Published in final edited form as:

Eur J Surg Oncol. 2016 November ; 42(11): 1625–1635. doi:10.1016/j.ejso.2016.08.008.

A systematic review and meta-analysis of oncological and renal function outcomes obtained after segmental ureterectomy versus radical nephroureterectomy for upper tract urothelial carcinoma

Dong Fang^{a,f}, Thomas Seisen^{b,c,f}, Kunlin Yang^a, Pei Liu^a, Xinxiang Fan^d, Nirmish Singla^e, Gengyan Xiong^a, Lei Zhang^a, Xuesong Li^{a,*}, Liqun Zhou^a

^aDepartment of Urology, Peking University First Hospital, Institute of Urology, Peking University, National Urological Cancer Centre, No. 8 Xishiku St, Xicheng District, Beijing 100034, China

^bAcademic Department of Urology, Pitié Salpêtrière Hospital, APHP, 47–83 Boulevard de l'Hôpital, Paris F-75013, France

^cUPMC University Paris 06, GRC5, ONCOTYPE-Uro, Institut Universitaire de Cancérologie, Paris F-75005, France

^dDepartment of Urology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, No.107 Yanjiang West Rd, Yuexiu District, Guangzhou 510120, China

^eDepartment of Urology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390, USA

Abstract

Objective: To perform a systematic review and meta-analysis of the comparative studies reporting oncological and renal function outcomes of segmental ureterectomy (SU) versus radical nephroureterectomy (RNU) for upper tract urothelial carcinomas (UTUC).

Materials and methods: A literature search on Pubmed, Embase, and the Cochrane library was conducted according to the PRISMA guidelines, and a meta-analysis was performed to assess cancer-specific survival (CSS), overall survival (OS), recurrence-free survival (RFS), intravesical recurrence free survival (IVRFS) and surgery-related variations in estimated glomerular filtration rate (eGFR).

Results: A total of 11 retrospective studies with 3963 patients who underwent either SU (n = 983; 24.8%) or RNU (n = 2980; 75.2%) were included. Although patients treated with SU were more likely to be diagnosed with favorable pathological features, the meta-analysis of unadjusted data revealed no significant difference between both groups in terms of CSS (HR 0.90, $p = 0.33$)

*Corresponding author. Fax: +86 10 66551726., pineneedle@sina.com (X. Li).

^fEqual study contribution.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.ejso.2016.08.008>.

Conflict of interest

The authors state they have no conflict of interest to disclose regarding current manuscript.

and OS (HR 0.98, $p = 0.93$). Accordingly, the meta-analysis of adjusted data confirmed equivalent CSS (HR = 0.90, $p = 0.47$) between SU and RNU. Similarly, no significant difference was found in terms of RFS (HR 1.06, $p = 0.72$) and IVRFS (HR 1.35, $p = 0.39$). However, a significant decreased risk of impaired renal function was observed after SU when compared to RNU (mean eGFR difference = 9.32 ml/1.73 m², $p = 0.007$).

Conclusion: Although adverse patient and tumor characteristics were not equally balanced between treatment arms, our systematic review and meta-analysis supports similar oncological outcomes between SU and RNU, with better preservation of renal function after SU. As such, SU should be preferably used as the first-line treatment for low-risk ureter tumors, while considered for selected cases of high-risk disease.

Keywords

Kidney-sparing surgery; Meta-analysis; Radical nephroureterectomy; Segmental ureterectomy; Upper tract urothelial carcinomas

Introduction

Radical nephroureterectomy (RNU) with bladder cuff removal is currently considered as the standard of care for the management of upper tract urothelial carcinomas (UTUC).¹ However, due to the potential cardiovascular morbidity associated with chronic renal failure, RNU could induce unnecessary increased risk of non-cancer related death.² Consequently, although it was traditionally restricted to imperative indications only, such as solitary kidney, chronic kidney disease and synchronous bilateral disease, kidney-sparing surgery (KSS) has been recently proposed as an alternative to RNU for the treatment of selected cases diagnosed with low-risk UTUC.³ This approach could reduce the risk of post-operative impaired renal function commonly related to the nephron loss at the time of RNU^{4,5} and, consequently, help to optimize the use of adjuvant or delayed cisplatin-based chemotherapy if needed.^{6–11}

Specifically, endoscopic surgery (ENDO) and segmental ureterectomy (SU) can be considered to spare the renal unit while maintaining oncological outcomes obtained after RNU.¹² Interestingly, a meta-analysis has recently demonstrated that overall survival (OS) and cancer specific survival (CSS) were equivalent between ENDO and RNU.¹³ However, although oncological outcomes of SU have been largely described over the last several years, there is no broad consensus regarding its efficacy when compared to RNU. Thus, we aimed to perform a systematic review and meta-analysis of comparative studies reporting oncological and renal function outcomes of SU versus RNU.

Materials and methods

Search strategy

Two authors (DF and KY) performed together a computerized bibliographic search of the Pubmed, Embase, and the Cochrane databases in July 2015, with an update search in March 2016. The following search terms (Segmental Ureterectomy OR Partial Ureterectomy OR Distal Ureterectomy OR Nephron Sparing OR Parenchymal sparing OR Kidney Sparing)

AND (Upper Tract Urothelial Carcinoma OR Upper Tract OR Urothelial Carcinoma OR Transitional Cell Carcinoma) AND (Radical OR Nephroureterectomy) were used according to a free text protocol that applied only “Human” and “English language” filters. Links to related articles and citations were also surveyed.

Inclusion criteria

According to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines, we used the Population, Intervention, Comparator, Outcome, and Study design (PICOS) approach to define study eligibility.¹⁴ Records were considered relevant for this systematic review and meta-analysis if they compared patients diagnosed with UTUC (P) and treated with SU (I) to those treated with RNU (C) for oncological and renal function outcomes (O) using survival and peri-operative estimated glomerular filtration rate (eGFR) analyses (S). Non comparative studies, case reports, review articles, editorials, letters and meeting abstracts were excluded during the systematic review process that also applied the following inclusion criteria:

1. Intervention group should exclusively include patients treated with SU or distal ureterectomy;
2. Control group should exclusively include patients treated with RNU;
3. Study should report at least one of the following outcomes: CSS, OS, recurrence-free survival (RFS), intravesical RFS (IVRFS) or surgery-related variations in estimated glomerular filtration rate (eGFR).

If two or more relevant publications originated from the same research group, we selected only the latest one.

Systematic review process

After duplicates removal, two authors (DF and KY) performed independent review of 118 abstracts to ultimately select 15 studies for full text assessment.^{15–29} Any discrepancies in study inclusions were resolved by consulting the senior author (XL). In accordance with the previously mentioned inclusion criteria, our final selection was comprised of 11 articles published between 2007 and 2015.^{19–29} The PRISMA flowchart depicting the systematic review process is shown in Fig. 1.

Quality of data assessment

Only mono- (n = 5) or multicentric (n = 6) studies with retrospective design were found during the literature search. No randomized or non-randomized prospective studies were available. Consequently, the assessment of oncological and renal function outcomes of SU versus RNU was supported by studies with level 3 evidence.

The quality of included studies was independently evaluated by two authors (KY and PL) using the modified Newcastle–Ottawa Scale³⁰ which contains three domains: patient selection, comparability of control and intervention groups and assessment of outcomes. A score of 0–9 stars was allocated to each study. We defined high quality as a score of 6e9 and low quality as a score <6. According to the results of Table 1, all included studies were

considered to be of high methodological quality. The other overall characteristics of included studies are shown in Table 1.

Data abstraction

Data were independently abstracted by two reviewers (DF and KY) from all included studies and subsequently crosschecked to ensure their accuracy. Any discrepancies in abstracted data were resolved by consulting the senior author (XL).

We started by abstracting baseline clinical (age, gender, bladder cancer history) and pathological (tumor stage, grade or focality, and lymph node or surgical margins status) characteristics of patients treated with SU or RNU and then, oncological and renal function outcomes were recorded as primary endpoints to compare effectiveness of SU versus RNU.

Outcomes measures

Oncological outcomes including CSS, OS, RFS and IVRFS were primarily assessed using available Hazard Ratios (HRs) from univariable analyses and their corresponding 95% confidence intervals (CIs). However, when unadjusted HRs were not available, we applied the formula described by Parmar et al.³¹ to calculate the data generated from published Kaplan–Meier curves using the software Engauge Digitizer version 4.1 (free software downloaded from <http://sourceforge.net>). For each oncological outcome, we calculated risk ratios (RRs) of potential confounders of treatment effect to assess the comparability of intervention and control arms. In addition, we abstracted HRs from multivariable analyses and their corresponding 95% CI when available to separately evaluate adjusted oncological outcomes of SU versus RNU.

Regarding renal function outcomes, we used the mean changes of eGFR to assess the surgery-related modifications. Mean pre- and post-operative eGFR were recorded with their available or calculated standard deviations (SDs) to evaluate the weighted mean difference. Specifically, for studies that only provided means and range values, the SDs were calculated using the technique proposed by Hozo et al.³²

Statistical analyses

A meta-analysis was performed for each oncological outcomes using available or calculated unadjusted HRs. In addition, we conducted separate meta-analyses to pool together adjusted HRs abstracted from multivariable analyses when available. Because HRs translate time-to-event outcomes, cumulative effects of surgical treatments were evaluated by the inverse variance method. Regarding the potential confounders assessment, we made cumulative analyses of RRs, whereas for renal function outcomes, we performed a meta-analysis of the weighted mean differences in terms of eGFR.

Our method consisted of using a fixed- or random-effect model according to the between-study heterogeneity. Statistical heterogeneity across included studies was assessed using both the Cochrane Q test and the I^2 statistic, which describes the percentage of total variation across studies caused by heterogeneity rather than chance. A p -value < 0.05 or an $I^2 > 50\%$ denoted the presence of significant between-study heterogeneity, which resulted in

the use of the random-effect model. Alternatively, when no significant between-study heterogeneity was found, we used the fixed-effect model to perform cumulative analyses.³³ The small-study effect and publication bias were evaluated by visual inspection of funnel plots for all comparisons.³⁴ All statistical analyses were performed using Review Manager 5.3 software (The Cochrane Collaboration, Copenhagen, Denmark).

Results

Baseline characteristics of population study

Overall, 3963 patients who underwent either SU ($n = 983$; 24.8%) or RNU ($n = 2980$; 75.2%) were included in this meta-analysis. When they were specified by the authors, indications for performing SU were highly variable across selected studies (Table 1). Consequently, the SU group gathered unknown proportions of imperative and elective cases of KSS for UTUC.

The baseline clinical and pathological characteristics of study population are reported in Supplementary Tables 1 and 2. Some significant differences were found between SU and RNU groups. Particularly, patients treated with RNU were more likely to be diagnosed with adverse clinical and pathological features including higher pT stage and tumor grade. Overall, the median follow-up of this worldwide cohort including patients from North America^{20,21,23,24,28,29}, Europe^{19,22,25} and Asia^{26,27} ranged from 26 (10–48) to 58 (3–260) months without any significant difference between intervention and control arm except in the study by Singla et al.²⁹

Cancer specific survival

All included studies except that by Singla et al.²⁹ provided unadjusted data on CSS but HRs were calculated from Kaplan Meier (KM) curves for 5 of them.^{19,21,23,27,28} The reported 5-year cumulative CSS rates ranged from 54 to 90% and 64 to 86% in SU and RNU groups, respectively (Supplementary Table 3). After performing a meta-analysis of unadjusted HRs, there was no significant difference between SU and RNU ($HR = 0.90$, 95% $CI = [0.73–1.11]$; $p = 0.33$) in terms of CSS (Fig. 2a). However, when analyzing the potential confounders for surgical treatment effect in studies that reported unadjusted data on CSS, some significant differences were found between both groups. Indeed, patients treated with SU were less likely to be diagnosed with adverse pathological features including non-organ confined ($RR = 0.68$, 95% $CI = [0.60–0.78]$; $p < 0.001$) (Fig. 2b) and high-grade ($RR = 0.89$, 95% $CI [0.83–0.95]$; $p = 0.0002$) (Fig. 2c) tumors with lymph node metastases ($RR = 0.40$, 95% $CI = [0.22–0.71]$; $p = 0.002$) (Fig. 2d). Nevertheless, there was no significant difference between both groups ($RR 1.25$, 95% $CI = [0.81–1.94]$, $p = 0.32$) in terms of positive surgical margins (Fig. 2e).

To address this limitation, Colin et al. performed subgroup analyses based on pT stage.²² No significant difference was found in terms of CSS between treatment arms in the group of patients with non-muscle invasive UTUC. In addition, Bagrodia et al. demonstrated that SU and RNU were equivalent in terms of CSS for the treatment of high-grade disease.²⁴ In

addition, adjusted HRs from multivariable analyses including potential confounders for CSS were available in three reports.^{20,22,26}

Interestingly, when restricting cumulative analyses to available adjusted data, the pooled HR was 0.90 with corresponding 95% CI = [0.68–1.19] ($p = 0.47$) (Supplementary Fig. 1).

Overall survival

Only four studies reported surgical treatment-related HRs from univariable analyses²⁵ or KM curves^{19,23,28} for OS and no adjusted data were available. The reported 5-year cumulative OS rates ranged from 40 to 72% and 43 to 67% in SU and RNU groups, respectively (Supplementary Table 3). After performing a meta-analysis of unadjusted HRs, there was no significant difference between SU and RNU (HR = 0.98, 95% CI = [0.63–1.53]; $p = 0.93$) in terms of OS (Supplementary Fig. 2a). However, no subgroup or multivariable analysis was performed to control for the pre-operative comorbidities of included patients. Although no data were available to assess the differences in general condition between both groups, we attempted to compare the main tumor characteristics. In the studies included for OS analysis, patients treated with SU were still less likely to exhibit non-organ confined features (RR = 0.58, 95% CI = [0.36–0.92]; $p = 0.02$) (Supplementary Fig. 2b).

Nevertheless, there was no significant difference in terms of high-grade disease (RR = 0.78, 95% CI = [0.59–1.03]; $p = 0.08$) (Supplementary Fig. 2c), positive lymph node status (RR = 0.55, 95% CI = [0.25–1.23]; $p = 0.15$) (Supplementary Fig. 2d) and positive surgical margins (RR = 0.54, 95% CI = [0.08–3.90]; $p = 0.54$) (Supplementary Fig. 2e) between both groups.

Recurrence-free survival

The definition of recurrence was highly variable among included studies. However, four reports defined RFS as local or metastatic relapse and corresponding HRs were available from univariable analysis²⁶ or KM curves.^{21,23,28} The reported 5-year cumulative RFS rates ranged from 28 to 84% and 22 to 69% in SU and RNU groups, respectively (Supplementary Table 3). After performing a meta-analysis of unadjusted HRs, there was no significant difference between SU and RNU (HR = 1.06, 95% CI = [0.76–1.48]; $p = 0.72$) in terms of RFS (Fig. 3a). However, when analyzing the potential confounders in the studies included for RFS analysis, we found that patients treated with SU were less likely to be diagnosed with adverse pathological features including non-organ confined (RR = 0.58, 95% CI = [0.38–0.88]; $p = 0.01$) (Fig. 3b), high-grade (RR = 0.79, 95% CI = [0.68–0.93]; $p = 0.004$) (Fig. 3c) tumors with lymph node metastases (RR = 0.41, 95% CI [0.18–0.93]; $p = 0.03$) (Fig. 3d), although there was no significant difference in terms of positive surgical margins (RR 0.69, 95% CI = [0.05–9.13], $p = 0.78$) (Fig. 3e). Interestingly, Colin et al. and Fukushima et al. performed subgroup analyses that showed no significant difference between treatment arms in the groups of patients diagnosed with either non-muscle or muscle invasive UTUC.^{22,26}

Intravesical recurrence-free survival

In addition, three studies provided unadjusted data on IVRFS^{24,25,27} but HRs were calculated from KM curves for two of them.^{24,27} The reported 5-year cumulative IVRFS rates ranged from 54 to 69.4% and 57 to 75.9% in SU and RNU groups, respectively (Supplementary Table 3). After performing a meta-analysis of unadjusted HRs, no statistical difference was observed between SU and RNU (HR = 1.16, 95% CI = [0.82–1.64]; $p = 0.39$) in terms of IVRFS (Supplementary Fig. 3a). Because no adjusted data was available, we performed cumulative analyses of the potential confounders of the treatment effect in the studies that provided unadjusted HRs for IVRFS. No significant difference in terms of tumor stage (RR = 0.83, 95% CI = [0.42–1.66]; $p = 0.60$) (Supplementary Fig. 3b) or tumor grade (RR = 0.83, 95% CI = [0.64–1.10]; $p = 0.19$) (Supplementary Fig. 3c) was found. However, although patients treated with SU were less likely to be diagnosed with multifocal tumors (RR = 0.25, 95% CI = [0.13–0.49]; $p < 0.0001$) (Supplementary Fig. 3d), they had higher rate of bladder cancer history (RR = 1.60, 95% CI = [1.00–2.55]; $p = 0.05$) (Supplementary Fig. 3e).

Renal function outcomes

Data on renal function before and after surgery were available in four included studies.^{23,26,27,29} Baseline renal function was similar between treatment groups in all reports except one²³ (Supplementary Table 1). The use of peri-operative chemotherapy was poorly described but Bagrodia et al. and Singla et al. reported that patients treated with SU or RNU were more likely to receive adjuvant or neoadjuvant chemotherapy, respectively.^{24,29} Nevertheless, the meta-analysis of the weighted mean changes in peri-operative eGFR revealed that RNU was associated with a significant decreased of 9.32 ml/1.73 m² ($p = 0.007$) when compared to the SU group (Fig. 4).

Discussion

The most recent European guidelines advocate the use of SU only for the treatment of either imperative cases or highly selected patients with low-risk UTUC defined according to CT-scan features, tumor grade from urinary cytology and more importantly ureteroscopic assessment.³ Such caution is justified by the theoretical drawback of SU, which consists in a potential increased risk of ipsilateral upper urinary tract recurrence and, thus, cancer-specific death when compared to radical extirpation surgery. Indeed, RNU logically allows for complete excision of the pelvicalyceal and ureteral urothelium while, according to the pan-urothelial field defect theory, a more conservative approach could result in repeated local recurrences.^{35,36} In addition, as tumor multifocality is frequently underestimated at the time of preoperative work-up, removal of the whole ipsilateral upper urinary tract may be a reasonable option to ensure optimal treatment of UTUC. Accordingly, the National Comprehensive Cancer Network guidelines also support the use of SU only in properly selected patients with low-grade middle or distal ureter tumors.³⁷ However, SU remains poorly assessed in the current literature and all these assumptions are mostly based on heterogeneous data from small retrospective cohort studies with low level of evidence.

To address this vacuum, we performed a systematic review and meta-analysis of oncological and renal function outcomes of SU based on data obtained from all the available comparative studies. Our findings support the equivalence between SU and RNU in terms of CSS, OS, RFS or IVRFS with a better renal function preservation when using KSS. Interestingly, as we included studies reporting the results of SU for imperative and elective cases of UTUC, such a conservative approach could theoretically be considered as the first line treatment in both settings. However, although we were able to obtain outcomes adjusted for the confounders of interest for CSS, oncological effectiveness of SU is mostly supported by unadjusted data precluding from controlling for patient and tumor characteristics among treatment arms. Also, subgroup analyses are scarce in the literature and underpowered to demonstrate any significant difference between SU and RNU as acknowledged by Bagrodia et al.²⁴

As a consequence, we performed meta-analyses of the baseline population characteristics among each included studies to explore the comparability of SU and RNU groups, and we found that patients treated with SU were mostly selected for favorable features. Indeed, significant differences existed in terms of tumor stage and grade between treatment arms, especially when analyzing CSS and RFS. In addition, the rate of positive lymph node disease was significantly higher in the RNU groups. Similarly, patients treated with radical extirpative surgery were more likely to be diagnosed with tumor multifocality, which has been previously reported to be related to IVRFS³⁸ but they had also lower rates of bladder cancer history. Only the risk of positive surgical margins was equivalent between SU and RNU groups but it could simply result from better tumor characteristics in the conservative treatment arm. Consequently, all these data taken together suggest that SU followed by ureteroureterostomy or ureteroneocystostomy should be used to electively treat patients with low-risk UTUC. Nonetheless, given that adjusted CSS was equivalent between intervention and control arms in the whole study population, SU could be considered in selected cases of high-risk UTUC.

As it spares the renal unit, the main benefit of SU is the theoretical preservation of post-operative renal function. Logically, such a conservative approach is considered along with endoscopic surgery as first line treatment in imperative cases including solitary kidney, chronic kidney disease and synchronous bilateral disease. However, our results suggested that all patients could experience better post-operative renal function after SU when compared to RNU and, thus, avoid unnecessary risk of post-operative dialysis that would deeply impact the quality of life. In addition, because of the removal of the obstructive part of the ureter, increased renal function has also been observed after SU.²³

Although we were not able to demonstrate a translation of such a benefit in terms of OS, we believe that the equal rates of deaths from any cause between treatment arms could actually favor SU. Indeed, it is preferred to perform KSS in patients with unfavorable general condition and significant comorbidities. As a consequence, the proportion of these patients was probably lower in the RNU group and the equivalence in terms of OS could result from the better preservation of the renal function among patients treated with SU. Furthermore, although the level of evidence remains low to propose SU for the elective treatment of clinically non-organ confined UTUC, the preservation of renal function after SU could also

help to optimize the use of adjuvant cisplatin-based chemotherapy when necessary and, thus, prolong survival.^{24,29}

Due to the recent advances in terms of equipment and technique, ENDO including notably ureteroscopic management of UTUC, has gained wider acceptance.^{39,40} However, compared to the ureteroscopic approach, the obvious benefits of SU are en bloc resection of the ureteral tumor with surrounding soft tissue and lymph node dissection. Adequate specimens for pathological evaluation can be obtained from such a surgery, which results in proper staging of the disease and risk-adapted adjuvant management of UTUC. Furthermore, the high cost of endoscopic devices and expertise can not be ignored for many institutions all around the world.²²

Although Yacoubi et al. recently demonstrated that there was also no significant difference between ENDO and RNU,¹³ we believe that SU could be a better alternative for the treatment of ureteral tumors because of the lower risk of local recurrence.¹⁸ Indeed, Bin et al. have previously reported that OS and CSS were similar between SU and RNU but local RFS was shorter after ENDO.²¹

We acknowledge that our meta-analysis is limited by the retrospective design of the included studies. However, this limitation is inherent to the field of UTUC where only reports with level 3 evidence are available. As a consequence, different data on patient's and tumor's characteristics were missing to perform adjusted analyses but we attempted to assess the comparability of treatment arms and adapted our findings accordingly.

In conclusion, although adverse patient and tumor characteristics were not equally balanced between both treatment arms, our systematic review and meta-analysis supports similar oncological outcomes of SU when compared to RNU. In addition, we found that preservation of the renal function is significantly better after SU when compared to RNU. These results suggest that SU should be used as the first line treatment for low-risk UTUC of the ureter, while considered for selected cases of high-risk UTUC. However, prospective clinical trials would be necessary to adequately compare the oncological and renal function outcomes of SU and RNU.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by grants from the Collaborative Research Foundation of Peking University Health Science Center and National Taiwan University, the College of Medicine (BMU20120318), the Natural Science Foundation of China (81402083, 81372746), the Natural Science Foundation of Beijing (7122183, 7152146), the clinical features research of Capital (No. Z151100004015173), and Research Foundation of Peking University First Hospital (No. 2015QN026). The authors thank the entire staff of the Department of Urology, Peking University First Hospital.

Role of the funding source

The role of fund for this manuscript: data collection.

Abbreviations:

KSS	Kidney-sparing surgery
RNU	Radical nephroureterectomy
SU	Segmental ureterectomy
UTUC	Upper tract urothelial carcinomas
CSS	Cancer-specific survival
OS	Overall survival
RFS	Recurrence-free survival
IVRFS	Intravesical recurrence free survival
eGFR	estimated glomerular filtration rate

References

1. Cummings KB. Nephroureterectomy: rationale in the management of transitional cell carcinoma of the upper urinary tract. *Urol Clin North Am* 1980;7(3):569–78. [PubMed: 7456169]
2. Raman JD, Lin YK, Kaag M, et al. High rates of advanced disease, complications, and decline of renal function after radical nephroureterectomy. *Urol Oncol* 2014;32(1). 47 e9–14.
3. Roupret M, Babjuk M, Comperat E, et al. European association of Urology guidelines on upper urinary tract urothelial cell carcinoma: 2015 update. *Eur Urol* 2015 11;68(5):868–79. [PubMed: 26188393]
4. Fang D, Xiong G, Li X, et al. Incidence, characteristics, treatment strategies, and oncologic outcomes of synchronous bilateral upper tract urothelial carcinoma in the Chinese population. *Urol Oncol* 2015; 33(2). 66 e1–11.
5. Fang D, Zhang L, Li X, et al. Risk factors and treatment outcomes of new contralateral upper urinary urothelial carcinoma after nephroureterectomy: the experiences of a large Chinese center. *J Cancer Res Clin Oncol* 2014;140(3):477–85. [PubMed: 24469253]
6. Kaag M, Trost L, Thompson RH, et al. Pre-operative predictors of renal function decline following radical nephroureterectomy for upper tract urothelial carcinoma. *BJU Int* 2013;114(5):674–9.
7. Lane BR, Smith AK, Larson BT, et al. Chronic kidney disease after nephroureterectomy for upper tract urothelial carcinoma and implications for the administration of perioperative chemotherapy. *Cancer* 2010;116(12):2967–73. [PubMed: 20564402]
8. Xylinas E, Rink M, Margulis V, et al. Impact of renal function on eligibility for chemotherapy and survival in patients who have undergone radical nephro-ureterectomy. *BJU Int* 2013;112(4):453–61. [PubMed: 23464979]
9. Kaag MG, O'Malley RL, O'Malley P, et al. Changes in renal function following nephroureterectomy may affect the use of perioperative chemotherapy. *Eur Urol* 2010;58(4):581–7. [PubMed: 20619530]
10. Hoshino K, Kikuchi E, Tanaka N, et al. Preoperative hydronephrosis: independent predictor for changes in renal function following nephroureterectomy. *Jpn J Clin Oncol* 2012;42(3):202–7. [PubMed: 22246718]
11. Rodriguez Faba O, Palou J, Breda A, et al. Predictive factors for impaired renal function following nephroureterectomy in upper urinary tract urothelial cell carcinoma. *Urol Int* 2014;92(2):169–73. [PubMed: 24280761]
12. Seisen T, Colin P, Roupret M. Risk-adapted strategy for the kidney-sparing management of upper tract tumours. *Nat Rev Urol* 2015; 12(3):155–66. [PubMed: 25708579]

13. Yakoubi R, Colin P, Seisen T, et al. 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. *Eur J Surg Oncol* 2014; 40(12):1629–34. [PubMed: 25108813]
14. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009;6(7):e1000100. [PubMed: 19621070]
15. Hall MC, Womack S, Sagalowsky AI, Carmody T, Erickstad MD, Roehrborn CG. Prognostic factors, recurrence, and survival in transitional cell carcinoma of the upper urinary tract: a 30-year experience in 252 patients. *Urology* 1998;52(4):594–601. [PubMed: 9763077]
16. Simhan J, Smaldone MC, Egleston BL, et al. Nephron-sparing management vs radical nephroureterectomy for low- or moderate-grade, low-stage upper tract urothelial carcinoma. *BJU Int* 2014;114(2):216–20. [PubMed: 24053485]
17. Lughezzani G, Jeldres C, Isbarn H, et al. Nephroureterectomy and segmental ureterectomy in the treatment of invasive upper tract urothelial carcinoma: a population-based study of 2299 patients. *Eur J Cancer* 2009;45(18):3291–7. [PubMed: 19615885]
18. Seisen T, Nison L, Remzi M, et al. Oncological outcomes of kidney-sparing surgery versus radical nephro-ureterectomy for the elective treatment of clinically organ-confined upper tract urothelial carcinoma of the distal ureter. *J Urol* 2015;195(5):1354–61. [PubMed: 26612196]
19. Giannarini G, Schumacher MC, Thalmann GN, Bitton A, Fleischmann A, Studer UE. Elective management of transitional cell carcinoma of the distal ureter: can kidney-sparing surgery be advised? *BJU Int* 2007;100(2):264–8. [PubMed: 17532855]
20. Jeldres C, Lughezzani G, Sun M, et al. Segmental ureterectomy can safely be performed in patients with transitional cell carcinoma of the ureter. *J Urol* 2010;183(4):1324–9. [PubMed: 20171666]
21. Bin X, Roy OP, Ghiraldi E, et al. Impact of tumour location and surgical approach on recurrence-free and cancer-specific survival analysis in patients with ureteric tumours. *BJU Int* 2012;110(11 Pt B):E514–9. [PubMed: 22578024]
22. Colin P, Ouzzane A, Pignot G, et al. Comparison of oncological out-comes after segmental ureterectomy or radical nephroureterectomy in urothelial carcinomas of the upper urinary tract: results from a large French multicentre study. *BJU Int* 2012;110(8):1134–41. [PubMed: 22394612]
23. Silberstein JL, Power NE, Savage C, et al. Renal function and oncologic outcomes of parenchymal sparing ureteral resection versus radical nephroureterectomy for upper tract urothelial carcinoma. *J Urol* 2012;187(2):429–34. [PubMed: 22177163]
24. Bagrodia A, Kuehhas FE, Gayed BA, et al. Comparative analysis of oncologic outcomes of partial ureterectomy vs radical nephroureterectomy in upper tract urothelial carcinoma. *Urology* 2013;81(5):972–7. [PubMed: 23523292]
25. Dalpiaz O, Ehrlich G, Quehenberger F, Pummer K, Zigeuner R. Distal ureterectomy is a safe surgical option in patients with urothelial carcinoma of the distal ureter. *Urol Oncol* 2014;32(1). 34 e1–8.
26. Fukushima H, Saito K, Ishioka J, et al. Equivalent survival and improved preservation of renal function after distal ureterectomy compared with nephroureterectomy in patients with urothelial carcinoma of the distal ureter: a propensity score-matched multicenter study. *Int J Urol* 2014;21(11):1098–104. [PubMed: 25041040]
27. Hung SY, Yang WC, Luo HL, Hsu CC, Chen YT, Chuang YC. Segmental ureterectomy does not compromise the oncologic outcome compared with nephroureterectomy for pure ureter cancer. *Int Urol Nephrol* 2014;46(5):921–6. [PubMed: 24202956]
28. Pedrosa JA, Masterson TA, Rice KR, et al. Oncologic outcomes and prognostic impact of urothelial recurrences in patients undergoing segmental and total ureterectomy for upper tract urothelial carcinoma. *Can Urol Assoc J* 2015;9(3e4):E187–92. [PubMed: 26085878]
29. Singla N, Gayed BA, Bagrodia A, et al. Multi-institutional analysis of renal function outcomes following radical nephroureterectomy and partial ureterectomy for upper tract urothelial carcinoma. *Urol Oncol* 2015;33(6). 268 e1–7.
30. Lo CK, Mertz D, Loeb M. Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments. *BMC Med Res Methodol* 2014;14:45. [PubMed: 24690082]

31. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival end-points. *Stat Med* 1998;17(24):2815–34. [PubMed: 9921604]
32. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005;5:13. [PubMed: 15840177]
33. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7(3):177–88. [PubMed: 3802833]
34. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315(7109):629–34. [PubMed: 9310563]
35. Miyake H, Hara I, Kamidono S, Eto H. Multifocal transitional cell carcinoma of the bladder and upper urinary tract: molecular screening of clonal origin by characterizing CD44 alternative splicing patterns. *J Urol* 2004;172(3):1127–9. [PubMed: 15311055]
36. Jones TD, Wang M, Eble JN, et al. Molecular evidence supporting field effect in urothelial carcinogenesis. *Clin Cancer Res* 2005;11(18):6512–9. [PubMed: 16166427]
37. National comprehensive cancer guidelines: bladder cancer including upper tract tumors and urothelial carcinoma of the prostate.V1: National comprehensive cancer network, Inc. p. Available at: <http://www.nccn.org>; 2009 [accessed].
38. Seisen T, Granger B, Colin P, et al. A systematic review and meta-analysis of clinicopathologic factors linked to intravesical recurrence after radical nephroureterectomy to treat upper tract urothelial carcinoma. *Eur Urol* 2015;67(6):1122–33. [PubMed: 25488681]
39. Bader MJ, Sroka R, Gratzke C, et al. Laser therapy for upper urinary tract transitional cell carcinoma: indications and management. *Eur Urol* 2009;56(1):65–71. [PubMed: 19108945]
40. Gadzinski AJ, Roberts WW, Faerber GJ, Wolf JS Jr. Long-term outcomes of nephroureterectomy versus endoscopic management for upper tract urothelial carcinoma. *J Urol* 2010;183(6):2148–53. [PubMed: 20399468]

Figure 1.
Preferred reporting items for systematic reviews and meta-analysis (PRISMA) flowchart.

Figure 2.

Forest plots of meta-analyses of unadjusted HRs for (A) cancer-specific survival (CSS) and Risk Ratios of available confounders: (B) Non-organ confined tumor; (C) High tumor grade; (D) Positive lymph node status; (E) Positive surgical margins.

Figure 4.

Forest plot of meta-analysis of weighted mean changes in eGFR after SU and RNU.

Table 1

Overall and methodological characteristics of the included studies.

Study	Country	Study design	NOS score	LoE	Number of patients		Indication for SU	Median follow-up [IQR], Months		Intervention vs control		Available outcomes	Subgroup analyses
					Overall	SU, n (%)		Overall	SU	RNU	p value		
Giannarini et al., 2007	Switzerland	Retrospective Monocentric	★★★★★	3	43 (100)	19 (44.2)	24 (55.8)	Unclear	50 [3–191]	49 [3–261]	NS	CSS, OS, IV-RFS, CL-RFS, IL-RFS	-
Jeldres et al., 2010	Canada	Retrospective Multicentric	★★★★★	3	1791 (100)	569 (31.8)	1222 (68.2)	Unclear	29	30	NS	CSS	+stage
Bin et al., 2012	USA	Retrospective Monocentric	★★★★★	3	50 (100)	17 (34.0)	33 (66.0)	Unclear	NA	NA	NA	CSS, RFS	
Colin et al., 2012	France	Retrospective Multicentric	★★★★★	3	468 (100)	52 (11.1)	416 (88.9)	Imperative and elective indications (single tumor < 2 cm)	NA [10–48]	NA	NA	CSS, RFS, MFS	+stage
Silberstein et al., 2012	USA	Retrospective Monocentric	★★★★★	3	120 (100)	33 (27.5)	87 (72.5)	Surgeon and patient preferences	4.2yr	NA	NA	CSS, OS, RFS, IL-RFS, MFS, Renal function outcomes	
Bagrodia et al., 2013	USA	Retrospective Multicentric	★★★★★	3	835 (100)	81 (9.7)	754 (90.3)	Surgeon and patient preferences	34 [1–246]	NA	NA	CSS, IV-RFS	+stage & grade
Dalpiaz et al., 2014	Austria	Retrospective Monocentric	★★★★★	3	91 (100)	49 (53.8)	42 (46.2)	Imperative indications Surgeon preference	51.5 [4–290]	51.1 [4–279]	NA	CSS, OS, IV-RFS, CL-RFS, IL-RFS	
Fukushima et al., 2014	Japan	Retrospective Multicentric	★★★★★	3	129 (100)	43 (33.3)	86 (66.7)	Unclear	50 [IQR 16–103]	NA	NA	CSS, RFS, CL-RFS, IL-RFS, Renal function outcomes	+stage
Hung et al., 2014	Taiwan	Retrospective Monocentric	★★★★★	3	112 (100)	35 (31.3)	77 (68.8)	Imperative and patient preference	NA	48.3 ± 27.0	43.8 ± 20.6	CSS, IV-RFS, MFS, Renal function outcomes	

Study	Country	Study design	NOS score	LoE	Number of patients		Indication for SU	Median follow-up [IQR], Months		Available outcomes	Subgroup analyses
					Overall	SU, n (%)		Overall	SU		
Pedrosa et al., 2015	USA	Retrospective Monocentric	★★★★★	3	131 (100)	35 (26.7)	Unclear	56.9 [0.2–181.1]	NA	CSS, OS, RFS	-
Singla et al., 2015	USA	Retrospective Multicentric	★★★★★	3	193 (100)	50 (25.9)	Surgeon preference	25.9 [1–150]	43.9 [IQR 18.8–82.1]	Renal function outcomes	
										<i>p</i> value	
									RNU		

NOS: Newcastle–Ottawa Scale; LoE: Level of Evidence; SU: Segmental Ureterectomy; RNU: Radical Nephroureterectomy; IQR: Interquartile Range; USA: United States of America; NS: Non Significant; CSS: Cancer-Specific Survival; OS: Overall Survival; RFS: Recurrence-Free Survival; IV-RFS: Intravesical Recurrence-Free Survival; CL: Contra-Lateral Recurrence-Free Survival; IL-RFS: Ipsi-Lateral Recurrence-Free Survival; MFS: Metastasis-Free Survival.