Influence of American Society of Anesthesiologists Score on Oncologic Outcomes in Patients With Upper Tract Urothelial Carcinoma After Radical Nephroureterectomy: A Large-Sample Study in Two Institutions

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Introduction: As a research team of urologists and an anesthetist, we sought to investigate the prognostic significance of American Society of Anesthesiologists (ASA) score in patients with upper tract urothelial cancer (UTUC) after radical nephroureterectomy (RNU). ASA physical status (ASA-PS) classification not only was found to be associated with increased comorbidities but also independently factors for predicting morbidity and mortality. Accurate risk assessment was being particularly important for patients being considered for surgery.

Methods: Records for 958 patients with UTUC who underwent RNU were reviewed. Clinicopathologic variables, including ASA-PS, were assessed at two institutions. Overall survival (OS), cancer-specific survival (CSS), intravesical recurrence-free survival (IRFS), and metastasis-free survival (MFS) were estimated using the Kaplan–Meier method and Cox regression analyses. We measured the independent predictive value of ASA-PS for mortality by multivariate regression. Association of ASA-PS and clinicopathologic variables was assessed.

Results: The group of patients with ASA = 2/3 had a shorter 5-year OS (67.6% and 49.9%), CSS (72.9% and 58.1%), and MFS (75.1% and 58.5%). The median follow-up time was 39 months. Kaplan–Meier curves showed that the group with ASA = 2/3 had significantly poorer OS, CSS, and MFS (p = 0.004, p = 0.005, p < 0.001).
**INTRODUCTION**

Although radical nephroureterectomy (RNU) with bladder cuff excision is considered the gold standard for the treatment of upper tract urothelial cancer (UTUC), distant relapses are common for locally advanced high-grade disease. UTUC is the most aggressive malignant tumor of the urinary system (1); 30% of patients demonstrate invasive and/or locally advanced disease, 30%–40% have regional lymph node (LN) involvement, and 20% have metastatic disease (2, 3). The 5-year cancer-specific survival (CSS) ranging from 50% to 80% is for UTUC patients who underwent RNU (4, 5). It is of great significance to establish effective prediction methods to assist clinicians in making treatment decisions and follow-up strategies. For UTUC patients, pathological stage, tumor grade, lymph node metastasis, and tumor multifocality are known to be well-established prognostic factors (6–8). Potential prognostic preoperative factors would benefit outcome prediction and individual patient treatment choices.

American Society of Anesthesiologists physical status (ASA-PS) classification, as a standardized way for anesthesiologists to convey information about the patient’s overall health status, allows outcomes to be stratified by a global assessment. It was first introduced in 1940 and has been updated. Nowadays, ASA-PS classification includes a 6-point scale (Table 1). It has been demonstrated as a significant prognostic factor for the treatment outcome of bladder cancer (9), hepatocellular cancer (10), and endometrial cancer (11). Given the positive effects of the RNU on clinical benefits, it is reasonable to speculate that the magnitude and the impact of established morbidity predictors may be altered in UTUC patients undergoing RNU.

For the purpose of investigating the influence of ASA scores on the long-term oncologic outcomes in patients diagnosed with UTUC, we set up several endpoints including overall survival (OS), CSS, intravesical recurrence-free survival (IRFS), and metastasis-free survival (MFS) and utilized the clinical data of 958 UTUC patients who underwent RNU in two Chinese institutions.

**METHODS**

**Patients**

Patients with one of the following conditions were excluded: (1) incomplete clinical or pathological data; (2) underwent neoadjuvant chemotherapy or radiotherapy; (3) non-primary UTUC; (4) preoperative distant metastasis; (5) presence of other tumor types. Additionally, when computed tomography urography or other imaging examinations could not provide enough information to help clinicians make a definite diagnosis, diagnostic ureteroscopy with or without biopsy was used. In our study, 518 patients underwent diagnostic ureteroscopy. Information on 958 patients’ clinical and pathological features, including ASA score, gender, age, tumor location and size, smoking history, hydronephrosis, concomitant non-muscle invasive bladder cancer (NMIBC) or history of NMIBC, surgical methods, tumor grade and pathological stage, lymph node metastasis, tumor architecture and differentiation, lymphovascular invasion (LVI), multifocality and history of adjuvant chemotherapy (AC), was collected from Renji Hospital and Second Affiliated Hospital, Zhejiang University School of Medicine. This study was approved by the institutional review board, and approval number was 2020-369. Pathological stage was uniformly adjusted with reference to the 2017 TNM classification system (12). The histological grade was assessed according to the 2016 WHO consensus classification (13). Tumor multifocality was defined as the synchronous presence of multiple tumors in the renal pelvis or ureter. ASA score was used to assess the physical status of patients before RNU. Patients after surgery were followed up by telephone and outpatient.

**Follow-Up**

The study endpoints were OS, CSS, IRFS, and MFS. According to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines, patients were assessed by computed tomography and/or magnetic resonance imaging to detect any findings suspected of disease progression every 3–4 months in the first year after surgery, every 6 months from the second through fifth year, and annually thereafter. In addition, history taking, physical examination, routine blood and serum chemistry lab work, urinary cytology, chest radiography, and cystoscopy were also included. OS was defined as the period from the date of surgery to patient death from any cause. CSS was defined as the time in months from date of surgery to cancer-related death. The
cause of death was determined by the treating physicians and institutional cancer registries, by chart review corroborated by death certificates, or by death certificates alone. IRFS was defined as the time in months from the date of surgery to bladder recurrence. MFS was defined as the time in months from date of surgery to tumor metastasis.

Statistical Method
Statistical tests were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Proportions of the variables were analyzed using the chi-square test. Variables that had a univariate association with OS, CSS, IRFS, and MFS (p < 0.05) were included in the multiple Cox regression model. Hazard ratio (HR) and 95% CI were presented for selected items. Kaplan–Meier method with the log-rank test was used to assess OS, CSS, IRFS, and MFS. Multivariate analysis was conducted using Cox regression model to evaluate ASA-PS as an independent predictor of survival. All statistical tests were two-sided, and p < 0.05 was considered statistically significant.

RESULTS
Baseline Clinicopathological Characteristics
Clinical and pathologic characteristics of 958 patients are shown in Table 2. There were 630 males (65.8%) and 328 females (34.2%), aged 30–89 years, with a median age of 67 years. Among them, 489 patients (51.1%) had UTUC located in the renal pelvis, 394 (41.1%) in the ureter, and 75 (7.8%) in both sites. A total of 225 patients (23.2%) had metastasis, including 96 (42.7%) with lung metastases, 52 (23.1%) with bone metastases, 42 (18.7%) with liver metastases, 15 (6.7%) with lymph node metastasis, nine (4.0%) with lobar muscle metastases, seven (3.1%) with posterior peritoneal metastasis, and four (1.7%) in other sites (Figure S1).

Intravesical recurrence and distant metastasis occurred in 192 (20.0%) and 225 patients (23.5%), respectively. To explore the prognostic significance of ASA scores in UTUC, Kaplan–Meier survival curves were generated, and groups were compared using the log-rank test. Patients with low ASA score (ASA = 1) had a significantly reduced rate of survival than those with high ASA score (ASA = 2/3) with regard to OS (Figure 1; p < 0.001), CSS (Figure 2; p < 0.001), and MFS (Figure 3; p < 0.001), but not IRFS (Figure 4; p = 0.586). The 5-year OS rates after RNU were 75.2% for the ASA = 1 group, 67.6% for the ASA = 2 group, and 49.9% for the ASA = 3 group. The 5-year CSS rate was 80.5% in patients with ASA = 1, 72.9% in patients with ASA = 2, and 58.1% in patients with ASA = 3. As to 5-year MFS rate, ASA = 1/2/3 group had 81.3%, 75.1%, and 58.5%, respectively. However, no significant differences in IRFS were observed among the different ASA scores.

Cox regression analyses were performed with ASA-PS score as reference. All-cause mortality and cancer-related mortality were increased in patients whose score was 3 or 2.

The univariate analysis also revealed that age ≥65 years, tumor location, hydronephrosis, history of or with NMIBC, tumor size, higher tumor grade and pathological stage, sessile tumor, lymph node metastasis, differentiation, LVI, and multifocality were significantly associated with OS, CSS, and MFS. Besides, AC was significantly associated with CSS/MFS but not OS.

A multivariate model was constructed to identify the factors associated with OS (Table 3) and CSS (Table 4). In multivariate analysis, ASA = 2 and ASA = 3 [hazard ratio (HR) = 1.535, p = 0.030; HR = 2.133, p = 0.001] were independent predictors of OS, along with age ≥65 years (HR = 1.869, p < 0.001), history of or with NMIBC (HR = 1.740, p < 0.001), high grade (HR = 1.665, p = 0.001), pT2−4 (HR = 1.585, p = 0.001), lymph node metastasis (HR = 1.898, p = 0.001), sessile tumor (HR = 1.360, p = 0.027), and differentiation (HR = 1.728, p = 0.009).

As to CSS, multivariable analysis also demonstrated that ASA = 2 and ASA = 3 (HR = 1.594, p = 0.041; HR = 2.347, p = 0.001) were independent predictors, along with age ≥65 years (HR = 1.660, p = 0.001), history of or with NMIBC (HR = 1.830,
<p>p < 0.001), high grade (HR = 2.209, p < 0.001), pT2–4 (HR = 1.665, p = 0.003), lymph node metastasis (HR = 1.555, p = 0.043), sessile tumor (HR = 1.383, p = 0.041), differentiation (HR = 1.654, p = 0.025), LVI (HR = 1.377, p = 0.046), and AC (HR = 1.380, p = 0.047).

Adjusting for multiple potential confounding factors, ASA = 2 (HR = 1.706, p = 0.017) and ASA = 3 (HR = 2.859, p < 0.001) remained independently associated with decreased MFS (Table 5). In addition, history of or with NMIBC (HR = 1.566, p = 0.013), high tumor grade (HR = 2.523, p < 0.001), pT2–4 (HR = 2.158, p < 0.001), lymph node metastasis (HR = 1.730, p = 0.009), and AC (HR = 1.651, p = 0.001) were independent prognostic factors.

However, no significant difference was found in patients with different ASA scores in IRFS (Table 6). History of or with NMIBC (HR = 1.576, p = 0.022) and tumor size (HR = 1.379, p = 0.03) showed a significant effect on patients in the multivariate analysis.

**TABLE 2 |** Clinicopathological characteristics of UTUC patients stratified by ASA scores.

| Variable                  | All (N = 958) | ASA 1 (N = 167) | ASA 2 (N = 663) | ASA 3 (N = 128) | p    |
|---------------------------|---------------|-----------------|-----------------|-----------------|------|
| Gender                    |               |                 |                 |                 |      |
| Female                    | 328 (34.2)    | 63 (37.7)       | 218 (32.9)      | 47 (36.7)       | 0.408|
| Male                      | 630 (65.8)    | 104 (62.3)      | 445 (67.1)      | 81 (63.3)       |      |
| Age, years                |               |                 |                 |                 |      |
| <65                       | 383 (40.0)    | 101 (60.5)      | 259 (39.1)      | 23 (18.0)       | <0.001*|
| ≥65                       | 575 (60.0)    | 66 (39.5)       | 404 (60.9)      | 105 (82.0)      |      |
| Tumor location            |               |                 |                 |                 | 0.598|
| Renal pelvis              | 489 (51.1)    | 89 (53.3)       | 322 (50.1)      | 68 (53.1)       |      |
| Ureter                    | 394 (41.1)    | 68 (40.7)       | 279 (42.1)      | 47 (36.7)       |      |
| Renal pelvis + Ureter     | 75 (7.8)      | 10 (6.0)        | 52 (7.8)        | 13 (10.2)       |      |
| Smoking                   |               |                 |                 |                 |      |
| No                        | 706 (73.7)    | 142 (85.0)      | 470 (71.0)      | 94 (73.4)       |      |
| Yes                       | 252 (26.3)    | 25 (15.0)       | 193 (29.0)      | 34 (26.6)       |      |
| Hydronephrosis            |               |                 |                 |                 | 0.295|
| No                        | 459 (47.9)    | 88 (52.7)       | 307 (46.3)      | 64 (50.0)       |      |
| Yes                       | 499 (52.1)    | 79 (47.3)       | 356 (53.7)      | 64 (50.0)       |      |
| History of or with NMIBC  |               |                 |                 |                 | 0.117|
| No                        | 839 (87.6)    | 149 (89.2)      | 585 (88.2)      | 105 (82.0)      |      |
| Yes                       | 119 (12.4)    | 19 (10.8)       | 78 (11.8)       | 23 (18.0)       |      |
| Surgical methods          |               |                 |                 |                 |      |
| Laparoscopic RNU          | 543 (56.7)    | 96 (57.5)       | 390 (59.3)      | 54 (42.2)       | 0.002*|
| Open RNU                  | 415 (43.3)    | 71 (42.5)       | 270 (40.7)      | 74 (57.8)       |      |
| Tumor size                |               |                 |                 |                 |      |
| ≤3 cm                     | 543 (51.6)    | 105 (62.9)      | 379 (57.2)      | 59 (46.1)       | 0.014*|
| >3 cm                     | 415 (48.4)    | 62 (37.1)       | 284 (42.8)      | 69 (53.9)       |      |
| Tumor grade               |               |                 |                 |                 | 0.753|
| Low                       | 275 (28.7)    | 44 (26.3)       | 193 (29.1)      | 38 (29.7)       |      |
| High                      | 683 (71.3)    | 123 (73.7)      | 470 (70.9)      | 90 (70.3)       |      |
| Pathological stage        |               |                 |                 |                 | 0.649|
| pT2–4                     | 441 (46.0)    | 79 (47.3)       | 299 (45.1)      | 63 (49.2)       |      |
| pT2–4                     | 517 (54.0)    | 88 (52.7)       | 364 (54.9)      | 65 (50.8)       |      |
| Lymph node metastasis     |               |                 |                 |                 | 0.918|
| No                        | 896 (93.5)    | 155 (92.8)      | 621 (93.7)      | 120 (93.8)      |      |
| Yes                       | 62 (6.5)      | 12 (7.2)        | 42 (6.3)        | 8 (6.2)         |      |
| Tumor architecture        |               |                 |                 |                 | 0.736|
| Papillary                 | 516 (53.9)    | 92 (55.1)       | 359 (54.1)      | 65 (50.8)       |      |
| Sessile                   | 442 (46.1)    | 75 (44.9)       | 304 (45.9)      | 63 (49.2)       |      |
| Differentiation           |               |                 |                 |                 | 0.613|
| No                        | 910 (95.0)    | 161 (96.4)      | 627 (94.6)      | 122 (86.5)      |      |
| Yes                       | 48 (5.0)      | 6 (3.6)         | 36 (5.4)        | 6 (4.7)         |      |
| LVI                       |               |                 |                 |                 |      |
| No                        | 808 (84.3)    | 152 (91.0)      | 554 (83.6)      | 102 (79.7)      | 0.018*|
| Yes                       | 150 (15.7)    | 15 (9.0)        | 109 (16.4)      | 26 (20.3)       |      |
| Multifocality             |               |                 |                 |                 | 0.146|
| No                        | 824 (86.0)    | 149 (89.2)      | 571 (86.1)      | 104 (81.3)      |      |
| Yes                       | 134 (14.0)    | 18 (10.8)       | 92 (13.9)       | 24 (18.7)       |      |
| Adjuvant chemotherapy     |               |                 |                 |                 | 0.003*|
| No                        | 762 (79.5)    | 122 (73.1)      | 526 (79.3)      | 114 (89.1)      |      |
| Yes                       | 196 (20.5)    | 45 (26.9)       | 137 (20.7)      | 14 (10.9)       |      |

ASA, American Society of Anesthesiologists; RNU, radical nephroureterectomy; UTUC, upper tract urothelial cancer.

*p < 0.05.

*Table 5*

*Table 6*
DISCUSSION

Together with Adult Comorbidity Evaluation-27 (ACE-27), Charlson Comorbidity Index (CCI), and Eastern Cooperative Oncology Group (ECOG) performance status, the ASA-PS was one of the most commonly used comorbidity indices in the literature (14, 15).

In contrast to the ASA score, however, an anesthetist does not need to complete the CCI in practice schedule. Recently, some researchers aimed to quantify the relationship between the CCI and the ASA grade; the former was determined from documented International Classification of Diseases (ICD) codes, and the latter was assigned by the anesthetist. They have found that the addition of the demographic variables made for a much better predictive model and helped to explain considerably more of the variance in ASA grade than did CCI alone (16). That means in the real life of assigning an ASA grade, anesthetists would take full factors into account, not only the medical condition but also factors that may adversely influence a patient's tolerance to an operative procedure. Such characteristics as well-documented data, such as age, body mass index (BMI), and lifestyle factors like smoking history,
but perhaps also alcohol consumption and sometimes even the complexity of the planned surgery (17). ASA score was much more comprehensive than we might expect. It is also reported that the ASA score is superior to other notable scoring systems including the Charlson score (18) in predicting surgical outcomes. Admittedly, for UTUC, two systems ought to be further compared in randomized controlled trials. Unlike the results of our study, the 2021 European Association of Urology (EAU) Guidelines of muscle-invasive and metastatic bladder cancer (19) strongly recommend to "Assess comorbidity by a validated score, such as the Charlson Comorbidity Index. The American Society of Anesthesiologists score should not be used in this setting".

ASA-PS has been demonstrated as a strong independent factor associated with postoperative morbidity and mortality (11, 20). Based on a large cohort of 6,301 patients who received surgery, Wolters et al. (21) have reported similar findings and found that high ASA score reflected delayed wound repair. Several studies have revealed that high ASA score was associated with prognosis in several urologic malignancies (9, 18, 22); limited evidence has shown that high ASA score was related to unfavorable prognosis in UTUC.
Our results suggested that ASA score $\geq 2$ was independently associated with poorer OS, CSS, and MFS, adjusting for a number of potential confounding variables. However, there was no significant difference with regard to IRFS between low and high ASA score groups in UTUC patients. This might indicate that ASA scores, as a general systemic status indicator, could not reflect localized disease completely. Additionally, we demonstrated the distinct relationship between ASA score and some clinicopathological characteristics, such as age, tumor size, LVI, and AC. Most of these indicators certainly had significant impact on the prognosis of UTUC patients (23–26).

### TABLE 3 | Univariable and multivariable Cox regression models to predict OS.

| Parameters | Univariable Analysis | Multivariable Analysis |
|------------|----------------------|------------------------|
|            | HR (95% CI) p        | HR (95% CI) p          |
| ASA score  | –                    | –                      |
| ASA 2/ASA 1| 1.815 (1.244–2.649)  | 1.535 (1.044–2.258)    |
| ASA 3/ASA 1| 3.020 (1.964–4.643)  | 2.333 (1.354–3.361)    |
| Gender (Male/Female) | 1.031 (0.812–1.309) | –                      |
| Age ($\geq 65/<65$ years) | 2.102 (1.634–2.704) | 1.869 (1.435–2.435) |
| Tumor location | –                    | –                      |
| Ureter/Renal | 1.181 (0.928–1.504)  | 0.818 (0.605–1.105)    |
| Renal Pelvis + Ureter/Renal Pelvis | 2.243 (1.566–3.212) | 1.340 (0.688–1.835) |
| Smoking (Yes/No) | 1.057 (0.786–1.422) | 0.713                  |
| Hydronephrosis (Yes/No) | 1.377 (1.097–1.728) | 1.148 (0.869–1.516) |
| History of or with NMIBC (Yes/No) | 2.507 (1.558–2.715) | 1.740 (1.289–2.351) |
| Surgical methods (LNU/ONU) | 1.129 (0.894–1.427) | –                      |
| Tumor size ($>$3 cm/$\leq$3 cm) | 1.419 (1.133–1.777) | 1.105 (0.872–1.399) |
| Tumor grade (High/Low) | 2.243 (1.828–2.311) | 1.665 (1.218–2.276) |
| Pathological stage (pT2–4/pTa-1) | 2.516 (1.972–2.310) | 1.585 (1.194–2.103) |
| Lymph node metastasis (Yes/No) | 2.898 (2.024–4.424) | 1.989 (1.294–2.778) |
| Tumor architecture (Sessile/Papillary) | 2.174 (1.726–2.738) | 1.360 (1.036–1.786) |
| Differentiation (Yes/No) | 3.431 (2.314–4.824) | 1.728 (1.147–2.602) |
| LVI (Yes/No) | 2.203 (1.699–2.657)  | 1.219 (0.912–1.629)    |
| Multiplicity (Yes/No) | 1.651 (1.249–2.183) | 1.191 (0.819–1.732) |
| Adjuvant chemotherapy (No/Yes) | 1.257 (0.954–1.665) | 0.104                  |

ASA, American Society of Anesthesiologists; HR, hazard ratio; LNU, laparoscopic nephroureterectomy; LVI, lymphovascular invasion; NMIBC, non-muscle invasive bladder cancer; ONU, open nephroureterectomy; OS, overall survival.

*p < 0.05.

### TABLE 4 | Univariable and multivariable Cox regression models to predict CSS.

| Parameters | Univariable Analysis | Multivariable Analysis |
|------------|----------------------|------------------------|
|            | HR (95% CI) p        | HR (95% CI) p          |
| ASA score  | –                    | –                      |
| ASA 2/ASA 1| 1.863 (1.204–2.884)  | 1.594 (1.020–2.490)    |
| ASA 3/ASA 1| 3.144 (1.921–5.145)  | 2.347 (1.390–3.962)    |
| Gender (Male/Female) | 1.016 (0.777–1.330) | –                      |
| Age ($>$65/<65 years) | 1.808 (1.370–2.386) | 1.660 (1.230–2.241) |
| Tumor location | –                    | –                      |
| Ureter/Renal | 1.222 (0.928–1.610)  | 0.829 (0.588–1.169)    |
| Renal Pelvis + Ureter/Renal Pelvis | 2.459 (1.665–3.654) | 1.153 (0.666–1.994) |
| Smoking (Yes/No) | 1.000 (0.724–1.374) | 0.999                  |
| Hydronephrosis (Yes/No) | 1.446 (1.117–1.872) | 1.134 (0.828–1.555) |
| History of or with NMIBC (Yes/No) | 2.150 (1.577–2.932) | 1.830 (1.309–2.560) |
| Surgical methods (LNU/ONU) | 1.057 (0.814–1.374) | 0.675                  |
| Tumor size ($>$3 cm/$\leq$3 cm) | 1.667 (1.290–2.154) | –                      |
| Tumor grade (High/Low) | 3.425 (2.387–4.914) | 2.209 (1.492–3.270) |
| Pathological stage (pT2–4/pTa-1) | 2.989 (2.244–3.982) | 1.666 (1.194–2.321) |
| Lymph node metastasis (Yes/No) | 2.959 (1.992–4.405) | 1.555 (1.013–2.387) |
| Tumor architecture (Sessile/Papillary) | 2.533 (1.938–3.309) | 1.383 (1.014–1.886) |
| Differentiation (Yes/No) | 3.714 (2.500–5.517) | 1.654 (1.065–2.569) |
| LVI (Yes/No) | 2.255 (1.948–3.431)  | 1.377 (1.005–1.886)    |
| Multiplicity (Yes/No) | 1.757 (1.289–2.396) | 1.182 (0.778–1.797) |
| Adjuvant chemotherapy (No/Yes) | 1.560 (1.164–2.089) | 1.380 (1.004–1.896)    |

ASA, American Society of Anesthesiologists; HR, hazard ratio; LNU, laparoscopic nephroureterectomy; LVI, lymphovascular invasion; NMIBC, non-muscle invasive bladder cancer; ONU, open nephroureterectomy; CSS, cancer-specific survival.

*p < 0.05.
Our results also showed that advanced age, high tumor grade and pathological stage, lymph node metastasis, sessile architecture, and differentiation were associated with worse OS and CSS, which was consistent with the results reported by Margulis et al. (27). Although previous studies have reported the prognostic value of ASA scores in UTUC patients (28, 29), our study is unique for several reasons. Primarily, in the present study, a total of 17 clinicopathological characteristics were analyzed, while a strong predictor of lymph node metastasis was not included in the study by Ho et al. (28) and only seven characteristics were collected in the study by Alexis et al. (29). Nearly twice as many in previous studies, a larger cohort had

### TABLE 5 | Univariable and multivariable Cox regression models to predict MFS.

| Parameters                      | Univariable Analysis | Multivariable Analysis |
|---------------------------------|----------------------|------------------------|
|                                 | HR (95% CI)          | p                      | HR (95% CI)          | p                      |
| ASA score                       | –                    | <0.001*                | –                    | <0.001*                |
| ASA 2/ASA 1                     | 1.716 (1.116–2.639)  | 0.014*                 | 1.706 (1.099–2.649)  | 0.017*                 |
| ASA 3/ASA 1                     | 2.857 (1.747–4.672)  | <0.001*                | 2.859 (1.692–4.831)  | <0.001*                |
| Gender (Male/Female)            | 0.855 (0.663–1.119)  | 0.254                  | –                    | –                      |
| Age (>65/<65 years)             | 1.446 (1.098–1.905)  | 0.009*                 | 1.309 (0.972–1.762)  | 0.076                  |
| Tumor location                  | –                    | 0.065                  | –                    | –                      |
| Ureter/Renal                    | 1.063 (0.803–1.405)  | 0.666                  | –                    | –                      |
| Renal Pelvis + Ureter/Renal Pelvis | 1.676 (1.085–2.589) | 0.020*                | –                    | –                      |
| Smoking (Yes/No)                | 1.119 (0.824–1.519)  | 0.472                  | –                    | –                      |
| Hydronephrosis (Yes/No)         | 1.569 (1.202–2.050)  | 0.001*                 | 1.120 (1.081–1.473)  | 0.420                  |
| History of or with NMIBC (Yes/No) | 1.787 (1.278–2.500) | 0.001*                 | 1.566 (1.099–2.230)  | 0.013*                 |
| Surgical methods (LNU/ONU)      | 1.168 (0.896–1.523)  | 0.251                  | –                    | –                      |
| Tumor size (>3 cm/≤3 cm)        | 1.519 (1.169–1.972)  | 0.002*                 | 1.233 (0.943–1.613)  | 0.126                  |
| Tumor grade (High/Low)          | 4.170 (2.767–6.283)  | <0.001*                | 2.158 (1.506–3.092)  | <0.001*                |
| Pathological stage (pT2–pT4)    | 3.772 (2.758–5.159)  | 0.002*                 | 1.143 (0.836–1.563)  | 0.401                  |
| Lymph node metastasis (Yes/No)  | 3.222 (2.257–4.878)  | <0.001*                | 1.306 (1.148–1.578)  | 0.009*                 |
| Tumor architecture (Sessile/Papillary) | 2.492 (1.896–3.275) | <0.001*                | 2.173 (0.836–1.563)  | 0.401                  |
| Differentiation (Yes/No)        | 3.181 (2.081–4.863)  | 0.001*                 | 1.454 (0.914–2.314)  | 0.114                  |
| LVI (Yes/No)                    | 2.413 (1.798–3.238)  | <0.001*                | 1.556 (1.097–2.176)  | 0.133                  |
| Multifocality (Yes/No)          | 1.889 (1.136–2.922)  | 0.005*                 | 1.215 (0.863–1.712)  | 0.265                  |
| Adjuvant chemotherapy (No/Yes)  | 1.969 (1.483–2.615)  | 0.001*                 | 1.651 (1.212–2.251)  | 0.001*                 |

ASA, American Society of Anesthesiologists; HR, hazard ratio; LNU, laparoscopic nephroureterectomy; LVI, lymphovascular invasion; MFS, metastasis-free survival; NMIBC, non-muscle invasive bladder cancer; ONU, open nephroureterectomy.

* p < 0.05.

### TABLE 6 | Univariable and multivariable Cox regression models to predict IRFS.

| Parameters                      | Univariable Analysis | Multivariable Analysis |
|---------------------------------|----------------------|------------------------|
|                                 | HR (95% CI)          | p                      | HR (95% CI)          | p                      |
| ASA score                       | –                    | 0.586                  | –                    | –                      |
| ASA 2/ASA 1                     | 1.174 (0.790–1.744)  | 0.428                  | –                    | –                      |
| ASA 3/ASA 1                     | 1.305 (0.780–2.185)  | 0.311                  | –                    | –                      |
| Gender (Male/Female)            | 1.361 (0.994–1.864)  | 0.055                  | –                    | –                      |
| Age (>65/<65 years)             | 1.180 (0.883–1.578)  | 0.265                  | –                    | –                      |
| Tumor location                  | 0.002*               | –                      | 0.176                | –                      |
| Ureter/Renal                    | 1.262 (0.932–1.708)  | 0.130                  | 1.230 (0.899–1.685)  | 0.196                  |
| Renal Pelvis + Ureter/Renal Pelvis | 2.258 (1.434–3.565) | <0.001*               | 1.658 (0.930–2.955)  | 0.086                  |
| Smoking (Yes/No)                | 1.026 (0.734–1.435)  | 0.881                  | –                    | –                      |
| Hydronephrosis (Yes/No)         | 1.093 (0.823–1.452)  | 0.537                  | –                    | –                      |
| History of or with NMIBC (Yes/No) | 1.947 (1.360–2.787) | <0.001*               | 1.576 (1.068–2.326)  | 0.022*                 |
| Surgical methods (LNU/ONU)      | 1.105 (0.824–1.452)  | 0.494                  | –                    | –                      |
| Tumor size (>3 cm/≤3 cm)        | 1.400 (1.055–1.859)  | 0.020*                 | 1.379 (1.032–1.843)  | 0.030*                 |
| Tumor grade (High/Low)          | 1.455 (1.053–2.012)  | 0.023*                 | 1.342 (0.965–1.865)  | 0.080                  |
| Pathological stage (pT2–pT4)    | 1.092 (0.822–1.451)  | 0.543                  | –                    | –                      |
| Lymph node metastasis (Yes/No)  | 1.140 (0.802–2.472)  | 0.233                  | –                    | –                      |
| Tumor architecture (Sessile/Papillary) | 1.089 (0.817–1.451) | 0.561                  | –                    | –                      |
| Differentiation (Yes/No)        | 1.375 (0.727–2.601)  | 0.327                  | –                    | –                      |
| LVI (Yes/No)                    | 1.002 (0.667–1.505)  | 0.993                  | –                    | –                      |
| Multifocality (Yes/No)          | 1.657 (1.162–2.364)  | 0.005*                 | 1.134 (0.717–1.792)  | 0.591                  |
| Adjuvant chemotherapy (No/Yes)  | 1.420 (1.021–1.975)  | 0.037*                 | 1.296 (0.928–1.809)  | 0.128                  |

ASA, American Society of Anesthesiologists; HR, hazard ratio; IRFS, intravesical recurrence-free survival; LNU, laparoscopic nephroureterectomy; LVI, lymphovascular invasion; NMIBC, non-muscle invasive bladder cancer; ONU, open nephroureterectomy.

*p < 0.05.
longer follow-up, and approximately 1,000 patients were retrospectively analyzed. Furthermore, given that survival is a heterogeneous endpoint, overall, cancer-specific, intravesical recurrence-free, and metastasis-free survival have all been involved.

Considering the underlying systemic disease with predisposition to poor recovery, infectious and cardiorespiratory complications were more common in patients with a high ASA score than in those with a low score. General condition and systemic illness were absolute barriers for systemic chemotherapy and also significant determinants of survival, as for ASA-PS, ranging from a healthy person (class I) to one with a bad/severe systemic disorder that is a constant threat to life (30). When the cardiopulmonary system is not strong and working inefficiently, oxygen will not circulate all around the body helping to feed and renew our body tissues and vital organs (liver, kidney, et al.). Especially, there is additional task for tumor-host's body to activate the antitumor effect, such as immunological function response. Different from other tumor types, renal insufficiency was an unavoidable problem for UTUC patients who underwent RNU. Renal insufficiency often constrains the choice of nephrotoxic chemotherapy regimen, which seems to be a challenge preventing the effective delivery of cisplatin-based chemotherapy (30–32). In this study, similarly, as ASA score increased, the proportion of AC has also risen (10.9%, 20.7%, and 26.9%, respectively, p = 0.003; Table 2). It turns out that higher ASA score results in damage to the tumor-bearing host and tolerance to systemic therapy. In other words, disorder of the immune function will decrease the antitumor ability and simultaneously increase tumor burden (33).

Additionally, preoperative hydronephrosis and multifocality were considered to be correlated with adverse prognosis (8, 34); in contrast, our results found that these two indicators were not independent predictors. Our study reveals that hydronephrosis and multifocality do not appear to have a significant influence on survival outcome; this result has also been confirmed by previous studies (8, 35). We need to acknowledge a selection bias for exclusion of patients receiving AC. Given their impaired renal function, patients with hydronephrosis are more likely to miss the opportunity to receive AC after radical nephroureterectomy (36). The prognostic impact of multifocal UTUC has also been poorly understood. The ability of chemotherapy of eradicating micrometastasis has been widely recognized (37). Thomas et al. (8) have reported that tumor multifocality was not an independent predictor of both disease progression (HR = 1.43, p = 0.019) and CSS (HR = 1.46, p = 0.027) in advanced UTUC (stratified by non-confined type, the confounding effect of AC cannot be adequately adjusted).

There were several limitations associated with this study. Firstly, a retrospective analysis may cause a selection bias. Secondly, potential predictors including BMI, history of aristolochic acid, and preoperative renal function were not available. Thirdly, lymphadenectomy was not routinely performed and the extent of lymph node dissection was not standardized because the pattern and benefits of lymphadenectomy were still controversial. Moreover, as widely acknowledged, surgical patients with higher ASA score developed substantially higher rates of perioperative medical complications (20). Unfortunately, we do not know the detailed information of patients who have suffered perioperative complications. It was really a huge effort for researchers from two institutions to collect undocumented clinical data for almost a thousand patients. This aspect was an unavoidable limitation in the current study but could be improved by further study. Based on a large number of cases, the detailed clinical and pathological data with long-term follow-up of UTUC patients from two institutions in China, this study was able to provide more convincing information to clinicians.

CONCLUSION

We suggest that RNU is safe for selected patients with UTUC. However, higher ASA score predicts poor clinical outcomes, and it was a significant prognostic factor for OS, CSS, and MFS. This prognostic factor may be a useful variable to include into future risk prediction and contribute to clinical decision-making. Long-term and larger-scale studies may produce more reliable results.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

ETHICS STATEMENT

This study was approved by institutional review board, and approval number was 2020-369.

AUTHOR CONTRIBUTIONS

YY and YW contributed to the conceptualization, methodology, validation, visualization, formal analysis, investigation, and writing the original draft. NZ contributed to the conceptualization, resources, and funding acquisition. XM contributed to the methodology, visualization, software, and validation. YH contributed to the methodology, visualization, and software. JH and NJ contributed to the methodology, data curation, validation, investigation, resources, and writing–review and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.723669/full#supplementary-material
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