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ORIGINAL ARTICLE

Association between response to neoadjuvant chemotherapy and survival outcome after radical surgery in patients with yielding pathological T2≤ and/or N+ urothelial carcinoma

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ABSTRACT

Background and Aim: In early 2022, the use of adjuvant nivolumab for patients with high-risk muscle-invasive urothelial carcinoma (MIUC) was approved in Japan, European countries, and USA based on the positive results of CheckMate 274 trial, which included participants who received neoadjuvant chemotherapy (NAC). Subgroup analyses of CheckMate 274 trial do not report response to NAC and benefit from adjuvant nivolumab. Herein, we investigated the association between response to NAC and survival outcomes after radical surgery in patients with residual MIUC and/or lymph node disease.
Methods: This multicenter retrospective study included a total of 95 NAC-treated patients with yielding pathological (yp) T2≤ and/or ypN+ UC on radical surgery specimens. Based on the comparison of clinical T and N category with yp T and N category, the patients were categorized into three groups: Down-staged ypT2≤ (n = 14), no-changed ypT2≤ (n = 39), and up-staged ypT2 ≤ groups (n = 42).
Results: There was no significant difference in extraurinary tract recurrence-free survival, cancer-specific survival, and overall survival after the radical surgery among three groups. Subgroup analysis of a bladder cancer cohort showed a marginal association between better response and longer cancer-specific survival (P = 0.073).
Conclusion: Our finding suggested that adjuvant nivolumab should be considered for all the patients with pathological ypT2≤ or ypN+ UC regardless of response to NAC. Further research is mandatory in finding predictive factors that serve in decision-making for NAC-treated patients who are likely to benefit from adjuvant nivolumab.
Relevance for Patients: To develop a decision-making tool for adjuvant nivolumab, we investigated the association between response to NAC and survival after radical surgery. Further research is mandatory in finding predictive factors that serve in decision-making for NAC-treated patients who are likely to benefit from adjuvant nivolumab.

1. Introduction

Urothelial carcinoma (UC) arises from the urinary tract mucosa in the renal pelvis, ureters, bladder, or urethra. Particularly, muscle-invasive UC (MIUC) is aggressive and associated with a poor clinical outcome, requiring multidisciplinary management. Radical nephroureterectomy (RNU) with bladder cuff remains the standard care for localized upper

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urinary tract UC (UTUC) [1]. According to reports of muscle-invasive UTUC in the 2000s, 5-year cancer-specific survival (CSS) rates of pT2, pT3, and pT4 were 75 – 84%, 54 – 56%, and 0 – 12%, respectively [2-4]. A randomized control trial (RCT) [5] and recent meta-analyses of 11 retrospective studies [6] revealed that for high-risk UTUC, RNU with both neoadjuvant chemotherapy (NAC) and adjuvant chemotherapy (AC) provides better survival than RNU alone. In the latest European Association of Urology Guidelines on UTUC, the evidence level of AC was positive level 1b, and platinum-based AC was recommended for patients having muscle-invasive UTUC and/or pN + disease without NAC [7]. In muscle-invasive bladder cancer (MIBC), cisplatin-based NAC followed by radical cystectomy (RC) is the current standard care based on level 1 evidences [7-9]. A systematic review and meta-analysis including 15 RCTs with >3000 patients demonstrated that cisplatin-based NAC decreased the risk of mortality by approximately 20% compared to RC without NAC [10].

The pathologic response to NAC, frequently defined as ≤ yielding pathological (yp) T1 and ypN0 was associated with favorable survival outcome after RC or RNU for patients with MIUC [11-13]. In contrast, residual MIUC disease, *that is*, ypT2≤ and/or ypN+ after NAC, was a strong poor prognostic factor for disease recurrence and death. Recently, the CheckMate 274 trial demonstrated that adjuvant nivolumab provided significant benefit on disease-free survival in NAC-treated patients with residual MIUC disease and/or ypN+ [14]. Although adjuvant nivolumab is recommended for the disease subset in several guidelines [7-9], many patients having UC are elderly and vulnerable, and immune checkpoint inhibitors (ICIs) can cause divergent immune-related adverse events, which are sometimes serious and lethal, requiring high-dose steroids [14-18]. Moreover, updated data of the CheckMate 274 trial demonstrated that Grade 3 – 4 treatment-related adverse events occurred in 18.2% and 7.2% of patients in the nivolumab and placebo arms, respectively [19]. Because the patient subset indicated for adjuvant nivolumab in the guidelines is heterogeneous, it would be vital to select patients who are likely to benefit from this treatment.

The association between response to NAC and survival outcomes after RC or RNU remains unclear. We hypothesized that patients with pre-NAC cT3 and post-NAC ypT2 (down-staged) could have better prognosis compared to those with pre-NAC cT2 and post-NAC ypT2 (no-changed). This study investigated the potential association by stratifying NAC-treated patients with MIUC into three groups: Down-staged ypT2≤, no-changed ypT2≤, and up-staged ypT2≤ groups.

2. Methods

2.1. Study cohorts of NAC-treated MIUC patients and data collection

This retrospective multicenter study was approved by the ethics committee of each participating institute (reference ID: 1298, 1958, 2891, H30-048, and 2018-036) of the Nishinihon Uro-Oncology Collaborative Group framework. Informed consent was obtained from the participants or bereaved families through posters and/or websites using the opt-out method [20]. We reviewed the medical charts of 214 consecutive patients with bladder cancer who underwent RC between 2000 and 2021 at the Nara Medical University Hospital and 1,775 patients with UTUC who underwent RNU between 1995 and 2018 at four hospitals across Western Japan (Figure 1). Inclusion criteria were as follows: (1) Patients receiving NAC for invasive UC before radical surgery and (2) pathologically diagnosed ypT2≤ and/or ypN+ UC in the radical surgery specimens. Exclusion criteria were as follows: Patients with critical data missing. Of 1989 patients, 95 (4.8%) who received NAC followed by radical surgery, RC, or RNU and diagnosed with ypT2≤ tumors and/or ypN+ were eligible for the analysis (Figure 1A).

2.2. Image interpretation for MIUC

All radiographic data of computed tomography (CT), CT urography, and/or magnetic imaging resonance (MRI) taken before the initiation of NAC were uploaded in a cloud medical imaging platform (Ambra Health, New York, NY, USA). The images were reevaluated and interpreted by a radiologist (Marugami N.) with special expertise in urogenital imaging, who was blinded to any other clinicopathological variables. Tumor stage (according to the Eighth Edition American Joint Committee on Cancer tumor-node-metastasis staging system) was determined based on multiplanar reconstruction, including axial, sagittal, and coronal CT images. To determine the clinical T stage (≤cT2, cT3, or cT4) of UTUC, the investigator performed comprehensive assessment using tumor appearance (filling defect/mass or wall thickening/stricture), margin (smooth or spiculated/irregular), texture (homogeneous, heterogeneous), hydronephrosis, and calcification [21,22].

2.3. Radical surgery and pathologic response to NAC

RC was performed with open surgery, standard laparoscopic surgery, and robotic surgery with lymph node dissection (LND) and urinary diversion. The LND procedures, including removal of the obturator, external iliac, common iliac, and parasacral lymph node chains, were performed basically according to the extended template [23]. RNU was performed through open or laparoscopic retroperitoneal access using a standard procedure consisting of whole kidney dissection, including the perirenal fat with the ureter and adjacent segment of the bladder cuff [24]. The methods used for the LND were inconsistent among surgeons and hospitals, which changed over time. In general, a template-based dissection that was dependent on the tumor location was performed in our collaborative academic hospitals for patients with UTUC [25].

We focused on pathologic response to NAC by comparing pre-NAC cT and post-NAC ypT categories. Patents with ypT less than cT and ypN0 were categorized into the down-staged ypT2≤ group, irrespective of their cN status. Patents with ypT more than cT and those with cTany cN- and ypTany ypN+ were categorized into an up-staged ypT2≤ group. Patients who met neither the down-staged ypT2≤ group nor the up-staged ypT2≤ group were categorized into a no-changed ypT2≤ group.

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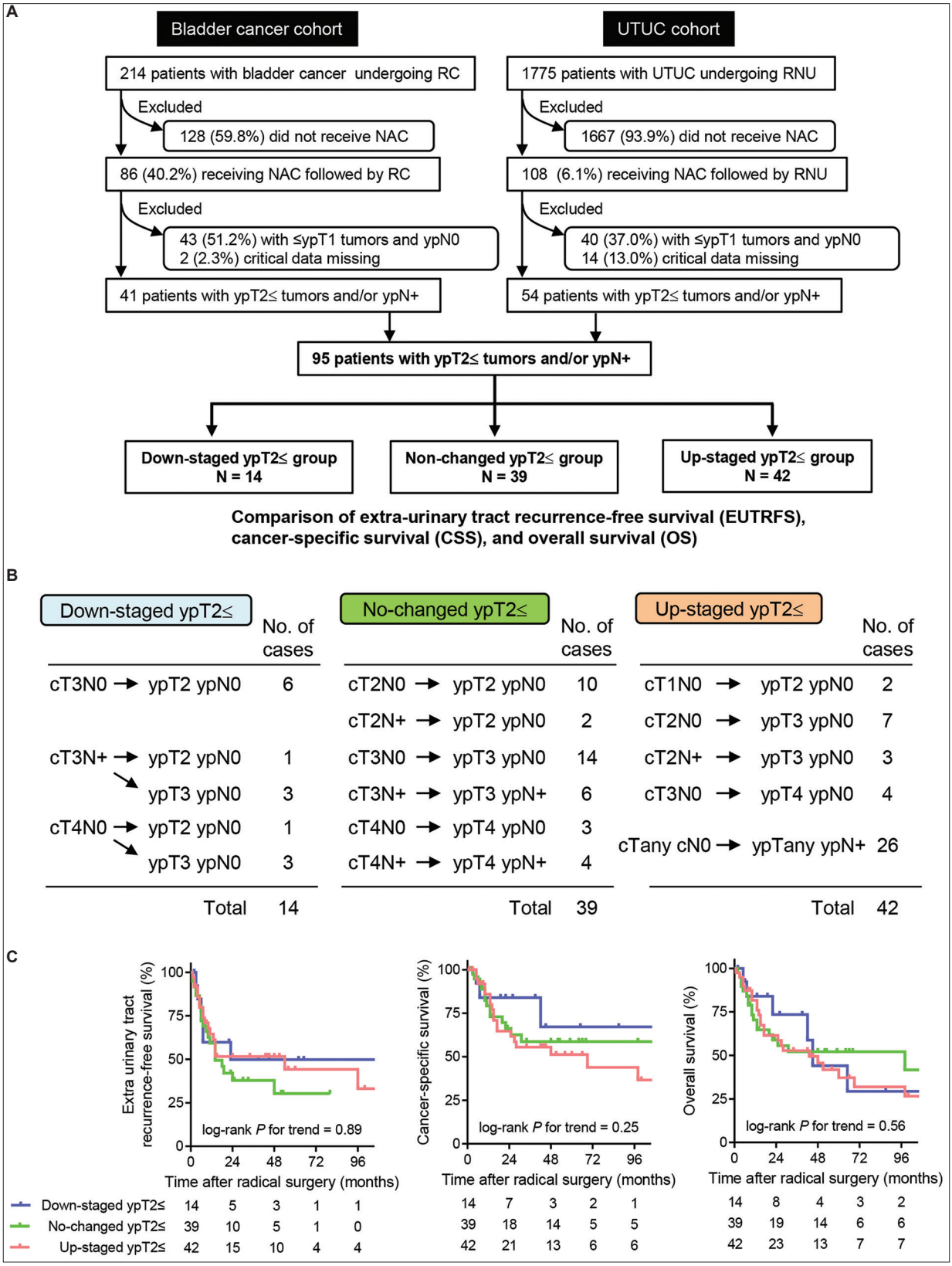

Figure 1. Flow chart for the patient's cohort data sets and schematic design of the study (A). Patterns of pathological response to NAC (B). Event-free survival curves were obtained from the day of radical surgery using the Kaplan–Meier method and compared using the log-rank test for trend (C). This study evaluated three endpoints: Extra-urinary tract recurrence-free survival, cancer-specific survival, and overall survival. Extra-urinary tract recurrence was defined as any recurrence, excluding bladder, upper urinary tract, and urethral recurrences.

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2.4. Follow-up and endpoints

A standard protocol was generally used for the follow-up after RC or RNU: Cystoscopy only for patients undergoing RNU, urinary cytology if needed, and abdominopelvic and chest CT or MRI are performed every 3 months for 2 years, every 6 months until 5 years, and then yearly [1,9]. This study evaluated three endpoints: Extra-urinary tract recurrence-free survival (EUTRFS), CSS, and overall survival (OS). Extra-urinary tract recurrence was defined as any recurrence, excluding bladder, upper urinary tract, and urethral recurrences. While urinary tract recurrence is generally considered non-life-threatening, EUTR includes life-threatening events, such as local recurrence in soft tissue, regional lymph node, or distant organs. Patients who were alive without events were censored at the date of the last follow-up, including the last imaging examination for EUTR and the last visit for cancer-specific death.

2.5. Statistical analysis

Data visualization and statistical analyses were performed using PRISM software version 9 (GraphPad Software, Inc., San Diego, CA, USA). Event-free survival curves from the day of radical surgery were obtained using the Kaplan–Meier method and compared by log-rank test for trend. Variables that potentially affected prognosis ($P < 0.05$) in univariate analysis were included in a step-wise Cox proportional hazards regression model. Regression model. Hazard ratio (HR) with 95% confidence interval (CI) was calculated to identify independent prognostic variables. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Patient characteristics and pathological response to NAC

Clinicopathological characteristics of the 95 patients consisting 41 with bladder cancer and 54 with UTUC are depicted in Table 1. Of note, the number of NAC cycles was 2 or less in 78% of patients with UTUC, while 56% of bladder cancer received three cycles of NAC. According to the pathological response to NAC, 14 (15%), 39 (41%), and 42 (44%) patients were categorized into down-staged ≥ypT2, no-changed ≥ypT2, and up-staged ≥ypT2 groups, respectively. The patterns of pathological response to NAC are shown in Figure 1B. The two most common patterns were cTany cN0 to ypTany ypN+ in 26 patients (up-staged group) and cT3N0 to ypT3 ypN0 in 14 patients (no-changed group).

To investigate possible factors associated with pathological response to NAC, we compared patient characteristics among down-staged ≥ypT2, no-changed ≥ypT2, and up-staged ≥ypT2 groups (Table 2). Sex, clinical T category, and clinical N category were found to be different among groups. More than half of male patients were categorized into the up-staged ypT2≤ group, while more than half of female patients were the no-changed ypT2≤ group. Majority of the patients with clinical N- tumor were categorized into the up-staged ≥ypT2 group. The regimen and cycles of NAC were not different among three groups.

3.2. Association between response to NAC and survival outcomes

There was no significant difference in EUTRFS, CSS, and OS among the three groups (Figure 1C). We performed univariate and multivariate analyses using the Cox proportional hazards regression model to found prognostic factors for EUTRFS, CSS, and OS in patients with ypT2 and/or ypN+ UC after NAC (Table 3). The univariate analysis of EUTRFS showed advanced tumor such as cT4 and ypT4 (*vs.* ypT2; HR = 3.33, $P = 0.009$) were significantly associated with a high risk of disease recurrence, whereas no independent prognostic factor was found in the multivariate analysis. Similar results were seen in the univariate analysis of CSS (ypT4 vs. ypT2; HR = 3.74, $P = 0.02$), and OS (ypT4 vs. ypT2; HR = 2.55, $P = 0.03$). Multivariate analysis was not performed in CSS and OS because the univariate analysis did not show multiple prognostic factors.

Table 1. Characteristic of patients with yielding pathological T2≤ and/or N+ urothelial carcinoma after neoadjuvant chemotherapy

Variables	Overall	Bladder cancer cohort	UTUC cohort
N (%)	95 (100%)	41 (100%)	54 (100%)
Age (years-old), mean±standard deviation	69.3±9.5	69.7±8.8	69.0±10.1
Sex			
Male	73 (77%)	31 (76%)	42 (78%)
Female	22 (23%)	10 (24%)	12 (22%)
ECOG-PS			
0	77 (81%)	37 (90%)	40 (74%)
1	12 (13%)	4 (10%)	8 (15%)
2	2 (2.1%)	0	2 (3.7%)
Unknown	4 (4.2%)	0	4 (7.4%)
Tumor multifocality			
Single	65 (68%)	31 (76%)	34 (63%)
Multiple	25 (26%)	10 (24%)	15 (28%)
Unknown	5 (5.3%)	0	5 (9.3%)

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Table 1. *(Continued)*

Variables	Overall	Bladder cancer cohort	UTUC cohort
Clinical T category			
cT1	6 (6.3%)	0	6 (11%) [#]
cT2	25 (27%)	15 (37%)	11 (20%)
cT3	44 (46%)	14 (34%)	30 (56%)
cT4	14 (15%)	12 (29%)	2 (3.7%)
Unknown	6 (6.3%)	0	6 (11%) [##]
Clinical N category			
cN0	75 (79%)	31 (76%)	44 (82%)
cN+	20 (21%)	10 (24%)	10 (18%)
NAC regimen			
GC	60 (63%)	25 (61%)	35 (65%)
MVAC	11 (12%)	5 (12%)	6 (11%)
Others	24 (25%)	11 (27%)	13 (24%)
The number of NAC cycles			
2 or less	53 (56%)	11 (27%)	42 (78%)
3	28 (29%)	23 (56%)	5 (9.2%)
4	6 (6.3%)	4 (9.7%)	2 (3.7%)
5 or more	4 (4.2%)	0	4 (7.4%)
Unknown	4 (4.2%)	3 (7.3%)	1 (1.8%)
Pathological T category			
ypTis	1 (1.1%)	0	1 (1.9%)
ypT1	5 (5.3%)	2 (4.9%)	3 (5.6%)
ypT2	28 (30%)	13 (32%)	15 (28%)
ypT3	47 (50%)	17 (42%)	30 (56%)
ypT4	14 (15%)	9 (22%)	5 (9.3%)
Pathological N category			
ypN0	57 (60%)	24 (59%)	33 (61%)
ypN+	38 (40%)	17 (41%)	21 (39%)
CIS			
No	80 (84%)	35 (85%)	45 (83%)
Yes	14 (15%)	6 (15%)	8 (15%)
Unknown	1 (1.1%)	0	1 (1.9%)
LVI			
No	41 (43%)	15 (37%)	26 (48%)
Yes	53 (56%)	26 (63%)	27 (50%)
Unknown	1 (1.1%)	0	1 (1.9%)
Variant histology			
No	90 (95%)	38 (93%)	52 (96%)
Yes	5 (5.3%)	3 (7.3%)	2 (3.7%)
Pathological response to NAC			
Down-staged ypT2≤	14 (15%)	6 (15%)	8 (15%)
No-changed ypT2≤	39 (41%)	20 (49%)	19 (35%)
Up-staged ypT2≤	42 (44%)	15 (37%)	27 (50%)

CIS: Carcinoma *in situ*; ECOG-PS: Eastern Cooperative Oncology Group-performance status; LVI: Lymphovascular invasion; GC: Gemcitabine and cisplatin combination chemotherapy; MVAC: Methotrexate, vinblastin, doxorubicin, and cisplatin combination chemotherapy; NAC: Neoadjuvant chemotherapy.
[#]Of six patients with cT1 UTUC, two had ypT2 ypN0 and the remaining four had ypN+ in the nephroureterectomy specimens after NAC;
[##]All six patients with unknown cT UTUC had ypN+ in the nephroureterectomy specimens after NAC

In addition, we conducted a subgroup analysis of the bladder cancer and UTUC cohorts. In 41 patients with bladder cancer (Figure 2), there was a marginal association between better response and longer CSS ($P = 0.073$), not EUTRFS and OS (Figure 2). In the analysis of the UTUC cohort, no difference was observed in EUTRFS, CSS, and OS among the three groups (Figure 3).

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Table 2. Comparison of baseline characteristics according to response to neoadjuvant chemotherapy in patients with yielding pathological T2≤ and/or N+ urothelial carcinoma

Variables	Down-staged ypT2≤	No-changed ypT2≤	Up-staged ypT2≤	*P*-value
N (%)	14 (100%)	39 (100%)	42 (100%)	-
Age (years-old), mean±standard deviation	69.4±6.8	68.3±10.5	70.2±9.4	0.66
Sex				
Male	13 (93%)	25 (64%)	35 (83%)	0.037
Female	1 (7.1%)	14 (36%)	7 (17%)	
ECOG-PS				
0	13 (93%)	32 (82%)	32 (76%)	0.52
1	1 (7.1%)	6 (15%)	5 (12%)	
2	0	0	2 (4.8%)	
Unknown	0	1 (2.6%)	3 (7.1%)	
Multiplicity				
Single	12 (86%)	28 (72%)	25 (60%)	0.29
Multiple	2 (14%)	10 (26%)	13 (31%)	
Unknown	0	1 (2.6%)	4 (9.5%)	
Clinical T category				
cT1	0	0	6 (14%)[#]	0.004
cT2	0	12 (31%)	13 (31%)	
cT3	10 (71%)	20 (51%)	14 (33%)	
cT4	4 (29%)	7 (18%)	3 (7.1%)	
Unknown	0	0	6 (14%)[##]	
Clinical N category				
cN0	13 (93%)	23 (59%)	39 (93%)	0.003
cN+	1 (7.1)	16 (31%)	3 (7.1%)	
NAC regimen				
GC	9 (64%)	30 (77%)	21 (50%)	0.16
MVAC	2 (14%)	3 (7.7%)	6 (14%)	
Others	3 (21%)	6 (15%)	15 (36%)	
The number of NAC cycles				
2 or less	8 (57%)	22 (56%)	23 (55%)	0.72
3	4 (29%)	14 (36%)	10 (24%)	
4	1 (7.1%)	1 (2.6%)	4 (9.5%)	
5 or more	0	1 (2.6%)	3 (7.1%)	
Unknown	1 (7.1)	1 (2.6%)	2 (4.8%)	
Pathological T category				
ypTis	0	0	1 (2.4%)	<0.001
ypT1	0	0	5 (12%)	
ypT2	11 (79%)	12 (31%)	5 (12%)	
ypT3	3 (21%)	20 (51%)	24 (57%)	
ypT4	0	7 (18%)	7 (17%)	
Pathological N category				
ypN0	14 (100%)	28 (72%)	15 (36%)	<0.001
ypN+	0	11 (28%)	27 (64%)	
CIS				
No	11 (79%)	31 (80%)	38 (91%)	0.1
Yes	2 (14%)	8 (20%)	4 (9.5)	
Unknown	1 (7.1%)	0	0	
LVI				
No	6 (42.9)	17 (43.6)	18 (42.9)	0.87
Yes	8 (57.1)	22 (56.4)	23 (54.8)	
Unknown	0	0	1 (2.4)	0.24
Variant histology				
No	14 (100%)	38 (97%)	38 (91%)	
Yes	0	1 (2.6%)	4 (9.5%)	

CIS: Carcinoma *in situ*; ECOG-PS, Eastern Cooperative Oncology Group-performance status; LVI, lymphovascular invasion; NAC, neoadjuvant chemotherapy [#]Of six patients with cT1 UTUC, two had ypT2 ypN0 and the remaining four had ypN+in the nephroureterectomy specimens after NAC; [##]All six patients with unknown cT UTUC had ypN+in the nephroureterectomy specimens after NAC

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Table 3. Prognostic analyses for survival outcomes after neoadjuvant chemotherapy followed by radical surgery in patients with ypT2 and/or ypN+ urothelial carcinoma using Cox proportional hazards regression model.

Variables	EUTRFS, univariate			EUTRFS, multivariate			CSS, univariate			OS, univariate		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age, years												
<70	1						1			1		
≥70	1.40	0.77 – 2.53	0.27				1.47	0.73 – 2.99	0.28	1.59	0.86 – 2.91	0.14
Sex												
Male	1						1			1		
Female	1.04	0.54 – 2.00	0.92				0.74	0.32 – 1.70	0.48	0.56	0.26 – 1.21	0.14
Tumor multifocality												
Single	1						1			1		
Multiple	0.92	0.67 – 1.27	0.61				1.01	0.70 – 1.46	0.95	1.07	0.80 – 1.43	0.65
Clinical T category												
cT1	1			1			1			1		
cT2	1.32	0.36 – 4.89	0.68	1.12	0.30 – 4.2	0.87	0.84	0.21 – 3.38	0.81	0.70	0.24 – 2.11	0.53
cT3	2.42	0.73 – 8.05	0.15	1.73	0.52 – 5.8	0.38	1.43	0.42 – 4.89	0.57	1.02	0.38 – 2.70	0.97
cT4	3.78	1.03 – 13.94	0.046	1.76	0.37 – 8.4	0.48	1.75	0.45 – 6.78	0.42	1.51	0.51 – 4.43	0.45
Clinical N category												
cN0	1						1			1		
cN+	1.36	0.85 – 2.16	0.20				0.90	0.49 – 1.65	0.73	0.80	0.46 – 1.38	0.42
NAC regimen												
GC	1						1			1		
MVAC	1.06	0.76 – 1.49	0.72				1.16	0.78 – 1.72	0.45	1.01	0.71 – 1.43	0.97
The number of NAC cycles												
2 or less	1						1			1		
3 or more	1.14	0.64 – 2.04	0.65				0.79	0.40 – 1.57	0.50	0.75	0.42 – 1.34	0.33
Pathological T category												
ypT2	1			1			1			1		
ypT3	1.60	0.79 – 3.21	0.19	1.49	0.73 – 3.1	0.28	2.35	0.95 – 5.85	0.07	1.25	0.63 – 2.49	0.52
ypT4	3.33	1.36 – 8.18	0.009	2.53	0.71 – 9.0	0.15	3.74	1.25 – 11.17	0.02	2.55	1.11 – 5.86	0.03
Pathological N category												
ypN0	1						1			1		
ypN+	1.18	0.82 – 1.69	0.37				1.17	0.77 – 1.76	0.46	1.04	0.72 – 1.49	0.83
CIS												
Negative	1						1			1		
Positive	0.57	0.24 – 1.35	0.20				0.68	0.26 – 1.80	0.44	1.20	0.65 – 2.22	0.56
LVI												
Negative	1						1			1		
Positive	1.49	0.88 – 2.52	0.14				1.36	0.72 – 2.55	0.34	1.68	0.98 – 2.87	0.057
Variant histology												
Negative	1						1			1		
Positive	1.12	0.35 – 3.61	0.85				1.63	0.50 – 5.36	0.42	1.17	0.36 – 3.77	0.79
Response to NAC												
Down-staged ypT2≤	1						1			1		
No-changed ypT2≤	1.51	0.61 – 3.74	0.38				1.59	0.45 – 5.57	0.47	1.07	0.42 – 2.69	0.89
Up-staged ypT2≤	1.09	0.44 – 2.71	0.86				1.98	0.58 – 6.74	0.27	1.25	0.51 – 3.07	0.63

CIS: Carcinoma in situ; ECOG-PS: Eastern Cooperative Oncology Group-performance status; LVI: Lymphovascular invasion; NAC: Neoadjuvant chemotherapy, #Of six patients with cT1 UTUC, two had ypT2 ypN0 and the remaining four had ypN+ in the nephroureterectomy specimens after NAC; ##All six patietns with unknown cT UTUC had ypN+ in the nephroureterectomy specimens after NAC.

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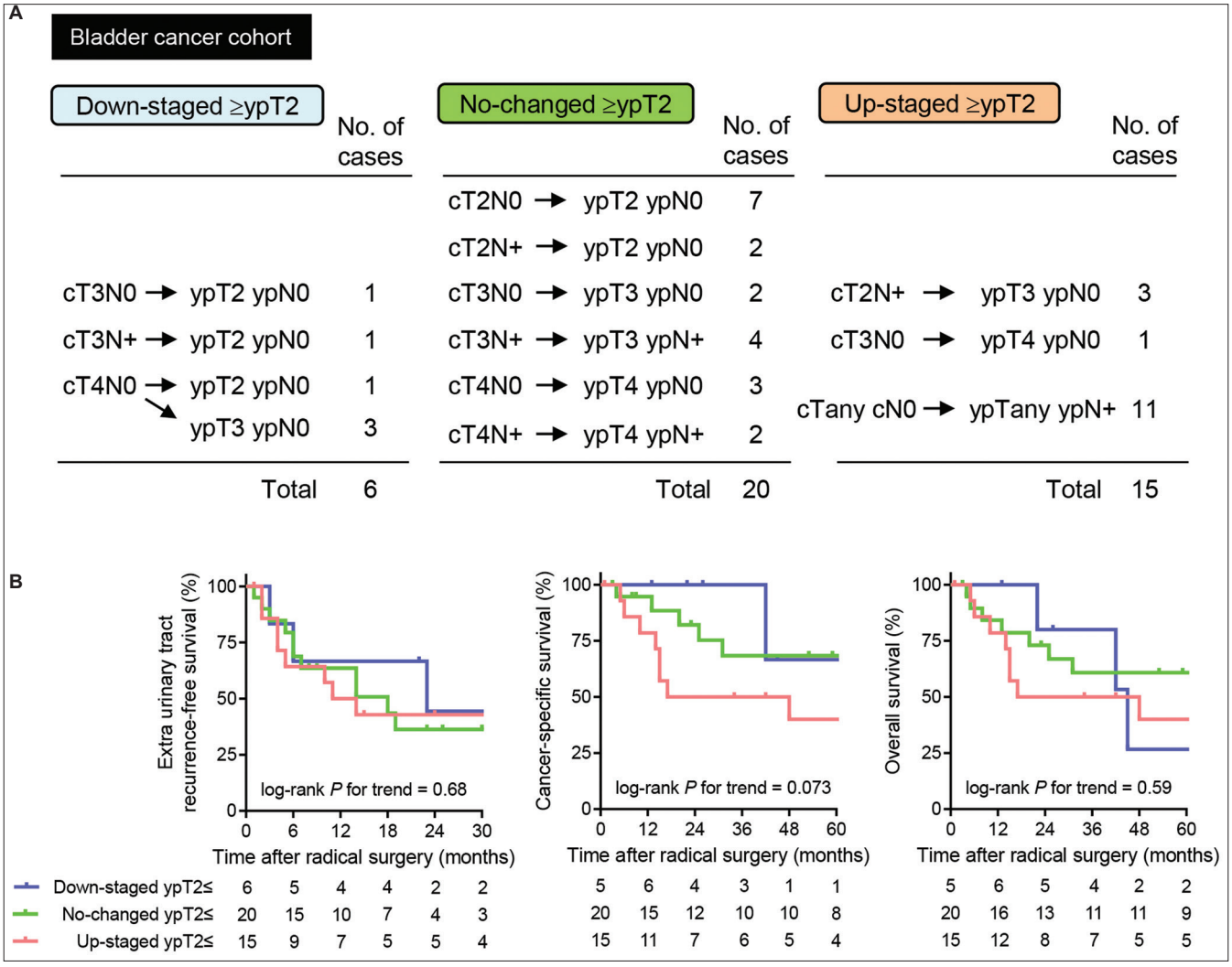

Figure 2. The subgroup analysis of bladder cancer cohort. The patterns of pathological response to neoadjuvant chemotherapy (A). Event-free survival curves were obtained from the day of radical surgery using the Kaplan–Meier method and compared using the log-rank test for trend (B). This study evaluated three endpoints: Extra-urinary tract recurrence-free survival, cancer-specific survival, and overall survival. Extra-urinary tract recurrence was defined as any recurrence, excluding bladder, upper urinary tract, and urethral recurrences.

4. Discussion

In this study, we investigated the potential association between response to NAC and survival after radical surgery in NAC-treated patients with residual MIUC disease and/or ypN+ disease. In contrast to our hypothesis, response to NAC was not significantly associated with favorable outcomes in this subset. However, in the subgroup analysis of the bladder cancer cohort, there was a marginal association between better response and longer CSS ($P = 0.073$). Our finding supports the guideline recommendation (7–9) in which all patients with residual MIUC and/or lymph node tumor are indicated for adjuvant nivolumab therapy. Our finding suggested that adjuvant nivolumab should be considered for all the patients with pathological ypT2≤ or ypN+ UC regardless of response to NAC.

The rationale for prior chemotherapy approach following ICI in the management of UC has been reported to date [26]. The prior chemotherapy can sensitize the tumor cells to ICIs through potential molecular mechanisms, including (i) enhancement of neo-antigen release; (ii) alteration of cytokine composition of the immunogenic tumor microenvironment toward antigen presentation and cytotoxic T cell infiltration; (iii) downregulation of immune-suppressing cells, such as myeloid-derived suppressor cells; and (iv) upregulation of PD-L1 expression on tumor cells [25]. This process is essential to prime tumor cells for an immune response, and it enhances anti-tumor activity of ICI drugs. Unfortunately, the CheckMate 274 trial has not yet updated data regarding response to NAC and benefit of adjuvant nivolumab (14). One of the biggest limitations of this study is that the cohorts did not include any patients who received adjuvant nivolumab. However, our group [27] and the Japanese Urological Oncology Research Group demonstrated a positive correlation between response to the following ICI (pembrolizumab) and response to previous chemotherapy in patients with advanced/metastatic

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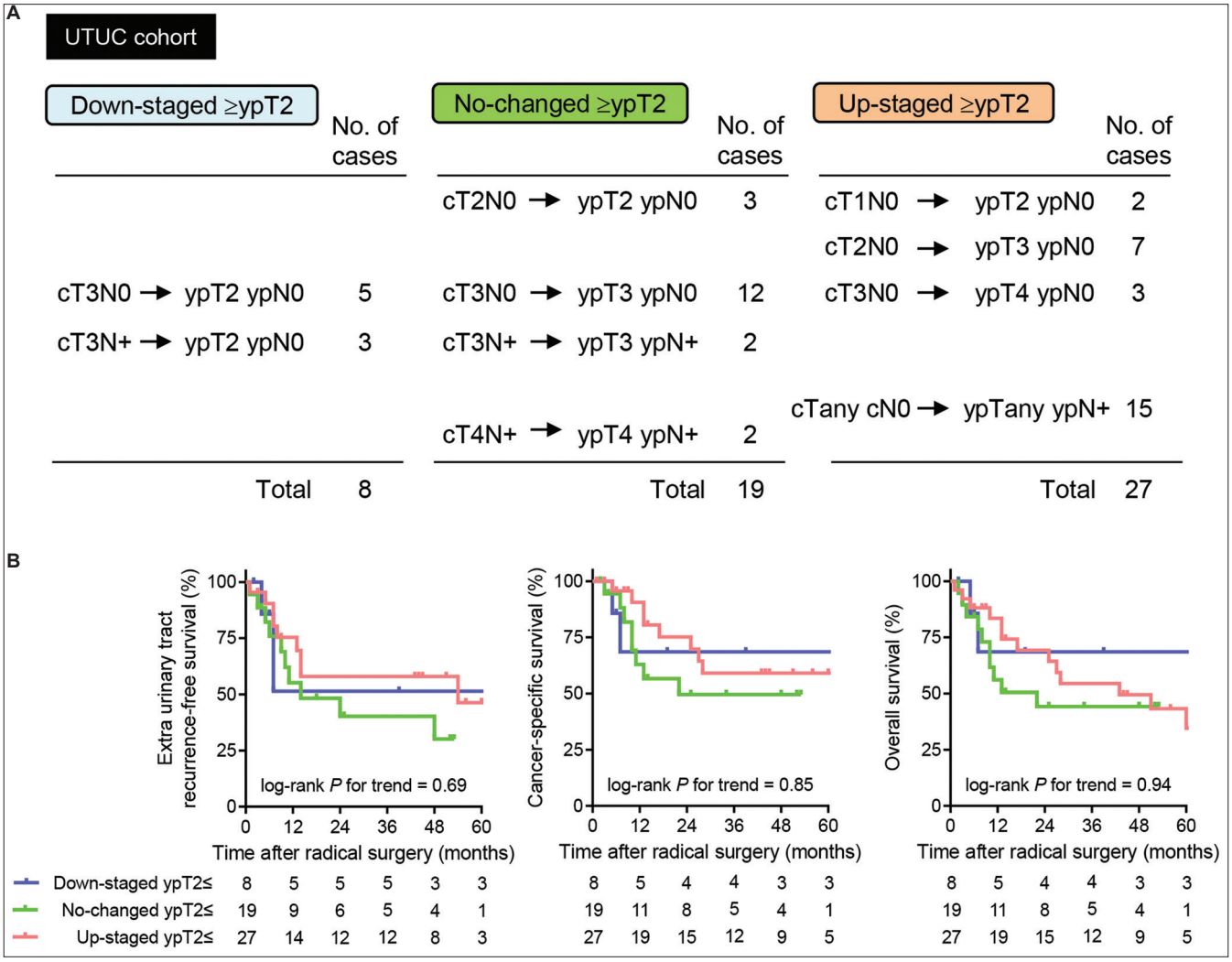

Figure 3. The subgroup analysis of the upper urinary tract urothelial carcinoma cohort. The patterns of pathological response to neoadjuvant chemotherapy (A). Event-free survival curves were obtained from the day of radical surgery using the Kaplan–Meier method and compared using the log-rank test for trend (B). This study evaluated three endpoints: Extra-urinary tract recurrence-free survival, cancer-specific survival, and overall survival. Extra-urinary tract recurrence was defined as any recurrence, excluding bladder, upper urinary tract, and urethral recurrences.

UC [27,28]. Considering these findings, response to NAC may provide a positive effect on adjuvant nivolumab.

The previous study showed that patients aged 70-year-old or more who underwent RNU for localized UTUC had worse outcomes compared to younger patients, concluding that older patients need an improved care and management to improve their outcomes [29]. Similarly, our cohort showed that patients aged 70-year-old or more had worse EUTRFS, CSS, and OS as compared to patients aged less than 70-year-old (Table 3). Substantial population of patients with UC are elderly and vulnerable, and ICIs can cause divergent immune-related adverse events, which are sometimes serious and lethal, requiring high-dose steroids [14-18]. Therefore, predicting positive efficacy of ICI before start of the treatment is vital to develop precision medicine in this medical field. Ferro *et al.* performed a large-scale systematic review and meta-analysis to find predictors of efficacy of ICIs in patients with advanced UC [30]. The quantitative analysis of 6524 patients demonstrated that no visceral metastatic lesion (HR = 0.67; 95% CI, 0.76 − 0.90) and high PD-L1 expression (HR = 0.74; 95% CI, 0.64 − 0.87) were significantly associated with favorable prognosis in risk of death. According to the subgroup analysis of CheckMate 274 trial, PD-L1 expression level at baseline associated with better disease-free survival in patients treated with adjuvant nivolumab as compared to the placebo as follow: HR 0.67 (95% CI, 0.40 − 0.80) in 1% ≤ PD-L1 tumor expression and HR 0.82 (95% CI, 0.63 − 1.06) in 1% > PD-L1 tumor expression [14]. The usefulness of PD-L1 expression level could not be validated in our study because PD-L1 expression level was not available and no patient was treated with nivolumab.

This study has other limitations. Accurate clinical staging before NAC is vital to determine the pathological response to NAC, especially in the UTUC cohort. The previous report evaluated the concordance between the ureteroscopy-based clinical T category and pathological T category, concluding concordant rate was 34.5%

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(208 out of 603 patients with UTUC) [31]. Discordance between the clinical TN category and pathological TN category was not avoidable in this study design. The retrospective study design has an inherent potential for selection bias, and the decision criteria for the implementation of NAC, chemotherapy regimen, timing of changing the treatment, and interval of radiographic evaluation were dependent on the institutional protocol and physician's discretion. The cohort was derived from multiple institutions, which may have introduced inconsistencies in surgical skills, clinical interpretation, and pathological diagnoses. The treatment strategy, modality, especially approval of gemcitabine plus platinum combination chemotherapy and advent of ICIs, and surgical skill change over time may have influenced outcomes. We did not include NAC-induced histological changes in the analysis, because only one patient with MIBC showed downgrading from high-grade UC in the transurethral resection specimens to low-grade UC in the radical surgery specimen. Lastly, statistical power may be limited due to the small number of patients and events in some subgroups.

We suggest that it is vital to select NAC-treated patients with residual MICU and/or lymph node disease who have a low risk of EUTR and a high risk of adverse events and financial toxicity for adjuvant nivolumab. The transurethral resection specimens and radical surgery specimens are easy to access after surgery. Based on the subgroup analysis of CheckMate 274 [14], the tumor positive score (cutoff, ≥1% or <1%) evaluated with anti-PD-L1 antibody (28-8 pharmDx, DAKO) can be a predictive biomarker. Not only assessment of tumor immune microenvironment including the extent of pro-tumoral inflammation and anti-tumoral inflammation but also molecular subtyping would be helpful to determine the accurate phenotyping and genotyping of MIUC. Routine clinical testing of immune checkpoint molecules, *for example*, PD-1 and PD-L1, and molecular subtyping with luminal markers such as GATA3, CK20, and p16 and basal type markers such as CK5/6 and CK20 should be considered for making decisions on perioperative systemic therapy in ICI era. Therefore, data accumulation is mandatory in finding predictive factors that are useful in decision-making for NAC-treated patients who are likely to benefit from adjuvant nivolumab.

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Conflicts of Interest

Nothing to declare.

Ethics Approval and Consent to Participate

This retrospective multicenter study was approved by the Ethics Committee of each participating institute (reference ID: 1298, 1958, 2891, H30-048, and 2018-036) of the Nishinihon Uro-Oncology Collaborative Group framework. Informed consent was obtained from the participants or bereaved families through posters and/or websites using opt-out method.

Consent for Publication

Not applicable.

Availability of Data

The data underlying this article will be shared on reasonable request to the corresponding author.

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