Comparison of the Oncological and Renal Function Outcomes of Partial Ureterectomy and Radical Nephroureterectomy in Upper Tract Urothelial Carcinoma: a Meta-analysis

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Abstract

Background

To perform a meta-analysis of comparative studies reporting oncological and renal function outcomes of partial ureterectomy and radical nephroureterectomy in upper tract urothelial carcinoma (UTCC).

Methods

A literature search of PubMed, Embase, and the Cochrane library was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, and a meta-analysis was performed to assess cancer-specific survival (CSS), overall survival (OS), recurrence-free survival (RFS), and perioperative variations in the estimated glomerular filtration rate (eGFR).

Results

Nineteen studies involving 4940 patients were included in our meta-analysis. No significant differences were found in the 5-year OS (HR=1.20, p=0.40), 5-year RFS (HR=1.21, p=0.37) and CSS (HR=0.89, p=0.20). A better preservation of renal function of PU compared with RNU changes in (eGFR) (WMD=-9.75, p=0.0006) between the patients undergoing the two types of surgery.

Conclusions

PU could achieve equal oncological outcomes and better postoperative renal function than RNU.

Background

Upper tract urothelial carcinomas (UTUCs) are rare and contribute for 5–10% of all urothelial malignancies[1]. Radical nephroureterectomy (RNU) with resection of the bladder cuff is considered a standard curative treatment for UTUC[2].
However, this treatment can increase cardiovascular morbidity as a result of renal unit. Partial ureterectomy, including endoscopic or segmental resection, could be considered a method to treat patients with UTUC. According to the European Association of Urology (EAU) guidelines, segmental resection of the distal ureter can be used even in patients with high-grade invasive distal ureteral urothelial carcinoma (UC)[2]. Partial ureterectomy (PU) consists of resecting the portion of the ureter compromised with UTUC, and endoscopic management can be performed through either antegrade or retrograde access to the upper urinary tract with percutaneous (PC) or ureteroscopic (URS) instruments, respectively. At present, segmental ureterectomy (SU) and progress in endoscopic surgery can be considered nephron-sparing procedures (NSP) and can be used to spare the renal unit in some cases such as those with low-stage tumor, renal insufficiency, or a solitary kidney[3–6]. Recently, with equal oncological control of these cases, expanded indications were used for patients with bilateral functioning kidneys.

However, the rarity of upper urinary tumors prevents the oncological outcomes after endoscopic surgery or PU from being shown. The endoscopic treatment of UTUC can increase the rate of bladder cancer recurrence. Radical surgical methods are associated with a lower bladder cancer recurrence rate [2,3]. However, in a series by Fang et al and Yakoubi et al, the type of approach was unlikely to impact subsequent bladder cancer, and equal oncological outcomes could be achieved[7, 8]. Nevertheless, due to the low incidence of UTUC, evidence-based data that evaluate the oncological efficacy of RNU with a conservative approach that includes three validated treatment modalities are rare. As a result, all the contemporary studies comparing RNU and PU have included patients with elective and imperative patients, and the available data are scarce. Fang et al conducted a meta-analysis included 11 studies. They pooled the data of studies which compared PU versus radical nephroureterectomy[7]. Seisen conducted a review comparing
endoscopic surgical techniques[9]. Yakoubi et al performed a meta-analysis exploring RNU versus endoscopic procedures for the treatment of UTUC[8]. We conducted a meta-analysis to evaluate whether oncological outcomes are equal between RNU and nephron-sparing ureterectomy (NSU)[9]. However, Fang and Yakoubi did not include studies which contained both SU and endoscopic procedures Thus, we aimed to perform a meta-analysis of the comparative studies reporting oncological and renal function outcomes of RNU versus PU.

Methods

Search strategy

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. We searched PubMed, Embase and the Cochrane Central Register for relevant studies published in English between May 1998 and May 2018[10]. We used the following search terms: “UTUC”, “Upper Tract Urothelial Carcinoma”, “Kidney Sparing”, “Segmental Ureterectomy”, “Partial Ureterectomy”, “Distal Ureterectomy” OR Nephron Sparing, “Radical Nephroureterectomy”. We also used the combined Boolean operators “AND” or “OR” in the Title/Abstract[10].

Inclusion and exclusion criteria

Two investigators (YLJ and LJJ) reviewed the articles. The inclusion criteria were as follows: (1) comparative analysis of RNU and NSU for the treatment of UTUC; and (2) the study reported at least one of the following outcomes: cancer-specific survival (CSS), overall survival (OS), recurrence-free survival (RFS) or surgery-related variations in the estimated glomerular filtration rate (eGFR).

The exclusion criteria were as follows: (1) case reports, reviews, editorial comments, meeting abstracts and articles without applicable data; (2) studies with insufficient data,
such as lacking hazard ratios (HRs) or information to calculate the HR and number; (3) studies that were not comparative; and (4) studies comparing PU, endoscopic studies without surgery and studies without comparison groups or single-arm studies. The process of identifying relevant studies is summarized in Figure 1.

**Data extraction and quality assessment**

These two authors extracted data, such as the OS, RFS, and CSS rates. The following data were recorded: (1) baseline comparative data; (2) clinical outcomes; and (3) postoperative complications.

We used the New-Ottawa Scale (NOS) to evaluate the included studies. The NOS scores were evaluated using a 9-point system. An NOS score of 7 or above was considered higher quality, and an NOS score of 3 or below was considered lower quality. Two reviewers (YLJ and LJQ) assessed the quality of the included studies. Table 2 Quality assessment of the included studies

**Statistical analysis**

We used Review Manager Version 5.2 software with the Mantel-Haenszel method (The Cochrane Collaboration, Oxford, UK) to perform the analysis of the included data. We used Cochran’s Q to evaluate the heterogeneity; if the value of Q was <50% or the P value was >0.01, the heterogeneity was low. However, if the value of Q was >50% or the P value was <0.01, heterogeneity existed. When I² was >50%, the random effects model was applied. For quantitative data, we used the weighted mean difference (WMD) or standard mean difference (SMD) for continuous variables. We used odd ratios (ORs) and 95% confidence intervals (CIs) for binary data[10]. The statistical significance level was set at 0.05. Oncological outcomes including OS, CSS and RFS were primarily assessed using HRs from univariate analyses and their corresponding 95% CIs.

**Results**
Nineteen studies were included in our study[11–29]. The process used to obtain these studies is summarized in Figure 1. From the selected databases, 119 studies were obtained. After screening the titles and abstracts, 29 studies were excluded. After detailed processing, 71 studies were excluded. Ultimately, 18 studies were included in our meta-analysis. Table 1 summarizes the baseline characteristics and assessments.

5-year OS

Nine studies reported 5-year OS. The pooled data of 5-year OS indicated no statistical differences between the RNU group and PU group (HR: 1.20, 95%CI: 0.78 to 1.84, $I^2 = 57\%$; $p = 0.40$ random-effects model, Fig. 2).

5-year CSS

Data related to the 5-year CSS were available in sixteen studies No significant difference between the RNU and PU groups was noted (HR: 0.89, 95%CI: 0.74 to 1.07, $I^2 = 16\%$; $p = 0.20$, fixed-effects model, Fig. 3).

5-year RFS

Five studies reported 5-year RFS. The pooled data of 5-year RFS indicated no statistical differences between the RNU group and SU group (HR: 1.21, 95%CI: 0.80 to 1.81, $I^2 = 58\%$; $p = 0.37$ random-effects model, Fig. 4).

Renal function

Five studies evaluated postoperative renal function. The pooled data showed that patients in PU group could get better preservation of renal function compared with those in RNU group ($n = 685$, WMD: -9.75, 95% CI: -15.35 to -4.15, $I^2 = 82\%$, $p = 0.0006$, random effects model, Fig. 5).

Discussion

This meta-analysis shows that PU could achieve equal oncological outcomes and better
preservation of renal function to those of RNU. We pooled 19 studies to compare 5-year OS rates, CSS, RFS and renal function. Our meta-analysis suggested that no significant differences were found in the 5-year OS, CSS and RFS between the RNU and PU groups. Data regarding OS were available in 9 studies. The present study demonstrated that OS exhibited no statistically significant differences between the groups (Figure 2) (p = 0.40). Similarly, Yakoubi et al also performed a meta-analysis involving 8 studies and reported that no significant differences were found for OS (HR: 1.47, p = 0.31). They did not include segmental ureterectomy, which could also involve nephron sparing surgery[8]. Similarly, Fang et al performed a meta-analysis involving 11 that showed that conservative management with SU was comparable to RNU for the treatment of UTUC in select cases and should be considered an option[8]. Dalpiaz et al and Fukushima et al reported no significant differences in OS. This finding was consistent with the results of our study[24, 25]. However, Lucas et al found that among 108 patients who received NU or RNU, 5-year OS was significantly different between the RNU and SU groups (P>0.05) [18]. In this study, they did not perform a subgroup analysis. We also pooled the data of both the adjusted and unadjusted HRs for OS and other oncological outcomes. Despite a trend towards worse CSS in the PU groups in a multivariate analysis, no significant difference between PU and RNU was reported [10,16]. However, we also found that data were poorly reported in general and that there was a significant selection bias in favour of PU, which was not controlled in survival analyses according to the risk of bias assessment. Although match-paired analyses or multivariate Cox regression models were commonly used to balance or adjust for covariates, the comparison of the clinical outcomes of PU and RNU suffered from a selection bias related to the presence of pathologic and other adverse clinical features in the PU and RNU groups, respectively. Moreover, Jeldres et al performed a large population-based study that indicated that the
operative modality (PU versus RNU) did not influence cancer-specific mortality (CSM) for advanced stage tumors, and they expanded the indication for PU[12]. Bin et al conducted a retrospective study that reviewed 60 patients with isolated primary ureteral tumors. They found no significant differences in the probability of CSS with regard to either tumor location or surgical approach (P = 0.523 and P = 0.904, respectively)[13]. However, Isbarn et al performed a large population-based study to clarify the prognostic significance of tumor location in patients with UTUC and showed that tumor location did not affect oncological outcomes in a multivariate analysis[30].

In addition, Lughezzani et al studied 2,299 patients with UTUC treated with PU or nephroureterectomy (NU) and did not find that surgery type affected CSM, which agreed with the findings of our study[31]. Roupret et al found that the surgical approach (SU or RNU) had no influence on CSS or RFS (P = 0.94 and P = 0.42, respectively) in multivariate analyses, and pT stage and pN stage were independent predictors for CSS (p<0.05) in a univariate analysis[17]. When compared to RNU, neither total ureterectomy (TU) nor SU significantly affected OS (p>0.05), RFS (p>0.05) or CSS (p>0.05). These results were similar to our results. The presence of urothelial recurrence also did not correlate with CSM (p = 0.73) or overall mortality (p = 0.39).

Fukushima et al included 1,329 patients with UTUC for clinical evaluation. They used a propensity scoring method (PSM) to balance potential baseline differences between groups. They also performed a subgroup analysis of patients with pTa–1 and pT2–4 disease, which indicated that the RFS and CSS of the DUx group were comparable to those of the NUx group (P = 0.50 and P = 0.99, P = 0.64 and P = 0.93, respectively)[25].

In our study, the patients in the PU group had better renal function than those in the RNU group. The use of perioperative 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[16, 28].

Only the risk of positive surgical margins was equivalent between the SU and RNU groups, but this finding could simply result from better tumor characteristics in the conservative treatment group. Since the adjusted CSS was equivalent between the two arms, SU could be considered in selected cases of high-risk UTUC[7].

Silberstein et al performed a study including 367 patients with UTUC. They found that the preservation of the renal unit resulted in significantly smaller decreases in renal function than RNU[15]. Furthermore, the patients who underwent PU were more likely to receive adjuvant chemotherapy (for the preservation of the eGFR renal function), which may prolong OS, than those who underwent RNU.

Regarding the comparative renal function outcomes of PU, few robust datasets are available in the current literature. Nevertheless, the main objectives of sparing the renal unit are to prevent the development of postoperative chronic kidney disease and to preserve quality of life. However, our results should be interpreted cautiously, as comparative data may be missing due to the selection criteria that did not systematically capture all of the studies reporting renal function outcomes. Similarly, Seisen et al also performed a systematic review that suggested that all PU patients experienced better postoperative renal function than RNU patients and thus improved quality of life.

We acknowledge that our meta-analysis is limited by the retrospective design of the included studies. As a consequence, different data on the tumor and patient features were missing in the adjusted analyses. Tumor multiplicity should be taken into account in patients with UTUC to predict tumor existence in other locations of the ipsilateral upper urinary tract. A general limitation inherent to meta-analyses of aggregated data extracted from published data is the limited number of potentially influential covariates that can be accounted for. We were unable to perform subgroup meta-analyses or meta-regression
that incorporated influential factors such as lesion size, age, and pathological features.

The selection biases of the original studies still exist in our study.

Conclusions

Our meta-analysis showed that PU and RNU provide equal cancer control in patients with UTUC. In addition, PU ensures better preservation of renal function than RNU. Therefore, PU is safe and provides good tumor control for UTUC treatment. Nonetheless, the evidence that supports these findings remains poor and potentially biased. Prospective clinical trials are necessary to adequately compare the oncological and renal function outcomes of PU and RNU in treating UTUC.

Abbreviations

UTCC: upper tract urothelial carcinoma; RNU: radical nephroureterectomy; PU: partial ureterectomy; NU: nephroureterectomy; SU: segmental ureterectomy; eGFR: estimated glomerular filtration rate; OS: overall survival; RFS: recurrence-free survival; CSS: cancer-specific survival; HR: hazard ratio; CI: confidence interval; WMD: weight mean difference; OR: odds ratio;

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.
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Authors Contributions
YLJ and LJQ designed the study. YLJ wrote the manuscript. YLJ, ZJ and LZ analyzed the data. WKE, YCH and ZXL searched the articles. All authors read and approved the final manuscript.

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Tables

**Table 1** Basic Characteristics of the Included Studies

| Study       | Year | Design | Sample Size | Mean Age (years) | Gender (M/F) |
|-------------|------|--------|-------------|------------------|--------------|
| Giannarini  | 2007 | R,S    | 19/24       | NA/NA            | NA/NA        |
| Jeldres     | 2010 | R,M    | 569/1222    | 72.7/61.7        | 367/202      |
| Bin         | 2012 | R,S    | 17/33       | NA/NA            | NA/NA        |
| Colin       | 2012 | R,S    | 52/416      | NA/NA            | 32/26        |
| Silberstein | 2012 | R,S    | 33/87       | 79.6/79.5        | 58/29        |
| Bagrodia    | 2013 | R,M    | 81/754      | NA/NA            | NA/NA        |
| Roupret     | 2006 | R,S    | 43/54       | NA/NA            | NA/NA        |
| Lucas       | 2008 | R,S    | 39/77       | 68/65            | NA/NA        |
| Gadzinski   | 2010 | R,S    | 34/62       | NA/NA            | NA/NA        |
| Raymundo    | 2011 | R,S    | 21/99       | 68.81/72.9       | 15/6         |
| Grasso      | 2012 | R,S    | 66/80       | NA/NA            | 46/34        |
| Fajkovic    | 2012 | R,S    | 20/178      | 71.9/68.9        | NA/NA        |
| Curess      | 2013 | R,S    | 59/70       | 69.4/78.1        | NA/NA        |
| Dalpiaz     | 2014 | R,S    | 49/42       | NA/NA            | 30/19        |
| Fukushima   | 2014 | R,M    | 43/86       | NA/NA            | 29/14        |
| Hung        | 2014 | R,S    | 35/77       | 69.29/66.71      | 18/17        |
| Pedrosa     | 2015 | R,S    | 35/96       | 69/71            | 23/12        |
| Singla      | 2015 | R,M    | 50/143      | 71/61            | 193/124      |
| Chen        | 2017 | R,M    | 78/53       | 68.5/64.7        | 42/36        |

S single center R retrospectively study M mutli-centers NA not available PU Partial

Ureterectomy RNU Radical Nephroureterectomy

**Table 2** Newcastle-Ottawa Scale for risk of bias assessment of the included studies
| Study          | Design | Selection                     | Comparability                  |
|---------------|--------|-------------------------------|-------------------------------|
|               |        | Representative ness of exposed cohort | Selective of nonexposed Cohort | Ascertainment of exposure | Outcome not present at start |
| Giannarini    | R      | *                             | *                             | *                        |
| Jeldres Bin   | R      | *                             | *                             | *                        |
| Colin         | R      | *                             | *                             | *                        |
| Silberstein   | R      | *                             | *                             | *                        |
| Bagrodia      | R      | *                             | *                             | *                        |
| Roupret       | R      | *                             | *                             | *                        |
| Lucas         | R      | *                             | *                             | *                        |
| Gadzinsk      | R      | *                             | *                             | *                        |
| Raymundo      | R      | *                             | *                             | *                        |
| Grasso        | R      | *                             | *                             | *                        |
| Fajkovic      | R      | *                             | *                             | *                        |
| Curess        | R      | *                             | *                             | *                        |
| Dalpiaz       | R      | *                             | *                             | *                        |
| Fukushi       | R      | *                             | *                             | *                        |
| Ma            | R      | *                             | *                             | *                        |
| Hung          | R      | *                             | *                             | *                        |
| Pedrosa       | R      | *                             | *                             | *                        |
| Chen          |        |                               |                               |                          |

*R Respectively study

**Figures**

- 119 of records identified through database searching
- 0 of additional records identified through other sources
- 12 of records after duplicates removed
- 17 of records excluded after title
Flow diagram of the process for the selection of relevant studies
Figure 2
Forest plot for the 5-year OS between the RNU and PU for UTUC

Figure 3
Forest plot for the 5-year CSS between the RNU and PU for UTUC
Table 1: Hazard Ratio Analysis

| Study or Subgroup | log(Hazard Ratio) | SE  | Weight | IV, Random, 95% CI | Hazard Ratio |
|-------------------|-------------------|-----|--------|-------------------|--------------|
| Bin 2012          | 0.174             | 0.5774 | 9.6%  | 1.19 [0.38, 3.69] |              |
| Fukushima 2014    | -0.473            | 0.3624 | 16.4% | 0.62 [0.29, 1.31] |              |
| Pedrosa 2015      | 0.5063            | 0.2750 | 22.4% | 1.66 [0.97, 2.06] |              |
| Raymundo 2011     | 0.5515            | 0.1603 | 30.3% | 1.74 [1.27, 2.38] |              |
| Silverstein 2012  | -0.1503           | 0.2906 | 21.4% | 0.86 [0.49, 1.52] |              |

Total (95% CI): 100.0% ± 1.21 [0.80, 1.81]

Heterogeneity: τ² = 0.12; Chi² = 8.59, df = 4 (P = 0.05), I² = 58%
Test for overall effect: Z = 0.90 (P = 0.37)

Figure 4

Forest plot for the 5-year RFS between the RNU and PU for UTUC

Figure 5

Forest plot for the postoperative renal function between the RNU and PU for UTUC