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

A
Non-metastatic high-risk upper tract urothelial carcinoma with RNU (n = 195)

Excluded (n = 11)
- cN+ (n = 7)
- ECOG PS greater than 2 (n = 2)
- CrCl < 30 ml/min (n = 2)

Patients included for analysis (n = 184)

RNU without NAC n = 87 (Ctrl group)
RNU with NAC n = 117 (NAC group)

B

| No. NAC regimen (%) | n = 117 |
|---------------------|---------|
| MVAC               | 17 (14.5) |
| GCis               | 90 (78.0) |
| GCb                | 10 (8.6)  |

No. NAC cycles
Median ± SD (range)
2 ± 0.2 (1.2)

C

Graph showing eGFR (ml/min 1.73m²) before and after NAC and control groups, with p-values for comparisons.
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.
| 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/1.73m²), 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 HR (95% CI) | P     | Multivariate HR (95% CI) | P     | Multivariate (IPTW model) HR (95% CI) | P     |
|-------------------|------------------------|-------|--------------------------|-------|--------------------------------------|-------|
| 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.
| Variable               | Univariate HR (95% CI) | P  | Multivariate HR (95% CI) | P  | Multivariate (IPTW model) HR (95% CI) | P  |
|------------------------|------------------------|----|--------------------------|----|--------------------------------------|----|
| 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) | P 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)     |         |