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Original Article

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Trends in the use of neoadjuvant chemotherapy and oncological outcomes for high-risk upper tract urothelial carcinoma: a multicentre retrospective study

Tomoko Hamaya[1], Shingo Hatakeyama[1], Toshikazu Tanaka[2], Yuka Kubota[1], Kyo Togashi[1], Shogo Hosogoe[1], Naoki Fujita[1], Ayumu Kusaka[1], Noriko Tokui[3], Teppei Okamoto[1], Hayato Yamamoto[1], Tohru Yoneyama[4], Takahiro Yoneyama[5], Yasuhiro Hashimoto[1] and Chikara Ohyama[1,5]

[1]Department of Urology, Hirosaki University Graduate School of Medicine, Hirosaki, [2]Department of Urology, Aomori Prefectural Central Hospital, Aomori, [3]Department of Urology, Odate Municipal General Hospital, Odate, [4]Department of Glycotechnology, and [5]Department of Advanced Transplant and Regenerative Medicine, Hirosaki University Graduate School of Medicine, Hirosaki, Japan

Objective

To evaluate temporal trends in neoadjuvant chemotherapy (NAC) utilisation and outcomes in patients with locally advanced upper tract urothelial carcinoma (UTUC).

Patients and Methods

We included 289 patients from seven hospitals who underwent radical nephroureterectomy (RNU) for locally advanced UTUC (≥cT3 or cN+) between 2000 and 2020. These patients received RNU alone or two to four courses of NAC with either a cisplatin- or carboplatin-based regimen. We evaluated the temporal changes in NAC use and compared the visceral recurrence-free, cancer-specific, and overall survival rates. The effect of NAC on oncological outcomes was examined using multivariate Cox regression analysis with inverse probability of treatment weighting (IPTW) models.

Results

Of 289 patients, 144 underwent NAC followed by RNU (NAC group) and 145 underwent RNU alone (Control [Ctrl] group). NAC use increased significantly from 19% (2006–2010), 58% (2011–2015), to 79% (2016–2020). Pathological downstaging was significantly higher in the NAC group than in the Ctrl group. The IPTW-adjusted multivariable analyses showed that NAC significantly improved the oncological outcomes in the NAC group compared with the Ctrl group. Moreover, carboplatin-based NAC significantly improved the oncological outcomes in the NAC group compared with the Ctrl group among patients with chronic kidney disease Stage ≥3. There were no significant differences in oncological outcomes between the cisplatin- and carboplatin-based regimens.

Conclusions

The use of NAC for high-risk UTUC increased significantly after 2010. Platinum-based short-term NAC followed by immediate RNU may not impede and potentially improves oncological outcomes.

Keywords

chronic kidney disease, neoadjuvant chemotherapy, upper tract urothelial carcinoma, survival, trend, #utuc, #uroonc

Introduction

Upper tract urothelial carcinoma (UTUC) is a relatively rare disease, accounting for 5–10% of UCs [1]. A locally advanced disease at diagnosis has been reported to be common in UTUC (~60%) compared to that in bladder cancer (15–25%) [2]. Although radical nephroureterectomy (RNU) is the 'gold standard' therapy for non-metastatic locally advanced UTUC, there has been no improvement in the prognosis of locally advanced UTUC over the past two decades despite improvements in surgical and medical treatments [3–7]. Interest in neoadjuvant chemotherapy (NAC) use for locally advanced UTUC is increasing based on studies of NAC for muscle-invasive bladder cancer (MIBC) [8–11]. As

demonstrated by a recent meta-analysis regarding the potential benefit of NAC for UTUC with a favourable pathological response and prognosis [12], a multimodal approach has the potential to improve survival in locally advanced UTUC. However, there is a lack of Level 1 evidence supporting the clinical benefit of NAC for locally advanced UTUC. Nevertheless, the use of NAC for locally advanced UTUC has slowly increased over time across the world [13–17]. In the present study, our aim was to evaluate the temporal trends in NAC utilisation and oncological outcomes in a representative cohort of patients with locally advanced UTUC.

Patients and Methods

Design and Ethics Statement

This retrospective, multicentre study was performed according to the ethical standards of the Declaration of Helsinki and approved by the Ethics Review Board of Hirosaki University School of Medicine (authorisation number; 2019-099). All hospitals approved the present study.

Patient Selection

Between January 2000 and September 2020, we performed RNU for 532 consecutive patients with UTUC at Hirosaki University Hospital, Aomori Rosai Hospital, Mutsu General Hospital, Tsugaru General Hospital, Odate Municipal Hospital, and Aomori Prefectural Central Hospital. The indications for NAC were locally advanced high-risk UTUC, including cT3–4 and/or cN+ diseases. We identified 289 high-risk patients who received NAC followed by RNU (NAC group) or RNU alone (Control [Ctrl] group) in our database.

Evaluation of Variables

The variables analysed in this study were age, sex, Eastern Cooperative Oncology Group Performance Status (ECOG PS), history of cardiovascular disease (CVD), hypertension, diabetes mellitus (DM), smoking, renal function, presence of hydronephrosis, regimen of chemotherapy, clinical stage, primary tumour site, visceral tumour recurrence, and prognosis. Clinical T stage was defined by the imaging conference with multiple radiologists. Renal function was evaluated by the estimated GFR (eGFR) using a modified version of the abbreviated Modification of Diet in Renal Disease Study formula for Japanese patients. The status of chronic kidney disease (CKD) was defined using CKD Stage ≥3 [18]. Toxicity was recorded prospectively using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Tumour response was analysed using Response Evaluation Criteria in Solid Tumors, version 1.1. Pathological response was evaluated by tumour downstaging (cT–pT), pT ≤1 rate, and lymphovascular invasion (LVI)-positive rate. Visceral recurrence-free survival (VRFS), cancer-specific survival (CSS), and overall survival (OS) were defined from the day of first treatment to the date of event onset or last follow-up. Visceral recurrence included lymph nodes, local pelvis, liver, lung, muscle-invasive tumour in urothelium, skin, muscle, brain, bone, and other metastases.

NAC

A regimen was selected based on guidelines regarding eligibility for the appropriate use of cisplatin according to established criteria [19]. Some patients with ECOG PS 1 were defined as cisplatin ineligible at a physician's discretion due to frailty, disability, or cognitive impairment. All patients with UTUC underwent chemotherapy at hospitalisation. Most patients received either gemcitabine plus cisplatin every 3 weeks or gemcitabine plus carboplatin (an area under the curve of 4–4.5) every 3 weeks for two to four cycles. Some patients received a standard dose of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) or docetaxel-based regimen. Radiological tumour response was assessed during the first and second course of NAC. We basically planned two courses of NAC and RNU within 90 days according to the recommendation of MIBC to avoid the delay of surgery. Additional NAC cycles were discussed and decided based on imaging results after the two courses of NAC.

Surgical Procedure

All patients underwent open or laparoscopic RNU as described previously [20]. The distal ureter was managed through the extravesical approach. A sampling dissection of regional lymph nodes was performed depending on the tumour stage. Postoperative complications were reviewed using the Clavien–Dindo classification.

Adjuvant or Salvage Chemotherapy

Adjuvant chemotherapy was administered to selected patients with pT3–4/pN+ who were not treated with NAC. Adjuvant chemotherapy was not routinely administered to patients with NAC until the report of a Phase III, open-label, randomised controlled trial of adjuvant chemotherapy in UTUC (the POUT trial) [21]. Salvage chemotherapy was indicated when recurrent disease was detected in these patients. A regimen was selected based on the eligibility for cisplatin use.

Patient Follow-up

After treatment, each patient was evaluated every 3–6 months using a blood and serum test, ultrasonography, urine cytology, cystoscope, and CT for the detection of tumour recurrence.

Outcome Evaluations

We compared the trend in the use of NAC for UTUC between the periods of 2006–2010, 2011–2015, and 2016–2020 and pathological effects (downstaging, pT ≤1 rate, and LVI-positive rate) between the Ctrl and NAC groups. The VRFS, CSS, and OS were evaluated using the Kaplan–Meier method with a log-rank test between the Ctrl and NAC groups. The effect of NAC on oncological outcomes was analysed in patients with preoperative CKD Stage 3 between the Ctrl and NAC groups. The effect of regimen used for the NAC group on oncological outcomes was evaluated between the cisplatin- and carboplatin-based regimens. Multivariable Cox regression analysis using inverse probability of treatment weighting (IPTW) models was performed to determine the effect of NAC on VRFS, CSS, and OS.

Statistical Analysis

Clinical data were analysed statistically using Bell Curve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan), GraphPad Prism 7.00 (GraphPad Software, San Diego, CA, USA), and R 4.0.2 (The R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were compared using Fisher's exact test or the chi-squared test. Quantitative variables were expressed as mean with standard deviation (SD) or median with interquartile range (IQR). The difference between the groups was compared statistically using Student's *t*-test for a normal distribution or the Mann–Whitney *U*-test for a non-normal distribution. The effects of NAC on oncological outcomes were investigated using multivariate Cox regression analysis with IPTW models, which re-weights the exposed and unexposed groups to emulate a propensity score-matched population. Variables included in the IPTW model were age, sex, ECOG PS (0–4), CVD, DM, smoking status, CKD Stage ≥3, and cT3–4/cN+. A hazard ratio (HR) with 95% CI was calculated. A $P < 0.05$ was considered to be statistically significant.

Results

Baseline Characteristics

Of 532 patients, we identified 289 high-risk patients who received NAC followed by RNU (n = 144, NAC group) or RNU alone (n = 145, Ctrl group; Fig. S1). There were no significant differences in preoperative patient characteristics between the groups (Table 1). The regimens in the NAC group were gemcitabine plus carboplatin in 105 (73%), gemcitabine plus cisplatin in 34 (24%), and others (MVAC or a docetaxel-based regimen) in five patients (3.5%). The median (IQR) cycles of NAC was 2 (2–2). The incidence of postoperative complications showed no significant differences between the Ctrl and NAC groups, and there were no Clavien–Dindo Grade IV or V complications (Table 1). In the Ctrl group, 115 patients had pT3–4/pN+ disease, which was the indication for adjuvant chemotherapy. However, the majority of patients refused it and the implementation rate of adjuvant chemotherapy was 7.0% (eight of 115). We recommended salvage therapy in all patients with recurrence.

Table 1 Characteristics of the patients.

Characteristic	All	Ctrl group	NAC group	*P*
N	289	145	144	
Age, years, mean (SD)	71 (9.2)	72 (9.2)	70 (9.2)	0.132
Gender, male, *n* (%)	195 (68)	91 (63)	104 (72)	0.086
ECOG PS >0, *n* (%)	33 (11)	20 (14)	13 (9.0)	0.384
Hypertension, *n* (%)	139 (48)	73 (50)	66 (46)	0.443
DM, *n* (%)	47 (16)	22 (15)	25 (17)	0.614
CVD, *n* (%)	49 (17)	24 (17)	25 (17)	0.877
Smoking, *n* (%)	128 (44)	56 (39)	72 (50)	0.052
Baseline eGFR, mL/min/1.73 m^2, mean (SD)	56 (17)	55 (19)	58 (16)	0.183
Hydronephrosis, *n* (%)	201 (70)	101 (70)	100 (69)	0.969
Cisplatin-based NAC, *n* (%)			38 (26)	
cT2/3/4, *n*	4/274/7	3/135/6	1/139/4	
cN+, *n* (%)	37 (13)	14 (9.6)	23 (16)	0.116
Original tumour sites, *n*				
Renal pelvis/ureter/multiple	109/160/20	65/68/12	44/92/8	
Postoperative complications, *n* (%)				
All	43 (15)	22 (15)	21 (15)	1.000
Clavien–Dindo Grade ≥III	10	7	3	
Pathological finding, *n* (%)				
pT3–4 or pN+	166 (57)	115 (80)	51 (35)	<0.001
Adjuvant chemotherapy, *n* (%)	9 (5.4)	8 (7)	1 (2)	0.278
Visceral recurrence, *n* (%)	107 (37)	64 (44)	43 (30)	0.012
Salvage chemotherapy, *n* (%)	100 (93)	59 (92)	41 (95)	0.699
Follow-up, months, median	40	39	40	

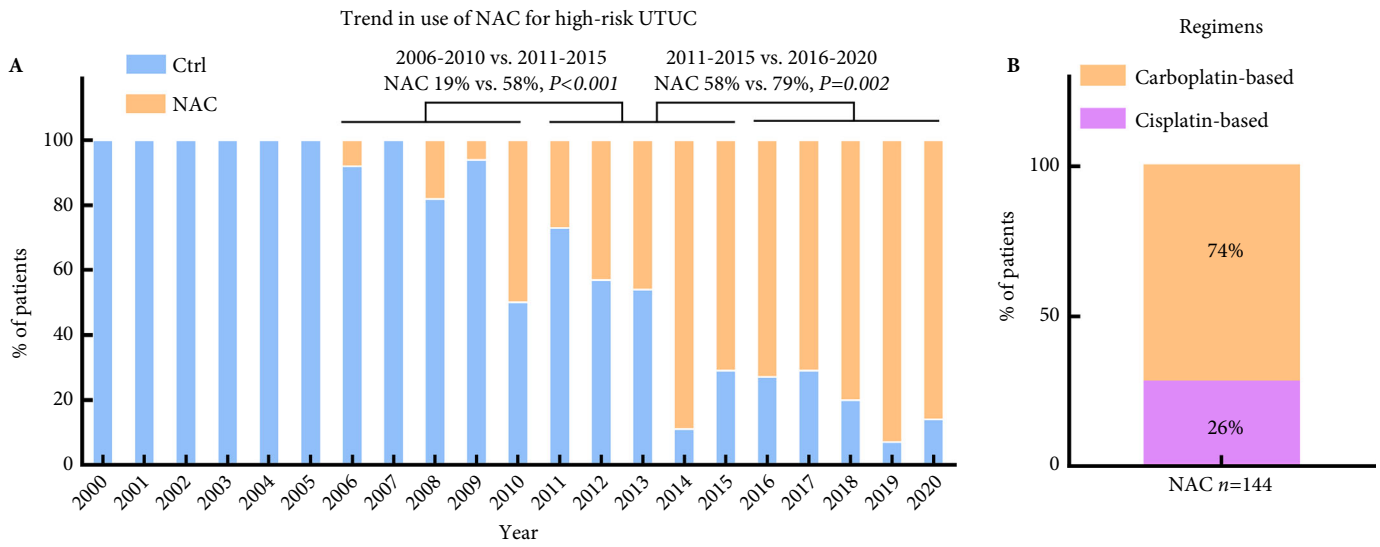


Fig. 1 Trend in the use of NAC for UTUC. Comparison of treatment trend in the use of NAC between 2006 and 2010 and 2011–2015 and between 2011–2015 and 2016–2020 (**A**). Types of NAC regimens for high-risk UTUC treatment (**B**).

The implementation rate in the Ctrl and NAC groups was 92% (59/64) and 95% (41/43), respectively (P = 0.699). The major regimens of adjuvant and/or salvage therapies were gemcitabine plus carboplatin, followed by gemcitabine plus cisplatin, MVAC, taxane-based regimens, and others (Table 1). One patient with normal renal function started a cisplatin-based regimen at the initial cycle experienced renal function decline (stage progression from CKD Stage 2 to 3A) and we switched to carboplatin-based regimen at the second cycle. The number of patients with CKD Stage 4 was three (2%) in this cohort. No patients experienced severe renal impairments after carboplatin-based regimens in patients with CKD Stage 3–4.

Trend in the Use of NAC for High-risk UTUC

The use of NAC for high-risk UTUC was 0% between 2000 and 2005. NAC use increased significantly from 19% (2006–2010), 58% (2011–2015), to 79% (2016–2020) in our practice (2006–2010 vs 2011–2015, P < 0.001; 2011–2015 vs 2016–2020, P = 0.002, Fig. 1A). Based on the elderly population of UTUC (median [IQR] age 73 [65–79] years), carboplatin-based regimens were selected for 74% of the patients (Fig. 1B).

Oncological Outcomes

Of 289 patients, 106 (37%) had tumour recurrence. The number of patients with recurrences in the lymph nodes, local pelvis, liver, lung, muscle-invasive tumour in urothelium, brain, bone, and others were 44 (15%), 19 (6.6%), 15 (5.2%), 19 (6.6%), 35 (12%), one (0.3%), 16 (5.5%), and five (1.7%), respectively.

There were significant differences in pathological effects between the Ctrl and NAC groups. The number of patients with pathological downstaging and pT ≤1 rate was significantly higher in the NAC group than in the Ctrl group. The LVI-positive rate was significantly lower in the NAC group than in the Ctrl group (P < 0.001; Fig. 2A). pT0 was observed in one (0.7%) and 11 (7.6%) patients in the Ctrl and NAC groups, respectively.

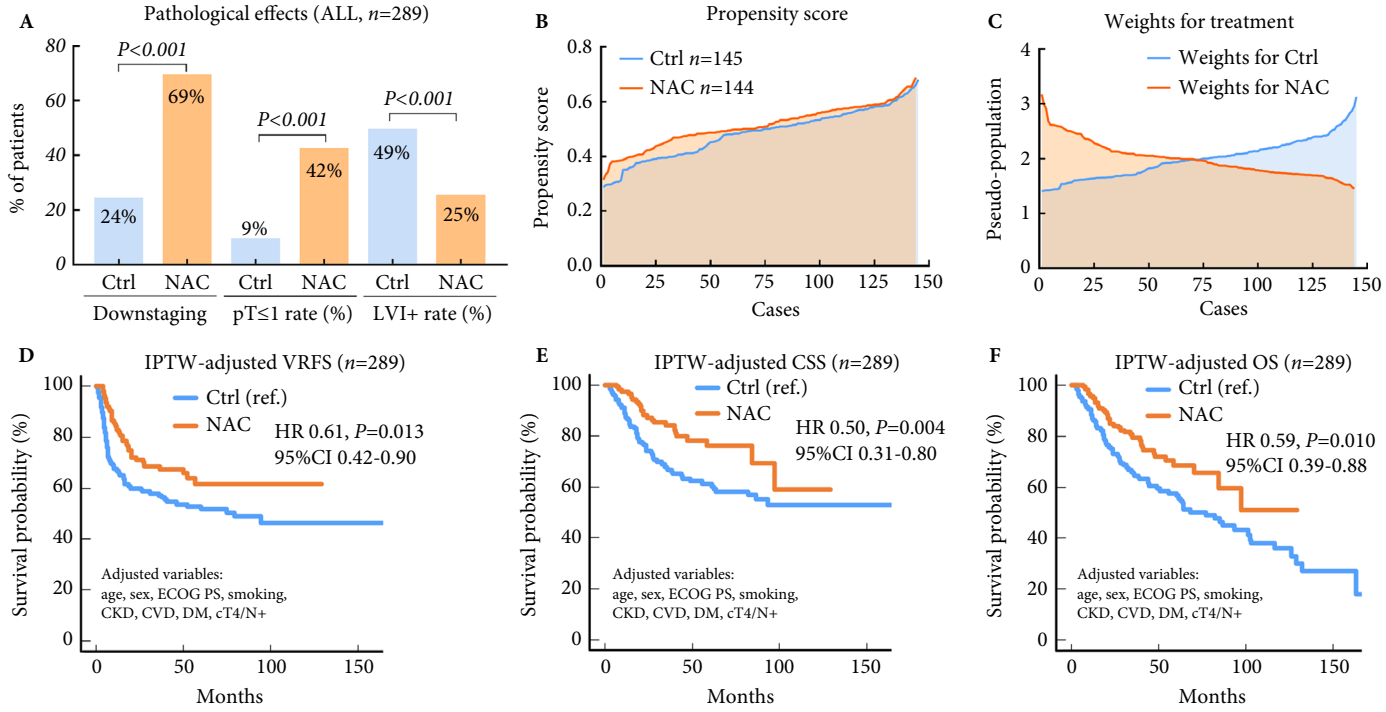
Comparison of Oncological Outcomes Between the Ctrl and NAC Groups (All Patients, n = 289)

The propensity score for NAC (Fig. 2B) and weights for treatment (Fig. 2C) were comparable and feasible between the groups, respectively. The IPTW-adjusted Cox regression analyses revealed significantly longer VRFS (Fig. 2D; HR 0.61, P = 0.013), CSS (Fig. 2E; HR 0.50, P = 0.004), and OS (Fig. 2F; HR 0.59, P = 0.010). Results of the unadjusted Kaplan–Meier analysis for VRFS, CSS, and OS are shown in the supplemental figure (Fig. S2A–C).

Comparison of Oncological Outcomes Between the Ctrl and NAC Groups (Patients with CKD Stage 3–4, n = 178)

A greater number of patients had pathological downstaging (P < 0.001), pT ≤1 rate (P = 0.007), and LVI-positive rate (P < 0.001) showed significant improvement in the NAC group compared with the Ctrl group (Fig. 3A). The propensity score for NAC (Fig. 3B) and weights for treatment (Fig. 3C) were comparable and feasible between the groups, respectively. The IPTW-adjusted Cox regression analyses revealed significantly longer VRFS (Fig. 3D; HR 0.59,

Fig. 2 Oncological outcomes between the Ctrl and NAC groups (n = 289). Comparison of pathological effects between the Ctrl and NAC groups (**A**). Propensity score distribution between the Ctrl and NAC groups (**B**). Propensity score-adjusted weights for treatment between the Ctrl and NAC groups (**C**). IPTW-adjusted VRFS between the Ctrl and NAC groups (**D**). IPTW-adjusted CSS between the Ctrl and NAC groups (**E**). IPTW-adjusted OS between the Ctrl and NAC groups (**F**).



P = 0.014), CSS (Fig. 3E; HR 0.49, P = 0.006), and OS (Fig. 3F; HR 0.57, P = 0.016). Results of the unadjusted Kaplan–Meier analysis for VRFS, CSS, and OS are shown in the supplemental figure (Fig. S2D–F).

Comparison of Oncological Outcomes Between the Cisplatin- and Carboplatin-Based Regimens (NAC Group, n = 144)

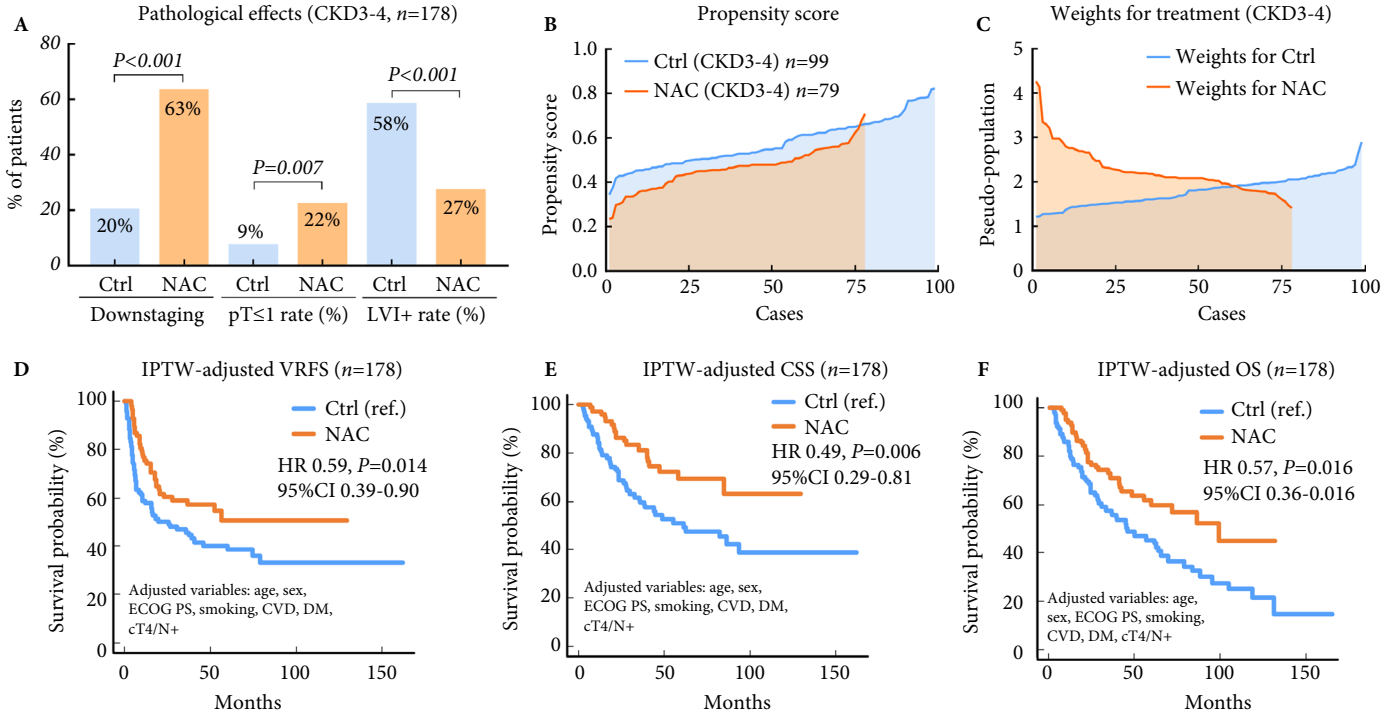
Baseline characteristics showed significant differences between the cisplatin- and carboplatin-based regimens in the number of patients aged >70 years (32% vs 64%, $P < 0.001$) and CKD Stage 3–4 (29% vs 75%, $P < 0.001$; Fig. 4A). The numbers of patients with pathological downstaging and LVI-positive rate were not significantly different between the groups. However, ypT ≤1 rate was significantly higher in the group with the cisplatin-based regimen (66%) than in the group with carboplatin-based regimen (Fig. 4B; 33%, $P < 0.001$). The IPTW-adjusted Cox regression analyses revealed no significant differences in VRFS (Fig. 4C; HR 1.28, P = 0.578), CSS (Fig. 4D; HR 2.25, P = 0.064), and OS (Fig. 4E; HR 1.73, P = 0.162). Results of the unadjusted Kaplan–Meier analysis for VRFS, CSS, and OS are shown in the supplemental figure (Fig. S2G–I). pT0 was observed in six (55%) and five (45%) patients in the cisplatin- and carboplatin-based regimens, respectively.

Discussion

The important findings of the present study were that NAC use for high-risk UTUC in our medical centres has considerably increased over the past decade. In addition, NAC use has the potential to improve oncological outcomes using platinum-based regimens. Moreover, our present findings are consistent with those of a recent meta-analysis that demonstrated the potential benefit of NAC for UTUC in terms of favourable pathological downstaging and prognosis compared with RNU alone [12]. These observations suggest that a multimodal approach is associated with improved survival in select patients with locally advanced UTUC. To our knowledge, the present study is the largest to evaluate the trends in NAC use and oncological outcomes in patients with UTUC, including patients with renal impairment.

Although the 2020 European Association of Urology guideline mentions a weak recommendation to ‘offer perioperative chemotherapy to patients with muscle invasive UTUC,’ the use of NAC for high-risk UTUC has been slowly increasing since 2010 in our medical centres. The primary

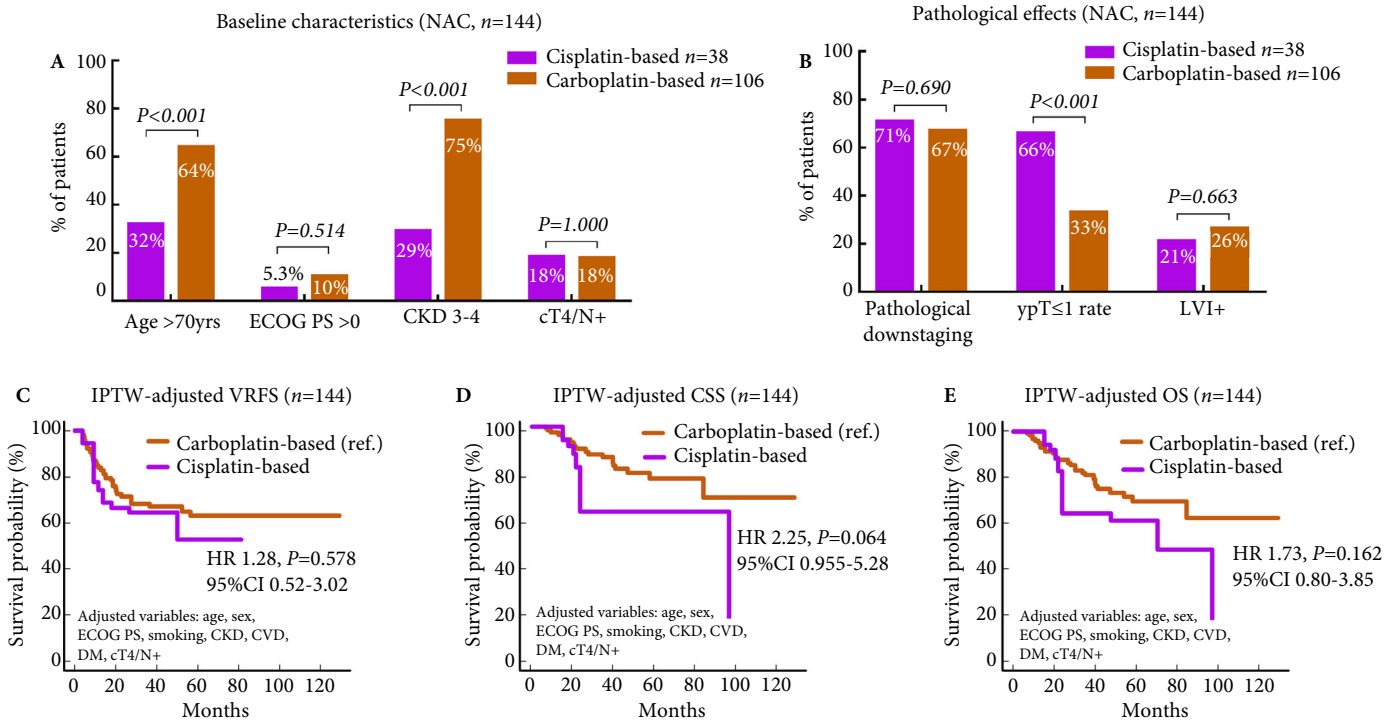
Fig. 3 Oncological outcomes between the Ctrl and NAC groups in patients with CKD Stage 3–4 (n = 178). Comparison of pathological effects between the Ctrl and NAC groups in patients with CKD Stage 3–4 (**A**). Propensity score distribution between the Ctrl and NAC groups in patients with CKD Stage 3–4 (**B**). Propensity score-adjusted weights for treatment between the Ctrl and NAC groups in patients with CKD Stage 3–4 (**C**). IPTW-adjusted VRFS between the Ctrl and NAC groups in patients with CKD Stage 3–4 (**D**). IPTW-adjusted CSS between the Ctrl and NAC groups in patients with CKD Stage 3–4 (**E**). IPTW-adjusted OS between the Ctrl and NAC groups in patients with CKD Stage 3–4 (**F**).



reason for this was the recognition of the survival benefit of NAC for MIBC [22]. As we had recognised the efficacy of NAC in MIBC, our interest was shifted toward locally advanced UTUC, which is one of the poor prognostic diseases in urology. We selected high-risk patients who had cT3–4 or N+ disease as potential candidates for NAC. Although optimal patient selection for NAC is challenging, we selected patients with ≥cT3 disease to enhance the benefit of NAC. In addition, we designed a short-term NAC followed by immediate RNU within 90 days to diminish the disadvantage of NAC, especially for non-responders. This strategy enabled us to use the waiting time of surgery in an effective and acceptable manner in clinical practice. Moreover, urologists in Japan can prescribe NAC and plan RNU as a component of sequential therapy in the urology ward. The other reasons may be the inclusion of carboplatin-based regimen for patients with renal impairment. Although several studies have suggested a slightly inferior efficacy of carboplatin for UC [6], our present study demonstrated acceptable efficacy of carboplatin-based NAC for high-risk UTUC. Furthermore, NAC use was not limited by the universal health insurance coverage system in Japan. In fact, several NAC studies for UTUC (six of 16 studies) have been reported from Japan [23–27] in a meta-analysis [12]. Despite several limitations, our present results suggest that short-term NAC followed by immediate RNU does not impede patient outcomes. We must be careful in administering NAC for treating UTUC to minimise complications until the presentation of Level 1 evidence.

We found that pathological downstaging, pT ≤1 rate, and lower LVI-positive rate were associated with better prognosis (Fig. 2A). Several studies have suggested that pathological downstaging is a potential endpoint of NAC in UTUC [16,17,28]. However, difficulty in making an accurate T stage diagnosis is a strong limitation of pathological downstaging. Although we defined clinical T stage by imaging conference with multiple radiologists, there is no definitive diagnostic tool for accurate clinical T staging for UTUC. A recent study suggested that a tumour size of 2 cm is a useful cut-off for identifying patients at risk of harbouring ≥pT2 UTUC [29]. However, accurate T-stage diagnosis is challenging despite the utility of tumour size [30]. We observed pathological downstaging in 24% of patients in the Ctrl group, which was the staging error in our practice. Interestingly, the rate of a staging error in the control arm was similar to that in the recent retrospective study of NAC for UTUC (22.4%) [17]. These results suggest that the staging error was observed in at

Fig. 4 Oncological outcomes between cisplatin- and carboplatin-based regimens in patients with NAC (n = 144). Comparison of baseline characteristics between cisplatin- and carboplatin-based regimens in patients with NAC (**A**). Comparison of pathological effects between cisplatin- and carboplatin-based regimens in patients with NAC (**B**). IPTW-adjusted VRFS between cisplatin- and carboplatin-based regimens in patients with NAC (**C**). IPTW-adjusted CSS between cisplatin- and carboplatin-based regimens in patients with NAC (**D**). IPTW-adjusted OS between cisplatin- and carboplatin-based regimens in patients with NAC (**E**).



least 22–24% of UTUC cases. Conversely, LVI-positive rate is a non-imaging and pathological outcome after NAC. As LVI positivity was significantly associated with poor prognosis in UTUC [17], it might be a useful endpoint for evaluating the efficacy of NAC for UTUC.

The other key finding of our present study was the potential benefit of NAC for patients with high-risk UTUC with renal impairment (Fig. 3A,D,E, and F). The utility of carboplatin in a neoadjuvant setting is debatable. Currently, only limited research provides useful information about the role of NAC in cisplatin-ineligible patients. One ongoing randomised trial (NCT02876861) evaluating the role of two to four cycles of NAC for patients with locally advanced UTUC includes patients who are eligible for cisplatin. A Phase II study of the ECOG–American College of Radiology Imaging Network (ECOG-ACRIN) 8141 trial planned to enrol 30 patients per arm (MVAC for cisplatin-eligible or gemcitabine + carboplatin for a creatinine clearance of 30–50 mL/min or less) with high-grade UTUC [14]. However, the gemcitabine + carboplatin arm was closed after the enrolment of six patients due to poor accrual. Therefore, no prospective study is available that has evaluated the utility of carboplatin-based regimens in the NAC setting. In contrast, the POUT trial demonstrated the potential benefit of carboplatin-based regimen in an adjuvant setting. A subgroup analysis of disease-free survival revealed marginal outcomes in disease-free survival with the gemcitabine + carboplatin regimen (HR 0.66, 95% CI 0.35–1.26; P = 0.21) compared to those with the gemcitabine + cisplatin regimen (HR 0.35, 95% CI 0.20–0.61; P < 0.001). However, no statistical difference was found in the disease-free survival between the gemcitabine + cisplatin and gemcitabine + carboplatin regimens (interaction test, P = 0.14). Therefore, the study suggested the feasibility of using carboplatin-based regimen for treating locally advanced UTUC. In the present study, we observed no clear disadvantage in tumour responses and prognosis between the Ctrl and NAC groups and between the gemcitabine + cisplatin and gemcitabine + carboplatin regimens, except for the inferior rate of ypT ≤1 in the carboplatin-based regimen. Although the limitations of the present study prevent us from drawing definitive conclusions, a carboplatin-based regimen is worth noting as a viable option for patients with locally advanced UTUC who are ineligible for cisplatin treatment. Further studies are required on this issue.

Several limitations must be acknowledged in the present study, including the limited sample size and the retrospective study design. We were unable to control

selection bias and other unmeasurable confounders. We could not obtain the safety profiles for patients receiving NAC as the inclusion of the present study was limited to those undergoing RNU, which is a significant selection bias. The information regarding dissected lymph nodes was limited because of the lack of a strong recommendation for template lymph node dissection. Improvement of medical technologies and supportive care system over time might have a meaningful effect on outcome improvement. Nevertheless, regardless of these limitations, our present study supports the potential benefit of NAC for high-risk UTUC even in patients with renal impairment. Well-designed, large-scale prospective studies are required to validate our present findings.

In conclusion, NAC use for patients with high-risk UTUC has increased significantly since 2010. Platinum-based short-term NAC followed by immediate RNU may not impede and potentially improves oncological outcomes. A carboplatin-based regimen might be a useful alternative for NAC in patients with UTUC with renal impairment. The results of the ongoing prospective studies are eagerly anticipated.

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Conflict of Interests

The authors have no conflicts of interest to declare.

Author Contributions

Conception and Design: Shingo Hatakeyamaand Chikara Ohyama. Acquisition of Data: Tomoko Hamaya, Kyo Togashi, Toshikazu Tanaka, Yuka Kubota, Shingo Hatakeyama, Naoki Fujita, Ayumu Kusaka, Noriko Tokui, Teppei Okamoto, Hayato Yamamoto, Takahiro Yoneyama and Yasuhiro Hashimoto. Analysis and interpretation of data: Shingo Hatakeyama. Drafting of the manuscript: Tomoko Hamaya and Shingo Hatakeyama. Critical Revision of the Manuscript: Chikara Ohyama. Statistical Analysis: Shingo Hatakeyama and Tohru Yoneyama.

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Correspondence: Shingo Hatakeyama, Department of Urology, Hirosaki University Graduate School of Medicine, 5 Zaifu-chou, Hirosaki 036-8562, Japan.

e-mail: shingoh@hirosaki-u.ac.jp

Abbreviations: CKD, chronic kidney disease; CSS, cancer-specific survival; Ctrl, Control (group); CVD, cardiovascular disease; DM, diabetes mellitus; ECOG PS, Eastern Cooperative Oncology Group Performance Status; eGFR, estimated GFR; HR, hazard ratio; IPTW, inverse probability of treatment weighting; LVI, lymphovascular invasion; MIBC, muscle-invasive bladder cancer; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; NAC, neoadjuvant chemotherapy; OS, overall survival; RNU, radical nephroureterectomy; (UT)UC, (upper tract) urothelial carcinoma; VRFS, visceral recurrence-free survival.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Patient selection.
Fig. S2. Unadjusted comparison of oncological outcomes.