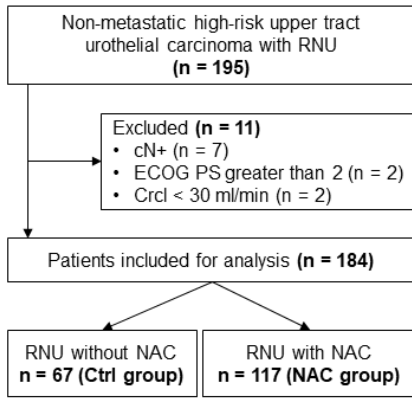


Supplementary figure S1. Patient selection flow diagram, NAC regimen and perioperative renal function

A



B

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

C

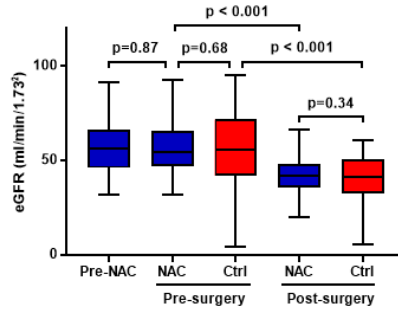
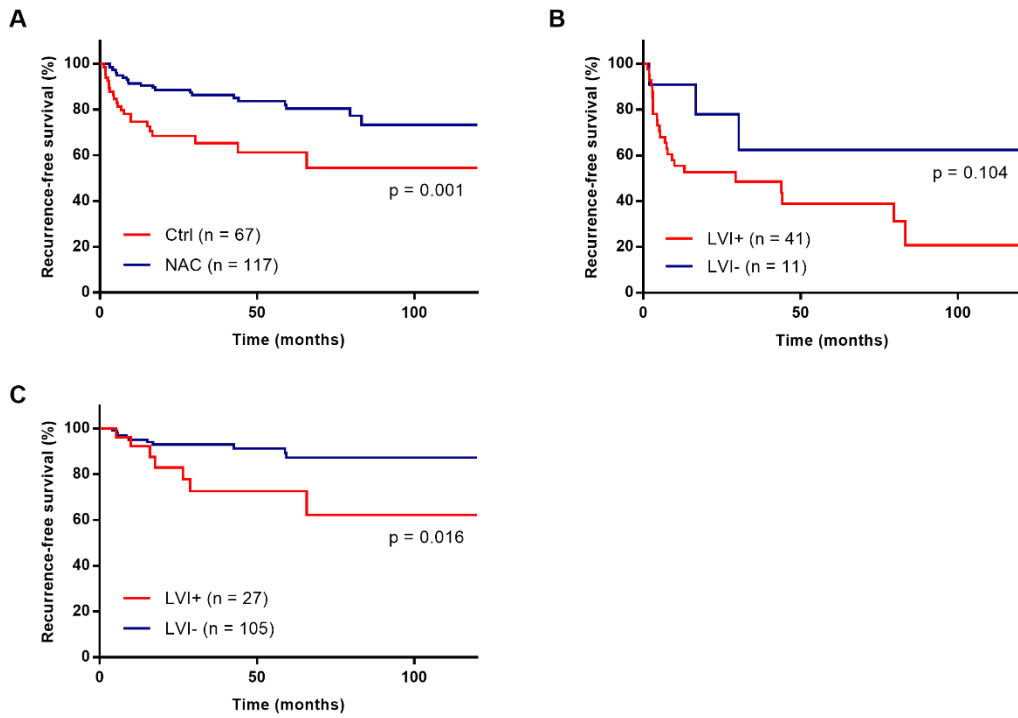


Figure S2. Oncological outcomes in subgroup analyses. (A) RFS in patients who received NAC or initial surgery without NAC. (B) RFS in patients with pT3 or higher disease. (C) RFS in patients with pT2 or lower disease.



Supplementary Table S1. Neoadjuvant chemotherapy related adverse events (CTCAE v4.0)

Adverse events	All	Grade ≥ 3
Neutropenia	98 (84%)	48 (41%)
Thrombocytopenia	96 (82%)	15 (13%)
Anemia	78 (67%)	8 (7%)
Nausea	88 (75%)	0 (0%)
Skin rash	7 (6%)	1 (0.8%)
Cre increased	10 (8.5%)	0 (0%)
Oral ulcer	3 (5.9%)	0 (0%)
Others	8 (6.8%)	0 (0%)

Supplementary Table S2. 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)	
Time frame of recruitment, n (%)				
2005–2009	38	13 (19.4)	25 (21.4)	0.347
2010–2014	67	23 (34.3)	44 (37.6)	
2015–2019	79	31 (46.3)	48 (41.0)	
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)	
Surgical approach, n (%)				
Open	23 (12.5)	9 (13.4)	14 (11.9)	0.819
Laparoscopic	161 (87.5)	58 (86.6)	103 (88.1)	
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
AC, n (%)				
No	156 (84.8)	55 (82.1)	101 (86.3)	0.523
Yes	28 (15.2)	12 (17.9)	16 (13.7)	

ECOG PS, Eastern Cooperative Oncology Group performance status; NAC, neoadjuvant chemotherapy; AC, adjuvant chemotherapy.

Supplementary Table S3. Cox proportional hazard regression models for recurrence free survival

Variable	Univariate		Multivariate		Multivariate (IPTW model)	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Age	1.020 (0.986-1.054)	0.249			1.016 (0.981-1.053)	0.372
Male sex	0.940 (0.473-1.866)	0.860			1.238 (0.612-2.504)	0.553
ECOG PS						
0	1 (reference)					
1	1.131 (0.349-3.658)	0.837			1.128 (0.298-4.266)	0.859
Clinical T stage						
cT1 or lower	1 (reference)					
cT2	1.835 (0.849-3.961)	0.122			1.589 (0.648-3.895)	0.311
cT3	3.858 (1.701-8.750)	0.001	2.996 (1.183-7.588)	0.020	3.716 (1.342-10.29)	0.012
Tumor location						
Renal pelvis	1 (reference)					
Ureter	1.035 (0.566-1.889)	0.912			1.727 (0.863-3.458)	0.123
Open approach	1.799 (0.833-3.886)	0.135			0.954 (0.403-2.256)	0.914
LVI+	5.161 (2.685-9.917)	<0.001	2.343 (1.063-5.164)	0.034	2.771 (1.220-6.293)	0.015
pDS	0.165 (0.064-0.419)	<0.001	0.250 (0.093-0.672)	0.006	0.251 (0.092-0.686)	0.007
pCR	0.743 (0.102-5.410)	0.769				
NAC	0.373 (0.204-0.682)	0.001	0.415 (0.224-0.769)	0.005	0.475 (0.251-0.896)	0.022
AC	1.924 (0.745-3.723)	0.138				

ECOG PS, Eastern Cooperative Oncology Group performance status; LVI, lymphovascular invasion; pDS, pathological downstaging; pCR, pathological complete response; NAC, neoadjuvant chemotherapy; AC, adjuvant chemotherapy.

Supplementary Table S4. Cox proportional hazard regression models for cancer specific survival

Variable	Univariate		Multivariate		Multivariate (IPTW model)	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Age	1.021 (0.983-1.061)	0.276			1.021 (0.976-1.067)	0.355
Male sex	1.182 (0.513-2.725)	0.695			1.860 (0.775-4.464)	0.164
ECOG PS						
0	1 (reference)					
1	0.999 (0.238-4.182)	0.998			1.440 (0.271-7.650)	0.669
Clinical T stage						
cT1 or lower	1 (reference)					
cT2	1.411 (0.589-3.380)	0.440			0.713 (0.251-2.031)	0.527
cT3	3.883 (1.622-9.295)	0.002	1.825 (0.674-4.942)	0.236	2.013 (0.622-6.512)	0.243
Tumor location						
Renal pelvis	1 (reference)					
Ureter	0.844 (0.426-1.670)	0.626			1.844 (0.773-4.399)	0.167
Open approach	1.963 (0.975-4.250)	0.097			1.433 (0.548-3.747)	0.462
LVI+	8.123 (3.514-18.78)	<0.001	4.782 (1.746-13.10)	0.002	6.723 (2.224-20.32)	<0.001
pDS	0.137 (0.042-0.449)	<0.001	0.280 (0.081-0.874)	0.035	0.310 (0.087-0.951)	0.044
pCR	0.969 (0.131-7.161)	0.976				
NAC	0.375 (0.189-0.746)	0.005	0.495 (0.246-0.897)	0.038	0.505 (0.276-0.953)	0.045
AC	1.823 (0.851-3.101)	0.119				

ECOG PS, Eastern Cooperative Oncology Group performance status; *LVI*, lymphovascular invasion; *pDS*, pathological downstaging; *pCR*, pathological complete response; *NAC*, neoadjuvant chemotherapy; *AC*, adjuvant chemotherapy.

Supplementary Table S5. Association of LVI with pathological characteristics

Characteristic	Total (n = 184)	LVI- (n = 116)	LVI+ (n = 68)	<i>P</i> value
Pathological T stage, n (%)				
pT0	5 (2.7)	5 (100)	0 (0)	<0.001
pTis/a	35 (19.0)	34 (97.2)	1 (2.8)	
pT1	56 (30.4)	50 (89.3)	6 (10.7)	
pT2	36 (19.6)	16 (44.4)	20 (55.6)	
pT3	45 (24.5)	11 (24.4)	34 (75.6)	
pT4	7 (3.8)	0 (0)	7 (100)	
Pathological N stage, n (%)				
pN0 or Nx	176 (95.6)	114 (64.8)	62 (35.2)	0.053
pN1	8 (4.4)	1 (12.5)	7 (87.5)	
Pathological downstaging, n (%)				
No	113 (61.4)	55 (48.7)	58 (51.3)	0.006
Yes	71 (38.6)	61 (85.9)	10 (14.1)	