Nephron-sparing Surgery Versus Radical Nephroureterectomy in the Treatment of Organ-localized Upper Urinary Tract Urothelial Carcinoma: A Population-based Study of 1581 Patients

Jianhui Qiu

Peking University First Hospital <https://orcid.org/0000-0002-4393-612X>

Hua Liu

Peking University First Hospital

Zixin Wang

Peking University First Hospital

Jingcheng Zhou

Peking University First Hospital

Yanqing Gong

Peking University First Hospital

Lin Cai

Peking University First Hospital

Kan Gong (✉ gongkan_pku@126.com)

Department of Urology, Peking University First Hospital, Beijing, China.; Institute of Urology, Peking University, Beijing, China. National Urological Cancer Center, Beijing, China. <https://orcid.org/0000-0001-7195-677X>

Research article

Keywords: Upper urinary tract urothelial carcinoma, SEER, Radical nephroureterectomy, Nephron-sparing surgery, competing-risk model, nomogram

Posted Date: November 20th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-111383/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Purpose: Nephron-sparing surgeries (NSS) have been widely used for patients with low-risk upper tract urothelial carcinoma (UTUC). We compared the prognosis of patients with organ-localized UTUC after NSS and radical nephroureterectomy (RN) through a population-based study and a propensity score matching (PSM) method. We further developed prognostic models for these patients using the Cox analysis and the competing-risk models.

Materials and methods: The follow-up dataset of 1580 patients with organ-localized UTUC were screened out from the Surveillance, Epidemiology, and End Results (SEER) registry. A PSM process with a caliper width of 0.05 was performed to match the patients accepting NSS with those accepting RN. The Cox analysis was used for overall survival (OS) and competing-risks models based on Fine-Gray regression for cancer-specific survival (CSS). A forward stepwise selection process was applied to select independent predictors for OS and CSS. After selecting the predictors, two nomograms were developed based on the Cox analysis and the competing-risk model and internal validations were performed using 1000 bootstrap resamples.

Results: Before PSM, RN was associated with better OS compared with NSS in the overall cohort (5-year OS rate: 65.1% vs. 55.6%, $p < 0.001$) and the patients with renal pelvic lesions (5-year OS rate: 68.6% vs. 52.8%, $p = 0.001$). Baseline variables were well balanced using the PSM method. After PSM, there was no significant difference in OS between the RN and NSS groups. Competing-risks models revealed that NSS was associated with poorer CSS compared with RN in the post-PSM cohort ($n = 766$; subdistribution hazard ratio/ SHR = 1.39, 95% confidence interval/ CI 1.03-1.89, $p = 0.033$) and in patients with ureteral lesions from the post-PSM cohort. Four independent predictors, which were age at diagnosis, AJCC T stage, histologic grade, and surgery methods, were selected out for OS and CSS through forward stepwise selection methods. Two nomograms for OS and CSS were respectively developed.

Conclusions: Patients accepting RN had a comparative or better outcome in each sample group. NSS achieved a similar prognosis for selective patients with organ-localized UTUC. Two nomograms were developed to predict OS and CSS with C-indexes of 0.672 and 0.643.

Background

Upper urinary tract urothelial carcinoma (UTUC) are rare tumors that account for 5%-10% of all urothelial malignancies with an incidence rate of 1.45-2.06 cases per 100,000 person-years [1, 2]. Radical nephroureterectomy (RN) with bladder cuff resection remains the gold standard therapy for patients with UTUC [3], but it is associated with some serious complications, such as chronic renal failure and failure-induced other system morbidities. Given that the elderly are more like to get affected by UTUC[2], RN is not suitable for all patients as an invasive procedure with the risk of complications. Besides some patients with medical comorbidities that make invasive procedures risky, patients with solitary kidney may also prefer nephron-sparing surgery (NSS). After carefully weighing the advantages and

disadvantages, NSS, which spares the morbidity associated with RN in the avoid of compromising oncological outcomes and kidney function, has been advocated in selected patients with low-risk UTUC [3–5].

Due to the rarity of UTUC, many studies about UTUC were limited by sample size and retrospective case series didn't have enough power to get conclusions. Surveillance, Epidemiology, and End Results (SEER) program gathered information on treatment and prognosis, which currently covers more than a fifth of the US population. In this study, a population-based study including patients with UTUC registered in SEER was performed to compare prognosis between patients accepting RN or NSS. To avoid bias and derive a more persuasive conclusion, a propensity score matching (PSM) method was performed to adjust baseline characteristics between the RN and NSS groups.

As UTUC is more common in the elderly, comorbidities of patients can't be ignored during follow-up and the process of survival analysis. Deaths from other noncancer causes can be competing events to cancer-specific deaths. The risk of competing mortality increases and the effect of treatment on survival diminishes with advancing age. In the presence of competing events, conventional Kaplan-Meier and Cox analysis methods may not be the best choices because these two methods regard competing events as independent censored events and overrate the incidence of target events [6, 7]. Instead, competing risk models based on the Fine-Gray regression can better discriminate the effects of clinical factors on special events [7]. Thus, competing-risks models were used in this study to construct prognostic models of organ-localized UTUC. Nomograms visualizing the prognostic models were also made to predict the 3-year and 5-year prognosis [8, 9].

Methods

3.1 Study population

The final diagnosis recorded in the SEER data (<https://seer.cancer.gov/data/>) was coded by the International Classification of Disease for Oncology-3 (ICD-O-3). We identified all subjects diagnosed with UTUC (topography codes: C65.9 and C66.9; histological code: 8120/3, 8122/3, 8130/3, 8131/3) between 2004 and 2015 in the SEER registry. Clinicopathological data of subjects, such as age, gender, race, American Joint Committee on Cancer (AJCC) TNM stage, histological grade, SEER registry location, marital status, survival time, clinical outcome, and other demographic characteristics needed in the study were exported. Only T1N0M0 and T2N0M0 patients with complete data were included in the study. Patients with more than one primary malignant tumor, or not receiving NSS or RN were excluded. Local tumor destruction (e.g., photodynamic therapy, cryosurgery, thermal ablation, and electrocautery), local tumor excision (e.g., polypectomy and excisional biopsy), partial nephrectomy for pelvis tumors, and partial ureterectomy for ureter tumors were all categorized as NSS. The SEER registry defines histologic grade as follows: G1, well-differentiated; G2, moderately differentiated; G3, poorly differentiated; G4, undifferentiated or anaplastic.

3.2 Propensity score matching

The PSM method was used to balance the baseline characteristics between the NSS and RN groups. Multivariate logistic regression analysis was used to get propensity scores for each subject based on gender, age at diagnosis, laterality (left or right), tumor location (pelvis or ureter), marital status, AJCC T stage, and histologic grade of tumors. NSS and RN groups were matched 1: 1 through a caliper width of 0.05 for the propensity score and the nearest neighbor matching.

3.3 Statistical analysis

Continuous variables were described using medians and ranges, while categorical variables were reported by proportions. The chi-square tests were adopted to compare the baseline categorical variables between the NSS group and RN group before and after PSM and the Mann-Whitney U tests for continuous variables. The study outcomes were cancer-specific survival (CSS) and overall survival (OS) according to the record of the SEER database. Kaplan-Meier method as well as log-rank tests were used to compare the OS between groups. Univariate and multivariate Cox regression analysis models were adopted to detect factors influencing OS. Competing risk models were used to assess the predictive factors of CSS.

X-tile version 3.6.1 (Robert L Camp, Yale University; <https://medicine.yale.edu/lab/rimm/research/software/>) was used to classify continuous variables (age at diagnosis) [10]. All analyses were performed using the Stata/SE version 15.1 (StataCorp, College Station, Texas), IBM SPSS Statistics version 23.0 (SPSS Inc., Chicago, IL, USA) and R statistical software (version 3.6.3; <https://www.r-project.org/>). All statistical tests were two-sided with $P < 0.05$ considered to be indicative of statistical significance. The “regplot”, “ggplot2” and “riskRegression” R packages were used to construct and verify prognostic models.

Results

4.1 Study population

14,135 patients diagnosed with UTUC between 2004 and 2015 were collected from the SEER database. Finally, 1580 eligible T1-2N0M0 patients with UTUC as the only primary tumor were included for further analysis as shown in Figure 1. 306 failure events and 302 competition events were observed in the overall cohort. Median follow-up period for the overall cohort and after PSM was 44 months and 41 months.

Baseline characteristics of patients between the RN and NSS groups before and after PSM were shown in Table 1. For the entire cohort, 1187 (75.1%) patients were treated with RN, and 393 (24.9%) were treated with NSS. Patients undergoing NSS were associated with increasing age and renal pelvis tumors compared with those receiving RN ($p < 0.001$). After PSM, a cohort of 766 patients was generated, 383 patients in each group. 10 of 393 patients from the NSS group didn't have the matched individuals from the RN group. The baseline characteristics were well balanced between the two groups in the PSM cohort

(Table 1; Figure 2). 167 failure events and 163 competition events were recorded in the post-PSM cohort. G4 was the most common histologic grade before and after PSM, accounting for above 40% in both the overall cohort and the post-PSM cohort.

4.2 Differences of prognosis between the RN and NSS groups

As shown in Figure 3, in the overall cohort, patients in the NSS group were associated with poorer OS compared with those in the RN group (5-year OS rate: 55.6% vs. 65.1%, $p<0.001$; Figure 3. A). After stratifying patients according to locations of lesions, for patients with ureteral tumors, there was no significant difference in OS between the RN and NSS groups (453 and 284 patients, respectively; 5-year OS rate: 59.6% vs. 56.9, $p=0.232$; Figure 3. B). For patients with renal pelvic tumors, RN was associated with better OS compared with NSS (734 and 109 patients, respectively; 5-year OS rate: 68.6% vs. 52.8%, $p=0.001$; Figure 3. C).

In the post-PSM cohort, NSS seemed to be associated with poorer OS compared with RN, whose differences between them were almost significant (5-year OS rate, 62.8% vs. 55.2%, $p=0.085$; Figure 3. D). This trend still existed in patients with renal pelvic tumors, for which RN was almost associated with better overall survival compared with NSS (5-year OS rate 67.5% vs. 52.8%: $p=0.055$; Figure 3. E). For ureteral tumors, OS between the two groups showed no significant difference (5-year OS rate, RN vs. NSS: 60.8% vs. 56.3%, $p=0.404$; Figure 3. F).

Competing-risks models revealed that the NSS group had poorer CSS compared with the RN group (subdistribution hazard ratio/ SHR=1.39, 95% confidence interval/ CI 1.03-1.89, $p=0.033$; Figure 4. A) in the post-PSM cohort. When the post-PSM cohort was stratified by tumor locations, RN was associated with better CSS in patients with ureteral tumors (SHR=1.44, 95% CI 1.01-2.06, $p=0.044$; Figure 4. B). There was no significant difference in survival between RN and NSS for renal pelvic tumors (SHR=1.24, 95%CI 0.689-2.24, $p=0.471$; Figure 4. C).

4.3 Independent prognostic factors of OS and CSS in the overall cohort

Age at diagnosis was divided into two groups as “>78.5 years old” and “<78.5 years old” using X-tile software for further building prognostic models. The results of univariate and multivariate Cox analysis for OS in the overall cohort were listed in Table 2. Univariate Cox analysis demonstrated that some characteristics of patients, which were age groups, tumor locations (renal pelvic tumors or ureteric tumors), AJCC T stage, histologic grade, marital status, surgery methods, were associated with OS in the overall cohort. Further multivariate Cox analysis including statistically significant variates in univariate Cox analysis by the forward-stepwise model selection revealed that age at diagnosis, AJCC T stage, and

histologic grade were independent prognostic factors for OS in the overall cohort (Table 2). The strongest predictor for OS was the age at diagnosis (hazard ratio/ HR=2.80, 95% CI, 2.38-3.22, $p<0.001$). Advance histologic grade (HR=1.38, 95% CI, 1.15-1.66, $p=0.001$) and T2 stage (HR=1.44, 95% CI, 1.22-1.70, $p<0.001$) had similar predictive strengths about poorer OS. Patients accepting NSS (HR=1.24, 95% CI, 1.04-1.48, $p=0.0018$) held poorer OS compared with patients accepting RN.

Competing-risks models based on the Fine-Gray models were used to assess CSS in the entire cohort. The results of univariate analysis for CSS in the overall cohort were shown in Table 3. Age groups, tumor location, AJCC T stage, histologic grade, and surgery methods were associated with CSS. Gender, race, tumor laterality, and marital status seemed not to be related to CSS. Statistically significant variables in the univariate analysis in the competing-risks models were included in multivariate analysis through forward-stepwise selection methods, which validated that older age at diagnosis, advanced AJCC T stage, advanced histologic grade, and NSS were independent predictors of CSS (Table 4). Age at diagnosis, AJCC T stage, and histologic grade hold a similar predictive power for competing risk of CSS. Compared with the younger group (age at diagnosis < 78.5 years old), the older group (age at diagnosis > 78.5 years old; SHR=1.82, 95% CI, 1.44-2.30, $p<0.001$) carried higher competing risks. Advanced AJCC T stages and advanced histologic grades were also strongly predictive for CSS. Patients with T2 tumors (SHR=1.88, 95% CI, 1.50-2.37, $p<0.001$) or patients with advanced histologic G3 or G4 tumors (SHR=1.83, 95% CI, 1.38-2.42, $p<0.001$) experienced increased competing events compared with patients with T1 tumors or patients with histologic G1 or G2 tumors. Although the predictive strength was not as strong as the other three factors, patients accepting NSS rather than RN also hold higher CSS risks (SHR=1.47, 95% CI, 1.15-1.88, $p=0.002$).

4.4 Developing nomograms for OS and CSS

As mentioned above, the final prognostic models for OS and CSS both included four factors, which were age at diagnosis, surgery methods, histologic grade, and AJCC T stage of tumors. The prognostic nomograms for OS (Figure 5) and CSS (Figure 6) using the overall cohort that integrated all these four significant independent factors were shown in Figure 5 and Figure 6. The nomogram for OS was based on multivariate Cox analysis to predict the 3-year and 5-year OS, while the nomogram for CSS was based on the competing risk model mentioned above to predict the 3-year and 5-year CSS. After adding up scores corresponding to each value and check against the bottom probability axis, the possibility of all-cause mortality or cancer-specific mortality was then got. The score of each value was shown in Table 5.

Then the overall cohort was used for internal validation of prognostic models. The nomogram for OS displayed a C-index of 0.672, as well as the nomogram for CSS, displayed a C-index of 0.643. Using 1000 resampled bootstrap data sets for cross-validation, the calibration plots for the two nomograms in the overall cohort were shown in Figure 7 and Figure 8. The Brier scores of corresponding models were also shown in the figures.

Discussion

This study reported a population-based study of organ-localized UTUC from the SEER registry using the PSM method to compare the prognosis after accepting RN and NSS. Two prognostic models for OS and CSS were developed and validated through multivariate Cox and competing-risks analysis. Nomograms visualizing the two models were shown in Figure 5 and Figure 6.

NSS has cut a figure in the field of UTUC in recent years. For certain groups of patients with low-risk UTUC, NSS was considered to avoid RN-related comorbidities without compromising oncologic control. Previous studies were often limited by sample capacity due to its rarity [3, 11, 12]. A previous multicenter retrospective study reported that patients treated with NSS had similar CSS and better OS compared with patients accepting RN in multivariate Cox analysis [12]. A recent systematic review conducted by Seisen et al including 22 studies got the conclusion that similar survival existed between KSS, which were ureteroscopic as well as percutaneous methods, and RN only for low-grade and noninvasive UTUC. Segmental ureterectomy may let selective patients with invasive or high-grade UTUC achieve comparable oncologic outcomes with RN. Thus, Seisen et al advocated that segmental ureterectomy could be one of the optional managements for selected patients with high-risk UTUC [11]. A meta-analysis conducted by Yakoubi et al included eight published retrospective studies reported that endoscopic NSS had similar OS and CSS with RN using the pool data on 1002 patients with localized UTUC. However, the power of the results was limited by the heterogeneity from the included studies and the low level of evidence [13]. There is a lack of high-quality research focusing on whether NSS is suitable for patients with UTUC.

This study simultaneously used the follow-up data from the SEER registry and the PSM method to control selected biases and other potential bias. The SEER registry covers plenty of individual patient data nearly representing the overall population [14]. The PSM method has been widely used in clinical researches to balance the baseline variables between the treatment and control groups [15, 16]. A cohort of eligible 1580 patients who were diagnosed with organ-localized UTUC between 2004 to 2015 was screened out according to Figure 1. After PSM, a cohort of 766 patients was created for further analysis. The baseline characteristics of the RN and NSS groups in the post-PSM cohort showed no significant difference (Table 1). We chose OS and CSS as the target events of this study. In the overall cohort, RN was associated with better OS compared with NSS ($p < 0.001$). RN was still associated with better OS in patients with renal pelvic UTUC ($p = 0.001$), whereas NSS achieved a similar OS with RN in patients with ureteral UTUC. After reducing bias through PSM, the OS between RN and NSS groups showed no significant difference ($p = 0.085$). NSS had a tendency to be associated with poorer OS in comparison to RN in the post-PSM cohort but there was still no significant difference (0.055).

Competing risk models have been adopted in many previous studies [17, 18]. Patients with advanced age often had comorbidities with an increased risk of competing mortality. The common Cox and Kaplan-Meier methods analyzed a combined endpoint, aggregating one or more deaths from other competing events. Thus, competing risk models based on Fine-Gray regression were used in this study to assess the CSS of patients as deaths from other noncancer causes were regarded as competing events to cancer-

specific deaths. In the post-PSM cohort, RN was associated with better CSS ($p=0.033$, Figure 4. A). After stratifying by tumor locations, RN was still related to better CSS in patients with ureteral tumors ($p=0.044$). CSS of patients with renal pelvic tumors was similar between the RN and NSS groups ($p=0.471$). Taking the above results for OS and CSS into consideration, NSS achieved a similar prognosis and comparative oncologic control with RN for selective patients. Patients accepting RN had comparative or better outcomes in each sample group.

Seldom studies have published competing risk models and nomograms for organ localized UTUC [19, 20]. A previous published prognostic model for UTUC confirmed tumor location, tumor grade, and tumor architecture as independent predictors of nonorgan localized disease [21]. In this study, four factors, which were age at diagnosis, histologic grade, AJCC T stage, and surgery methods, were included in the prognostic models. Two nomograms based on the Cox model and the competing risk model respectively were developed and validated. Because of the lack of external follow-up data, only the inner validation of nomograms using 1000 resampled bootstrap methods was performed [22]. Surgeons and patients could simply and quickly get the 3-year or 5-year prognosis using the nomograms.

The power of our prognostic models was the large population-based sample and Fine-Gray regression that can distinguish target events and competing-risks events. There are some shortcomings in our prognostic models. Some characteristics were not available, such as family history, smoking history, treatment detail, chemical exposure, and laboratory indexes [23, 24]. Additionally, there was a lack of external datasets to validate the models. In the future, we aimed at the validation of the models using follow-up data of our center.

Conclusions

NSS could achieve a comparative oncologic outcome and overall outcome with RN in selective patients with organ-localized UTUC. As the gold standard treatment for UTUC, RN was appropriate for patients from each subgroup. Age at diagnosis, tumor location, histologic grade, and surgery methods were independent predictors for OS and NSS. Two nomograms were developed on the basis of these four factors. Multicentral prospective randomized controlled clinical trials are urgently needed to assess the oncologic outcomes of UTUC with NSS or RN management.

Declarations

Ethics approval and consent to participate

Since all the follow-up information analysed in this article were from the SEER database (<https://seer.cancer.gov/data/>), informed consents were not needed. As long as data usege agreement was signed, data in the SEER database become available to the public.

Consent of publication

Not applicable.

Availability of data and materials

The datasets for this study can be found at <https://seer.cancer.gov/data/>.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

This work was supported by the National Natural Science Foundation of China (No. 81872081) and the Fundamental Research Funds for the Central Universities (grant BMU2018JI002).

Authors' contributions

Conceptualization and literature review: JQ and HL. Data acquisition and filtration: JQ, HL and KG. Data processing: JQ, HL and LC. Data plotting: JQ, JZ and YG. Original draft writing: JQ, HL and JZ. Draft review and revision: JC, YG, LC and KG.

Acknowledgements

Not applicable.

References

1. Visser O, Adolfsson J, Rossi S, Verne J, Gatta G, Maffezzini M, Franks KN, RARECARE working group (2012) Incidence and survival of rare urogenital cancers in Europe. *European Journal of Cancer (Oxford, England: 1990)*, 48(4):456–464. <https://doi.org/10.1016/j.ejca.2011.10.031>
2. Raman JD, Messer J, Sielatycki JA, Hollenbeak CS (2011) Incidence and survival of patients with carcinoma of the ureter and renal pelvis in the USA, 1973-2005. *BJU international*, 107(7):1059–1064. <https://doi.org/10.1111/j.1464-410X.2010.09675.x>
3. Rouprêt M, Babjuk M, Compérat E, Zigeuner R, Sylvester RJ, Burger M, Cowan NC, Gontero P, Van Rhijn BWG, Mostafid AH, Palou J, Shariat SF (2018) European Association of Urology Guidelines on Upper Urinary Tract Urothelial Carcinoma: 2017 Update. *European Urology*, 73(1):111–122. <https://doi.org/10.1016/j.eururo.2017.07.036>
4. Gadzinski AJ, Roberts WW, Faerber GJ, Wolf JS (2010) Long-term outcomes of nephroureterectomy versus endoscopic management for upper tract urothelial carcinoma. *The Journal of Urology*, 183(6):2148–2153. <https://doi.org/10.1016/j.juro.2010.02.005>
5. Lucas SM, Svatek RS, Olgin G, Arriaga Y, Kabbani W, Sagalowsky AI, Lotan Y (2008) Conservative management in selected patients with upper tract urothelial carcinoma compares favourably with

- early radical surgery. *BJU international*, 102(2):172–176. <https://doi.org/10.1111/j.1464-410X.2008.07535.x>
6. Huang X-D, Zhou G-Q, Lv J-W, Zhou H-Q, Zhong C-W, Wu C-F, Zheng Z-Q, He X-J, Peng L, Ma J, Sun Y (2018) Competing risk nomograms for nasopharyngeal carcinoma in the intensity-modulated radiotherapy era: A big-data, intelligence platform-based analysis. *Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology*, 129(2):389–395. <https://doi.org/10.1016/j.radonc.2018.09.004>
 7. Carmona R, Zakeri K, Green G, Hwang L, Gulaya S, Xu B, Verma R, Williamson CW, Triplett DP, Rose BS, Shen H, Vaida F, Murphy JD, Mell LK (2016) Improved Method to Stratify Elderly Patients With Cancer at Risk for Competing Events. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, 34(11):1270–1277. <https://doi.org/10.1200/JCO.2015.65.0739>
 8. Zhang Z, Geskus RB, Kattan MW, Zhang H, Liu T (2017) Nomogram for survival analysis in the presence of competing risks. *Annals of Translational Medicine*, 5(20)<https://doi.org/10.21037/atm.2017.07.27>
 9. Zhang Z, Cortese G, Combescure C, Marshall R, Lee M, Lim HJ, Haller B (2018) Overview of model validation for survival regression model with competing risks using melanoma study data. *Annals of Translational Medicine*, 6(16)<https://doi.org/10.21037/atm.2018.07.38>
 10. Camp RL, Dolled-Filhart M, Rimm DL (2004) X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*, 10(21):7252–7259. <https://doi.org/10.1158/1078-0432.CCR-04-0713>
 11. Seisen T, Peyronnet B, Dominguez-Escrig JL, Bruins HM, Yuan CY, Babjuk M, Böhle A, Burger M, Compérat EM, Cowan NC, Kaasinen E, Palou J, Rhijn BWG van, Sylvester RJ, Zigeuner R, Shariat SF, Rouprêt M (2016) Oncologic Outcomes of Kidney-sparing Surgery Versus Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma: A Systematic Review by the EAU Non-muscle Invasive Bladder Cancer Guidelines Panel. *European Urology*, 70(6):1052–1068. <https://doi.org/10.1016/j.eururo.2016.07.014>
 12. Seisen T, Nison L, Remzi M, Klatte T, Mathieu R, Lucca I, Bozzini G, Capitanio U, Novara G, Cussenot O, Compérat E, Renard-Penna R, Peyronnet B, Merseburger AS, Fritsche H-M, Hora M, Shariat SF, Colin P, Rouprêt M (2016) Oncologic Outcomes of Kidney Sparing Surgery versus Radical Nephroureterectomy for the Elective Treatment of Clinically Organ Confined Upper Tract Urothelial Carcinoma of the Distal Ureter. *The Journal of Urology*, 195(5):1354–1361. <https://doi.org/10.1016/j.juro.2015.11.036>
 13. Yakoubi R, Colin P, Seisen T, Léon P, Nison L, Bozzini G, Shariat SF, Rouprêt M (2014) Radical nephroureterectomy versus endoscopic procedures for the treatment of localised upper tract urothelial carcinoma: a meta-analysis and a systematic review of current evidence from comparative studies. *European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology*, 40(12):1629–1634. <https://doi.org/10.1016/j.ejso.2014.06.007>

14. Doll KM, Rademaker A, Sosa JA (2018) Practical Guide to Surgical Data Sets: Surveillance, Epidemiology, and End Results (SEER) Database. *JAMA surgery*, 153(6):588–589. <https://doi.org/10.1001/jamasurg.2018.0501>
15. Jiang Y, Yao Z, Zhu X, Wu B, Bai S (2020) Risk factors and oncological outcome for intravesical recurrence in organ-confined upper urinary tract urothelial carcinoma patients after radical nephroureterectomy: A propensity score-matched case control study. *International Journal of Surgery (London, England)*, 76:28–34. <https://doi.org/10.1016/j.ijssu.2020.02.015>
16. Chen J, Wang Z, Zhao J, Zhu S, Sun G, Liu J, Zhang H, Zhang X, Shen P, Shi M, Zeng H (2019) Pelvic lymph node dissection and its extent on survival benefit in prostate cancer patients with a risk of lymph node invasion >5%: a propensity score matching analysis from SEER database. *Scientific Reports*, 9(1):17985. <https://doi.org/10.1038/s41598-019-54261-4>
17. Yang J, Pan Z, He Y, Zhao F, Feng X, Liu Q, Lyu J (2019) Competing-risks model for predicting the prognosis of penile cancer based on the SEER database. *Cancer Medicine*, 8(18):7881–7889. <https://doi.org/10.1002/cam4.2649>
18. Nygård L, Vogelius IR, Fischer BM, Kjær A, Langer SW, Aznar MC, Persson GF, Bentzen SM (2018) A Competing Risk Model of First Failure Site after Definitive Chemoradiation Therapy for Locally Advanced Non-Small Cell Lung Cancer. *Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer*, 13(4):559–567. <https://doi.org/10.1016/j.jtho.2017.12.011>
19. Syed JS, Nguyen KA, Suarez-Sarmiento A, Johnson K, Leapman MS, Raman JD, Shuch B (2018) Survival outcomes for patients with localised upper tract urothelial carcinoma managed with non-definitive treatment. *BJU International*, 121(1):124–129. <https://doi.org/10.1111/bju.14042>
20. Lu X, Wang Y, Jiang L, Gao J, Zhu Y, Hu W, Wang J, Ruan X, Xu Z, Meng X, Zhang B, Yan F (2019) A Pre-operative Nomogram for Prediction of Lymph Node Metastasis in Bladder Urothelial Carcinoma. *Frontiers in Oncology*, 9<https://doi.org/10.3389/fonc.2019.00488>
21. V M, Rf Y, Pi K, Y L, Cg W, R Z, E K, A W, Jd R, M R, M R, F M, C B, W K, Sf S (2010) Preoperative Multivariable Prognostic Model for Prediction of Nonorgan Confined Urothelial Carcinoma of the Upper Urinary Tract. *The Journal of urology*, 184(2):453–8. <https://doi.org/10.1016/j.juro.2010.03.142>
22. A I, D S, Gv R, Ks P (2008) How to Build and Interpret a Nomogram for Cancer Prognosis. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*, 26(8):1364–70. <https://doi.org/10.1200/JCO.2007.12.9791>
23. Apolo AB, Ostrovnaya I, Halabi S, Iasonos A, Philips GK, Rosenberg JE, Riches J, Small EJ, Milowsky MI, Bajorin DF (2013) Prognostic Model for Predicting Survival of Patients With Metastatic Urothelial Cancer Treated With Cisplatin-Based Chemotherapy. *JNCI Journal of the National Cancer Institute*, 105(7):499–503. <https://doi.org/10.1093/jnci/djt015>
24. Sonpavde G, Pond GR, Rosenberg JE, Bajorin DF, Choueiri TK, Necchi A, Di Lorenzo G, Bellmunt J (2016) Improved 5-factor prognostic classification of patients receiving salvage systemic therapy for

Tables

Table 1. Baseline characteristics of patients between NSS and RN group before and after PSM.
Abbreviations: PSM, propensity-score matching; NSS, nephron-sparing surgery; RN, radical nephroureterectomy; NA, not available; IQR, interquartile range; The word "Unmarried" in marital status means unmarried, divorced, widowed, separated and never married, etc.

Characteristics	Overall cohort (n=1580)			After PSM (n=766)		
	RN group (n=1187)	NSS group (n=393)	p value	RN group (n=383)	NSS group (n=383)	p value
Follow-up period (months), median (IQR)	44 (22, 78)		NA	41 (19, 72)		NA
	45 (23, 80)	34 (18, 69)	NA	45 (21, 75)	34 (18, 69)	NA
Age at diagnosis (y), median (IQR)	71 (63, 78)	75 (66, 81)	<0.001	74 (66, 81)	75 (66, 81)	0.218
Gender, n(%)						
Male	673 (57.6%)	222 (56.5%)	0.942	205 (53.5%)	216 (56.4%)	0.424
Female	514 (43.3%)	171 (43.5%)		178 (46.5%)	167 (43.6%)	
Race, n(%)						
White	1042 (87.8%)	345 (87.8%)	0.191	342 (89.3%)	340 (88.8%)	0.781
Black	54 (4.5%)	11 (2.8%)		8 (2.1%)	11 (2.9%)	
Others	91 (7.7%)	37 (9.4%)		33 (8.6%)	32 (8.4%)	
Laterality, n(%)						
Left	594 (50%)	212 (53.9%)	0.180	203 (53.0%)	205 (53.5%)	0.885
Right	594 (50%)	181 (46.1%)		180 (47.0%)	178 (46.5%)	
Tumor location, n(%)						
Renal pelvis	734 (61.8%)	109 (27.7%)	<0.001	113 (29.5%)	109 (28.5%)	0.750
Ureter	453 (38.2%)	284 (72.3%)		270 (70.5%)	274 (71.5%)	
Clinical T stage, n(%)						
T1	745 (62.8%)	260 (66.2%)	0.225	256 (66.8%)	250 (65.3%)	0.647
T2	442 (37.2%)	133 (33.8%)		127 (33.2%)	133 (34.7%)	

Histologic grade, n(%)						
G1	69 (5.8%)	47 (12.0%)	<0.001	35 (9.1%)	40 (10.4%)	0.920
G2	282 (23.8%)	101 (25.7%)		103 (26.9%)	100 (26.1%)	
G3	256 (21.6%)	76 (19.3%)		79 (20.6%)	75 (19.6%)	
G4	580 (48.9%)	169 (43.0%)		166 (43.3%)	168 (43.9%)	
Marital status, n(%)						
Unmarried	445 (37.5%)	153 (38.9%)	0.609	154 (40.2%)	150 (39.2%)	0.768
Married	742 (62.5%)	240 (61.1%)		229 (59.8%)	233 (60.8%)	

Abbreviations: PSM, propensity-score matching; NSS, nephron-sparing surgery; RN, radical nephroureterectomy; NA, not available; IQR, interquartile range; The word "Unmarried" in marital status means unmarried, divorced, widowed, separated and never married, etc.

Table 2. Outcomes of univariate and multivariate Cox analysis for OS in overall cohort (n=1580).

Univariate Analysis				Multivariate Analysis		
	HR	95%CI	P-value	HR	95%CI	P-value
Age groups (y)						
<78.5	Reference			Reference		
>78.5	2.93	2.49-3.45	<0.0001	2.80	2.38-3.22	<0.001
Gender						
Male	Reference					
Female	1.01	0.865-1.19	0.857			
Race						
Other	Reference					
White	1.00	0.745-1.33	0.978			
Black	1.24	0.777-1.98	0.364			
Laterality						
Left	Reference					
Right	1.00	0.855-1.18	0.977			
Tumor Location						
Renal pelvis	Reference					
Ureter	1.38	1.18-1.62	<0.001			
AJCC T stage						
T1	Reference			Reference		
T2	1.56	1.33-1.83	<0.001	1.44	1.22-1.70	<0.001
Histologic grade						
G1&G2	Reference			Reference		
G3&G4	1.53	1.28-1.83	<0.001	1.38	1.15-1.66	0.001
Marital status						
Unmarried	Reference					
Married	0.742	0.632-0.872	<0.001			
Surgery methods						
RN	Reference			Reference		

NSS	1.42	1.19-1.69	<0.001	1.24	1.04-1.48	0.018
-----	------	-----------	--------	------	-----------	-------

Abbreviations; OS, overall survival; HR, hazard ratio; CI, confidence interval; RN, radical nephroureterectomy; NSS, nephron-sparing surgery. The word "Unmarried" in marital status means unmarried, divorced, widowed, separated and never married, etc.

Table 3. Univariable analysis for CSS in the overall cohort (n=1580) using the competing risk model.

Characteristics	Cumulative incidence function			SHR	P-value
	12-mo	36-mo	60-mo		
Age at diagnosis (y)	NA	NA	NA	1.03	<0.0001
Age groups					<0.0001
<78.5	0.0411	0.125	0.170	Reference	
>78.5	0.0783	0.228	0.304	1.95	<0.0001
Gender					0.496
Male	0.0499	0.149	0.201	Reference	
Female	0.0537	0.160	0.215	1.08	0.496
Race					0.657
Other	0.0600	0.177	0.238	Reference	
White	0.0506	0.151	0.204	0.840	0.373
Black	0.0545	0.162	0.212	0.906	0.763
Laterality					0.917
Left	0.0513	0.153	0.206	Reference	
Right	0.0519	0.154	0.208	1.01	0.917
Tumor location					0.002
Renal pelvis	0.0434	0.131	0.177	Reference	
Ureter	0.0609	0.180	0.241	1.42	0.002
AJCC T stage					<0.001
T1	0.0373	0.114	0.155	Reference	
T2	0.0765	0.223	0.297	2.09	<0.001
Histologic grade					<0.0001
G1	0.0280	0.0865	0.119	Reference	
G2	0.0301	0.0928	0.127	1.08	0.808
G3	0.0630	0.187	0.252	2.29	0.004
G4	0.610	0.182	0.245	2.21	0.004
Marital status					0.159
Unmarried	0.0568	0.168	0.226	Reference	

Married	0.0484	0.149	0.196	0.849	0.159
Surgery methods					0.002
RN	0.0463	0.139	0.189	Reference	
NSS	0.0672	0.198	0.264	1.47	0.002

Abbreviations: SHR, subdistribution hazard ratio; CI, confidence interval; RN, radical nephroureterectomy; NSS, nephron-sparing surgery. The word "Unmarried" in marital status means unmarried, divorced, widowed, separated and never married, etc.

Table 4. Multivariable analysis for CSS in overall cohort (n=1580) using the competing risk model (p<0.0001).

Variables	SHR	95%CI	P-value
Age groups			
<78.5	Reference		
>78.5	1.82	1.44-2.30	<0.001
AJCC T stage			
T1	Reference		
T2	1.88	1.50-2.37	<0.001
Histologic grade			
G1&G2	Reference		
G3&G4	1.83	1.38-2.42	<0.001
Surgery methods			
RN	Reference		
NSS	1.47	1.15-1.88	0.002

Abbreviations: SHR, subdistribution hazard ratio; CI, confidence interval; RN, radical nephroureterectomy; NSS, nephron-sparing surgery.

Table 5. The scores of each value in **Figure 5** and **Figure 6**.

Variables	Nomogram for OS	Nomogram for CSS
Age groups		
<78.5	0	0
>78.5	100	100
AJCC T stage		
T1	0	0
T2	35	90
Histologic grade		
G1&G2	0	0
G3&G4	31	91
Surgery methods		
RN	0	0
NSS	21	56

Abbreviations: OS, overall survival; CSS, cancer-specific survival; RN, radical radical nephroureterectomy; NSS, nephron-sparing surgery.

Figures

Figure 1

The flow chart of study participant selection. Abbreviations: UTUC, upper urinary tract urothelial carcinoma.

Figure 2

The plots of the PSM process. A. the love-plot (dot chart) of the standardised percentage bias for each covariate before and after PSM. B. the kernel density plot of propensity score before and after PSM. Abbreviations: PSM, propensity score-matching; RN, radical nephroureterectomy; NSS, nephron-sparing surgery.

Figure 3

The Kaplan-Meier curves stratified by surgery methods before and after PSM. A. the OS curves before PSM (N=1580). B. the OS curves of patients with ureteral lesions before PSM (N=737). C. the OS curves of patients with renal pelvic lesions before PSM (N=843). D. the OS curves after PSM (N=766). E. the OS curves of patients with renal pelvic lesions after PSM (N=222). F. the OS curve of patients with ureteral

lesions after PSM (N=544). Abbreviations: PSM, propensity score-matching; OS, overall survival; RN, radical nephroureterectomy; NSS, nephron-sparing surgery.

Figure 4

The CIF curves stratified by surgery methods after PSM. A. the CIF curves after PSM (N=766). B. the CIF curves of patients with ureteral lesions after PSM (N=544). C. the CIF curves of patients with renal pelvic

lesions after PSM (N=222). Abbreviations: CIF, cumulative incidence function; PSM, propensity score-matching; RN, radical nephroureterectomy; NSS, nephron sparing surgery.

Figure 5

The nomogram for predicting the 3-year ACM and 5-year ACM probabilities of patients with organ-localized UTUC. Abbreviations: ACM; all-cause mortality; RN, radical nephroureterectomy; NSS, nephron-sparing surgery; UTUC, upper urinary tract urothelial carcinoma.

Figure 6

The nomogram for predicting the 3-year CSM and 5-year CSM probabilities of patients with organ-localized UTUC. Abbreviations: CSM, cancer-specific mortality; UTUC, upper urinary tract urothelial carcinoma; RN, radical nephroureterectomy; NSS, nephron-sparing surgery.

Figure 7

Calibration curves for predicting the 3-year (A) and 5-year (B) ACM of organ-localized UTUC in the overall cohort (N=1580). Abbreviations: ACM, all-cause mortality; UTUC, upper urinary tract urothelial carcinoma.

Figure 8

Calibration curves for predicting the 3-year (A) and 5-year (B) CSM of organ-localized UTUC in the overall cohort (N=1580). And their Brier scores were also shown in the figures. Abbreviations: CSM, cancer-specific mortality; UTUC, upper urinary tract urothelial carcinoma.