranted to validate these findings and clarify the underlying mechanisms.

In this study, both AC and NAC improved MFS and OS, suggesting their effectiveness as perioperative treatment strategies for UTUC. The POUT trial demonstrated significant benefits of adjuvant gemcitabine plus platinum-based chemotherapy after RNU in patients with invasive UTUC (3, 4). With a median follow-up of 65 months, the trial showed improved 5-year disease-free survival (62% *vs.* 45%, p=0.001) and OS (66% *vs.* 57%, p=0.049).

The treatment landscape for invasive UC has markedly improved with the advent of immune checkpoint inhibitors (ICIs) (20, 21). The NIAGARA trial demonstrated that combining durvalumab with NAC in cisplatin-eligible MIBC patients improved 24-month event-free survival (67.8% *vs.* 59.8%, p<0.001) and OS [82.2% *vs.* 75.2%, hazard ratio (HR)=0.75, p=0.01] (22). The ongoing iNDUCT trial is investigating durvalumab with platinum-based chemotherapy in patients with UTUC (23). While immunochemotherapy represents a promising strategy, a subset of patients remains ineligible for ICIs, and platinum-based chemotherapy continues to be a critical treatment option (24). Despite growing interest in PC, evidence comparing AC, NAC, and no-PC in UTUC remains limited. Further research with larger cohorts is warranted to validate these findings.

Study limitations. First, its retrospective design and small sample size may limit the generalizability of the findings. Second, perioperative chemotherapy regimens, including drug selection and dosage, were not standardized and were determined at the discretion of the attending physicians, potentially introducing selection bias. Third,

cystatin C data were not available in this study. Since both eGFR and cystatin C are standard markers for assessing renal function (25), further assessment incorporating cystatin C is warranted.

Conclusion

Both AC and NAC appear safe from a renal function perspective and may be viable options for patients with invasive UTUC.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this manuscript.

Authors' Contributions

Concept and design: Minato Yokoyama. Acquisition, analysis, or interpretation of data: All Authors. Drafting of the manuscript: Motohiro Fujiwara. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Motohiro Fujiwara. Administrative, technical, or material support: Motohiro Fujiwara. Supervision: Minato Yokoyama.

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Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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