Two cycles of neoadjuvant chemotherapy improves survival of upper tract urothelial carcinoma patients

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Introduction and Objectives

Upper tract urothelial carcinoma (UTUC) is frequently upstaged after surgery and is associated with poor prognosis. However, the efficacy of neoadjuvant chemotherapy (NAC) and optimal No. of NAC cycles for UTUC have been poorly defined. In this study, we evaluated if two cycles of NAC improves clinical outcomes of high-risk cN0M0 UTUC patients in our institute.

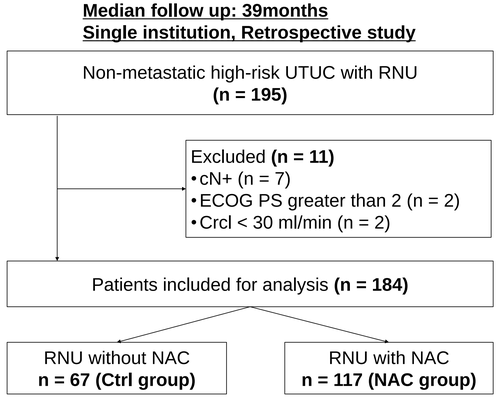
Materials and Methods

A total of 184 patients who received radical nephroureterectomy (RNU) at Fujita Health University between 2005 and 2018 were retrospectively analyzed (Figure 1A). The study group comprised 117 patients with UTUC who received 2 cycles of platinum-based NAC (Figure 1B) followed by surgery. The control group consisted of 67 patients who underwent initial surgery without NAC. We compared two groups in demographics, overall survival (OS), cancer specific survival (CSS), recurrence free survival (RFS, visceral) and independent prognostic factors. Kaplan-Meier methods, log-rank test and cox proportional hazard regression models were used for statistical analysis. Pathological downstaging (pDS) was defined as a pathologic tumor stage that was at least one stage lower than the pre-NAC clinical stage.

Study design

Figure 1. Patient selection flow diagram, NAC regimen and perioperative renal function

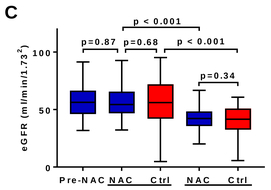
A



B

No. NAC regimen (%), n = 117	
MVAC	17 (14.5)
GCis	90 (76.9)
GCb	10 (8.6)
No. of NAC cycles	
Median ± SD (range)	2 ± 0.2 (1-2)

C



Results

Table 1. Patient characteristics

Characteristic	Total (n = 184)	Ctrl (n = 67)	NAC (n = 117)	*P* value
Age (Median, IQR), y	72 [65-77]	73 [65-79]	71 [65-77]	0.182
Sex, n (%)				
Male	136 (73.9)	46 (68.7)	90 (76.9)	0.227
Female	48 (26.1)	21 (31.3)	27 (23.1)	
ECOG PS, n (%)				
0	172 (93.5)	62 (92.5)	110 (94.0)	0.562
1	12 (6.5)	5 (7.5)	7 (6.0)	
Tumor location, n (%)				
Renal pelvis	81 (44.0)	29 (43.3)	52 (44.4)	0.619
Ureter	113 (56.0)	38 (56.7)	65 (55.6)	
Hydronephrosis, n (%)				
No	77 (41.8)	33 (49.3)	44 (37.6)	0.162
Yes	107 (58.2)	34 (50.7)	73 (62.4)	
History of bladder cancer, n (%)				
No	138 (75.0)	49 (73.1)	89 (76.1)	0.724
Yes	46 (25.0)	18 (26.9)	28 (23.9)	
Multifocality, n (%)				
No	123 (66.8)	43 (64.2)	80 (68.4)	0.237
Yes	68 (33.2)	31 (35.8)	37 (31.6)	
eGFR (ml/min/1.73m^2), mean ± SD				
Before NAC			57.4 ± 14.3	
Before surgery	56.8 ± 16.3	56.1 ± 19.7	57.1 ± 14.1	0.728
After surgery	41.7 ± 10.3	40.7 ± 11.7	42.3 ± 9.5	0.656
Adjuvant chemotherapy, n (%)				
No	156 (84.8)	55 (82.1)	101 (86.3)	0.523
Yes	28 (15.2)	12 (17.9)	16 (13.7)	

Table 2. Tumor characteristics

Characteristic	Total (n = 184)	Ctrl (n = 67)	NAC (n = 117)	*P* value
Clinical T stage, n (%)				
cTis/Ta	5 (2.7)	3 (4.5)	2 (1.7)	0.238
cT1	62 (33.7)	24 (35.8)	38 (32.5)	
cT2	82 (44.6)	28 (41.8)	54 (46.2)	
cT3	35 (19.0)	12 (17.9)	23 (19.6)	
Pathological T stage, n (%)				
pT0	5 (2.7)	0 (0)	5 (4.3)	0.185
pTis/a	35 (19.0)	13 (19.4)	22 (18.8)	
pT1	56 (30.4)	16 (23.9)	40 (34.2)	
pT2	36 (19.6)	12 (17.9)	24 (20.5)	
pT3	45 (24.5)	23 (34.3)	22 (18.8)	
pT4	7 (3.8)	3 (4.5)	4 (3.4)	
Pathological N stage, n (%)				
pN0	176 (95.6)	64 (95.5)	112 (95.7)	0.713
pN1	8 (4.4)	3 (4.5)	5 (4.3)	
Concomitant CIS, n (%)				
No	168 (91.3)	62 (92.4)	106 (90.6)	0.707
Yes	16 (8.7)	5 (7.6)	11 (9.4)	
Lymphovascular invasion, n (%)				
No	118 (64.1)	36 (53.7)	82 (70.1)	**0.045**
Yes	66 (35.9)	31 (46.3)	35 (29.9)	
Surgical margins status, n (%)				
Negative	177 (96.2)	63 (94.0)	114 (97.4)	0.259
Positive	7 (3.8)	4 (6.0)	3 (2.6)	
Pathological downstaging, n (%)				
No	113 (61.4)	52 (77.6)	61 (52.1)	**0.006**
Yes	71 (38.6)	15 (22.4)	56 (47.9)	

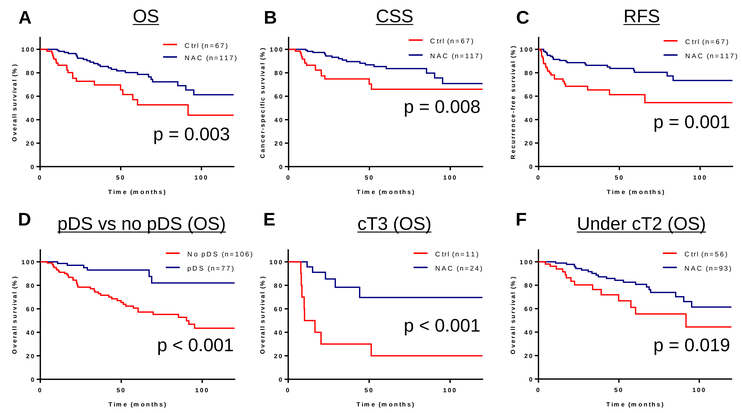
Table 3. Multivariable Cox regression models for OS

	Univariable		Multivariable		Multivariable (IPTW model)	
Variable	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age	1.037 (1.002-1.073)	0.037	1.046 (1.006-1.086)	0.023	1.042 (0.998-1.087)	0.059
Male gender	1.295 (0.624-2.691)	0.488			1.472 (0.670-3.234)	0.335
ECOG PS						
0	1 (reference)					
1	1.943 (0.764-4.937)	0.163			1.240 (0.366-4.196)	0.729
cT stage						
cT≤1	1 (reference)					
cT2	1.100 (0.546-2.216)	0.790			1.244 (0.575-2.690)	0.579
cT3	2.570 (1.226-5.386)	0.012	2.074 (0.829-5.185)	0.119	3.580 (1.509-8.495)	**0.004**
Tumor location						
Renal pelvis	1 (reference)					
Ureter	0.773 (0.430-1.387)	0.388			1.021 (0.511-2.041)	0.952
LVI+	3.659 (1.996-6.705)	<0.001	2.215 (0.954-5.142)	0.064	2.521 (1.021-6.223)	**0.045**
RM+	4.424 (1.559-12.56)	0.005	4.268 (1.410-12.93)	0.010	4.680 (1.516-14.45)	**0.007**
pN+	4.913 (2.071-11.66)	<0.001	9.236 (3.369-25.32)	<0.001	9.118 (3.165-26.27)	**<0.001**
pDS	0.214 (0.091-0.508)	<0.001	0.372 (0.145-0.955)	0.039	0.269 (0.112-0.651)	**0.003**
NAC	0.417 (0.231-0.754)	0.003	0.493 (0.261-0.931)	0.029	0.468 (0.245-0.892)	**0.021**
AC	1.562 (0.773-3.160)	0.214				

Table 4. Multivariable Cox regression models for OS in NAC group

	Univariable		Multivariable		Multivariable (IPTW model)	
Variable	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age	1.028 (0.978-1.080)	0.269			1.045 (0.979-1.116)	0.182
Male gender	3.856 (0.908-16.37)	0.067			5.385 (1.215-23.87)	0.026
ECOG PS						
0	1 (reference)				1 (reference)	
1	0.971 (0.130-7.239)	0.977			2.075 (0.217-19.77)	0.525
cT stage						
cT≤1	1 (reference)				1 (reference)	
cT2	1.875 (0.751-4.679)	0.178			0.981 (0.354-2.717)	0.971
cT3	2.317 (0.744-7.216)	0.147			2.049 (0.566-7.414)	0.274
Tumor location						
Renal pelvis	1 (reference)				1 (reference)	
Ureter	0.557 (0.250-1.244)	0.153			1.169 (0.446-3.067)	0.750
LVI+	5.404 (2.352-12.42)	<0.001	3.987 (1.521-10.45)	0.004	5.862 (2.140-16.06)	**<0.001**
RM+	8.378 (1.829-38.38)	0.006	4.435 (0.925-21.25)	0.062		
pN+	4.664 (1.586-13.72)	0.005	3.326 (1.105-10.01)	0.032	3.457 (0.936-12.75)	0.062
pDS	0.317 (0.118-0.850)	0.022	0.747 (0.242-2.299)	0.611		
NAC regimen						
MVAC	1 (reference)					
GCis	0.932 (0.362-2.400)	0.8843				
GCb	1.668 (0.322-8.644)	0.5420				
NAC cycles						
1	1 (reference)					
2	1.334 (0.553-3.216)	0.526				
AC	2.103 (0.960-4.524)	0.17				

Figure 2. Oncological outcomes



Summary

- There were no significant differences between the two groups in baseline characteristics and perioperative renal function (Table 1, Figure 1C).
- Significantly lower LVI was observed in the NAC group than the Ctrl group (Table 2).
- pDS rate was 48% in the NAC group which was significantly higher than 22% in the Ctrl group (Table 2).
- The NAC group showed significantly better 5-year OS (79% vs 53%; p = 0.003), 5-year CSS (84% vs 66%; p = 0.008) and 5-year RFS (80% vs 61%; p = 0.001) compared to Ctrl group (Figure 2A, 2B, 2C).
- Comparison of OS between with pDS and without pDS demonstrated significantly better OS in with pDS group (p=<0.001) (Figure.2D).
- Although NAC showed more obvious OS benefit in cT3 patients, also improved OS in under cT2 patients (Figure 2E, 2F).
- Multivariate cox proportional hazards models identified cT3, LVI+, RM+, pN+, NAC and pDS as independent prognostic factors for OS. (Table 3).
- LVI after NAC was identified as predictor in NAC group.

Conclusions

- Two cycles of NAC induced pDS and improved survival of high-risk cN0M0 UTUC patients.
- Reduced number of NAC cycles may offer clinical benefits of low chemo-associated toxicity, appropriate surgery without delay in chemo-resistant case and sufficient cancer regression with pDS.
- Further prospective studies are needed to identify the clinical benefit of NAC and optimal number of NAC cycles for UTUC.

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