Review Article Outcomes after radical nephroureterectomy and segmental ureterectomy in urothelial cancer of ureter: a meta-analysis

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Abstract: To compare the prognostic effects of segmental ureterectomy (SU) and radical nephroureterectomy (RNU) for urothelial cancer of the ureter (UUC). Databases including Pubmed, Embase and Cochrane online library were selected for systematic review of retrospective trials that comparing outcomes of SU and RNU in the patients with UUC. Interested data including hazard radio (HR) for overall survival (OS), cancer specific survival (CSS), intravesical recurrence free survival (IRFS), recurrence free survival (RFS) and metastasis free survival (MFS) were extracted by two reviewers independently from selected trials. Meta-analysis was performed using RevMan 5.3 software. Eight eligible trials evaluating SU vs RNU for UUC were identified including 895 SU cases and 2149 RNU cases. The results showed no significant difference between the two kinds of surgical methods in HR for OS (P=0.86), CSS (P=0.23), IRFS (P=0.95), RFS (P=0.17) and MFS (P=0.23). Our analysis showed that SU had equivalent prognostic effect for UUC compared with RNU, which was considered the standard method. Because of the inherent limitations of the included studies, further large sample, multi-centric studies and randomized control trials should be undertaken to confirm our findings.

Keywords: Urothelial carcinoma, ureter, meta-analysis, segmental ureterectomy, radical nephroureterectomy

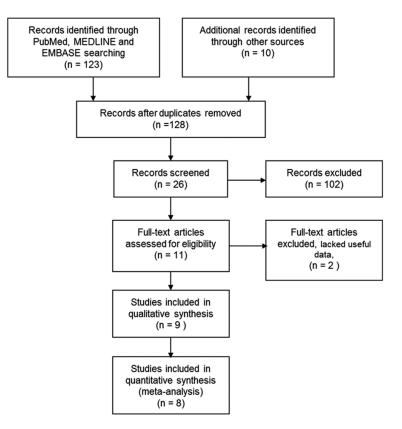
Introduction

Upper tract urothelial carcinomas are uncommon, accounting for only 5-10% of urothelial carcinomas [1]. For upper tract urothelial cancers, pyelocaliceal tumors are about twice as common as ureteral tumors [2]. Approximately 60% of ureteral urothelial carcinomas are invasive at diagnosis, while the invasive rate is 15-25% for bladder cancer [3], and they are associated with 22-47% bladder recurrence after operations [4]. Moreover, upper tract urothelial carcinomas usually have a poor prognosis, especially those invade the muscle are associated with <50% 5-year specific survival [5]. So, according to the current guideline, radical nephroureterectomy (RNU) is considered as the standard surgical method for high-grade ureteral and pelvic urothelial cancers, and kidney sparing surgeries (KSS) are only recommended for low-grade cancer [6].

However, renal removal always results in higher rates of chronic renal diseases, higher risk of

dialysis and overall non-cancer mortality [7]. With the view of reserving the renal function, KSS have been applied in all grades of urothelial cancer [8-10]. In recent meta-analysis postoperative survival assessment such as overall survival (OS), cancer specific survival (CSS), intravesical recurrence free survival (IRFS), recurrence free survival (RFS) and metastasis free survival (MFS) revealed that there was no significant difference between KSS and RNU for both low and high grade urothelial carcinomas [11]. As the techniques develop, KSS involves a wide range of methods including ureteroscopy management, percutaneous management and segmental ureteral resection among others. Segmental ureterectomy (SU) is now considered an option for not only imperative cases such as renal insufficiency and solitary functional kidney, but also for high-grade ureteral urothelial carcinoma [12].

Although a number of studies evaluated the oncological outcome of SU compared with RNU



Inclusion criteria and exclusion criteria

The included trials met followed requirements: (1) studies comparing SU with RNU, (2) patients with urothelial cancer in ureter, (3) hazard ratio (HR) values describing association between surgical methods and survival outcomes available.

Studies were excluded in the meta-analysis if: (1) the inclusion criteria were not met, (2) no outcomes of interest were reported or impossible to calculate or extrapolate the necessary data from the published results, (3) some patients with multifocal tumor such as pelvic cancer, (4) children were included in the studies.

Figure 1. Flowchart showing the selection of studies for meta-analysis.

Data extraction and quality assessment

in patients with ureteral urothelial carcinoma (UUC) [13-20], because of paucity of UUC cases, strong evidences are still lacking. Here we constructed the meta-analysis, which summarized the published literatures, comparing SU with RNU on the oncological survival for UUC after surgical approaches.

Materials and methods

The present meta-analysis was conducted in adherence to the recommendations of the Meta-analysis of Observational Studies in Epidemiology group (MOOSE) guidelines [21].

Study selection

A systematic search of Pubmed, Embase and Cochrane online library was performed to identify all studies published up to July 1, 2016 which compared SU with RNU with the following MESH search headings: "comparative studies", "segmental ureterectomy", "radical nephroureterectomy" and "urothelial cancer of the ureter". The "related articles" function was used to broaden the search, and all abstracts, studies, and citations were reviewed. Two reviewers independently extracted the following data including: first author, year of publication, country, study interval, study design, number of patients who underwent SU or RNU, tumor grade, mean age of the patients and length of follow-ups. The study qualities were assessed by using Newcastle-Ottawa Scale (NOS) [22]. The NOS is based on the following three subscales: selection (4 items), comparability (1 item), and outcome (3 items) [22]. A "star system" (range 0-9) has been developed for assessment.

The interested results included hazard ratio (HR) and corresponding 95% CI for overall survival (OS), cancer specific survival (CSS), intravesical recurrence free survival (IRFS), recurrence free survival (RFS) and metastasis free survival (MFS).

In all cases of missing or incomplete data, the corresponding authors were contacted, but no additional information was provided. If we received no response, the methods introduced by Tierney were also used to calculate or estimate the useful data from other information,

First author/year	Country	Study interval	Study type	Tumor grade	Mean age (Range)	No. of patients, SU/RNU	Follow-up, months	Study quality Stars rating
Gianluca 2007	Switzerland	1974-2004	Retrospective	G1-G3	72 (31-86)	19/24	58 (3-260)	6
Claudio 2010	SEER#	1988-2006	Retrospective	Low, high	72 (30-95)	569/1222	30	5
Pierre 2012	France	1995-2010	Retrospective	G1-G3	70.1 (66-76.8)/69.1 (61-76)	52/416	26 (10-48)	5
Aditya 2013	USA	1992-2006	Retrospective	Low, high	69 (32-97)	58/214	34 (1-246)	6
Hiroshi 2014	Japan	1977-NA	Retrospective	G1-G3	NA	43/86	50 (16-103)	7
Orietta 2014	Austria	1984-2011	Retrospective	G1-G3	71.5 (52-88)/70.3 (49-88)	49/42	51.5 (4-290)	6
Shih 2014	Taiwan	2004-2010	Retrospective	Low, high	68	35/77	48.3/43.8	5
Thomas 2016	Multi-institution*	2004-2013	Retrospective	Low, high	69 (59-76)	70/68	30.7 (17-69)	6

Table 1. Characteristics of included studies

#SEER = Surveillance, Epidemiology and End Results database; *Multi-institution including 34 participating European centers; SU = segmental ureterectomy; RNU = radical nephroureterectomy; NA = not available.

Univariate OS Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV. Fixed. 95% Cl	Hazard Ratio IV. Fixed, 95% Cl
Gianluca 2007	-0.171 (0.8478	11.5%	0.84 [0.16, 4.44]	<u> </u>
Orietta 2014	-0.0348 0	0.3062	88.5%	0.97 [0.53, 1.76]	-
Total (95% CI) Heterogeneity: Chi ² = (0.02, df = 1 (P = 0.88);	² = 0%	100.0%	0.95 [0.54, 1.67]	+
Test for overall effect:	Z = 0.18 (P = 0.86)			0.01	0.1 1 10 100 Favours (SU) Favours (RNU)
Multivariate OS				Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Fixed, 95% CI	IV, Fixed, <u>95%</u> CI
Thomas 2016	0.2231 0	0000	100.0%	4 05 14 00 4 401	
	0.2201 0	0.0035	100.0%	1.25 [1.09, 1.43]	-

Figure 2. Forest plot and meta-analysis of HR for overall survival (OS).

Univariate CSS	le r [Users vd Defie]	6F	Mainhé	Hazard Ratio	Veen			d Ratio	
Study or Subgroup	log[Hazard Ratio]		Weight	IV, Fixed, 95% Cl				d, 95% Cl	
Gianluca 2007	0.2913		8.6%	1.34 [0.65, 2.74]			-		
Claudio 2010	-0.2989		49.5%	0.74 [0.55, 1.00]			-		
Pierre 2012	-0.0113	0.3794	8.0%	0.99 [0.47, 2.08]	2012				
Aditya 2013	0.0587	0.2497	18.5%	1.06 [0.65, 1.73]	2013				
Orietta 2014	-0.0436	0.4582	5.5%	0.96 [0.39, 2.35]	2014				
Hiroshi 2014	0.157	0.4075	6.9%	1.17 [0.53, 2.60]	2014			-	
Shih 2014	-0.7755	0.6234	3.0%	0.46 [0.14, 1.56]	2014	←			
Total (95% CI)			100.0%	0.88 [0.71, 1.09]			-		
Heterogeneity: Chi ² = 4	, ,	; l² = 0%				0.2	0.5	1 2	5
Test for overall effect: 2	Z = 1.19 (P = 0.23)					0.2		Favours [RNU]	Ŭ
Multivariate CSS				Hazard Ratio			Hazaro	d Ratio	
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Fixed, 95% Cl	Year		IV, Fixed	<u>l, 95% Cl</u>	
Pierre 2012	0.228	0.3942	23.2%	1.26 [0.58, 2.72]	2012		_		
Hiroshi 2014	0.4492	0.4389	18.7%	1.57 [0.66, 3.70]	2014		_		
Thomas 2016	0.01	0.249	58.1%	1.01 [0.62, 1.65]	2016		-	-	
Total (95% CI)			100.0%	1.15 [0.80, 1.67]			•		
Heterogeneity: Chi ² = 0	.82, df = 2 (P = 0.66)	; l ² = 0%							100
Test for overall effect: Z	z = 0.75 (P = 0.45)					0.01	0.1 Favours [SU]	1 10 Favours [RNU]	100

Figure 3. Forest plot and meta-analysis of HR for cancer specific survival (CSS).

such as the Kaplan-Meier curves [23]. All disagreements about eligibility were resolved by discussion until a consensus was reached.

Statistical analysis

We incorporate data from both univariate and multivariate analysis in our meta-analysis. All the statistical analyses were performed using RevMan 5.3 (Cochrane Library Software, Oxford, UK). The generic inverse variance method was applied. Log [HR] and SE were obtained by the calculator. All the pooled effects were determined by the z test and P<0.05 was considered statistically significant. The quantity of heterogeneity among included studies was assessed by chi-square-based Q test and I² test, when I²<50%, P>0.05, the evidences showed no significant heterogeneity, we used fixed-effects (FE) model, otherwise we used random-effects (RE) model. Sensitivity analyses were perfor-

Univariate IRFS			Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	E Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
Orietta 2014	0.0233 0.326	52.5%	1.02 [0.54, 1.94]	- -
Shih 2014	-0.0556 0.342	47.5%	0.95 [0.48, 1.85]	+
Total (95% CI)		100.0%	0.99 [0.62, 1.57]	
Heterogeneity: Chi ² =	0.03, df = 1 (P = 0.87); l ² = 0)%		
Test for overall effect:	7 = 0.06 (P = 0.95)		0.01	0.1 1 10 100
	2 0.00 (1 0.00)			Favours [SU] Favours [RNU]
Multivariate IRFS			Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	E Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Thomas 2016	0.0677 0.174	5 100.0%	1.07 [0.76, 1.51]	•
Total (95% CI)		100.0%	1.07 [0.76, 1.51]	
()	nliaabla			
Heterogeneity: Not ap			0.01	0.1 1 10 100
Test for overall effect:	Z = 0.39 (P = 0.70)			Favours [SU] Favours [RNU]

Figure 4. Forest plot and meta-analysis of HR for intravesical recurrence free survival (IRFS).

Univariate RFS Study or Subgroup	log[Hazard Ratio]	SE V		Hazard Ratio IV, Fixed, 95% Cl Year		Hazard Ratio IV. Fixed, 95% Cl	
Pierre 2012	0.1454 0	.2141	43.2%	1.16 [0.76, 1.76] 2012			
Aditya 2013	0.4483 0	.2137	43.3%	1.57 [1.03, 2.38] 2013			
Hiroshi 2014	-0.478 0	.3824	13.5%	0.62 [0.29, 1.31] 2014			
Total (95% CI)		1	00.0%	1.21 [0.92, 1.60]		•	
Heterogeneity: Chi ² = 4	4.56, df = 2 (P = 0.10); l	² = 56%			0.01		100
Test for overall effect:	Z = 1.37 (P = 0.17)				0.01	0.1 1 10 Favours [SU] Favours [RNU]	100
Multivariate RFS				Hazard Ratio		Hazard Ratio	
Multivariate RFS Study or Subgroup	log[Hazard Ratio]	SE	Weight			Hazard Ratio IV, Fixed, 95% Cl	
	log[Hazard Ratio] 0.1567	SE 0.22	•	IV, Fixed, 95% CI			
Study or Subgroup	0.1567		36.4%	t IV, Fixed, 95% CI			
<u>Study or Subgroup</u> Hiroshi 2014	0.1567	0.22 0.4326	36.4% 9.4%	IV. Fixed, 95% CI 1.17 [0.76, 1.80] 1.06 [0.45, 2.47]			
<u>Study or Subgroup</u> Hiroshi 2014 Pierre 2012	0.1567 0.0583	0.22 0.4326	36.4% 9.4%	IV, Fixed, 95% Cl 1.17 [0.76, 1.80] 1.06 [0.45, 2.47] 0.94 [0.66, 1.34]			
Study or Subgroup Hiroshi 2014 Pierre 2012 Thomas 2016 Total (95% CI)	0.1567 0.0583	0.22 0.4326 0.1804	36.4% 9.4% 54.2% 100.0 %	IV, Fixed, 95% Cl 1.17 [0.76, 1.80] 1.06 [0.45, 2.47] 0.94 [0.66, 1.34]	0.2		

Figure 5. Forest plot and meta-analysis of HR for recurrence free survival (RFS).

med by omitting a certain study each time. The funnel plots were used to assess the publication bias of the included studies.

Results

Characteristics of selected studies

After screening (**Figure 1**) eight trials [13-20] were selected and enrolled in our meta-analysis, including 895 patients who underwent SU and 2149 patients who underwent RNU respectively. All these selected studies were retrospective comparing trials. The characteristics of these studies are shown in **Table 1**.

Outcomes of survival variables

Five survival variables were analyzed, OS, CSS, IRFS, RFS and MFS. Two trials [13, 18] reported univariate OS, which was (HR: 0.95; 95% CI: 0.54-1.67; P=0.86), while only one study [20] reported multivariate OS (HR: 1.25; 95% CI: 1.09-1.43; P=0.001) (**Figure 2**). The pooled univariate CSS was (HR: 0.88; 95% CI: 0.71-1.09; P=0.23) based on seven trials [13-19], and the multivariate CSS was (HR: 1.15; 95% CI: 0.80-1.67; P=0.45) based on three trials [15, 17, 20] (**Figure 3**). Univariate IRFS was reported in two studies [18, 19], showing (HR: 0.99; 95% CI:

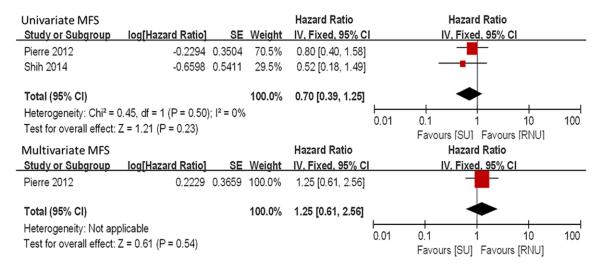


Figure 6. Forest plot and meta-analysis of HR for metastasis free survival (MFS).

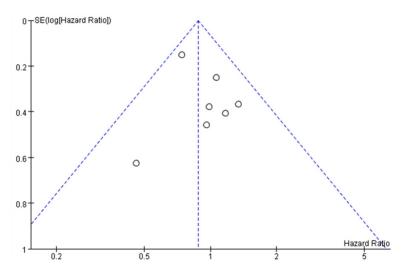


Figure 7. Funnel plot of univariate HR for cancer specific survival (CSS).

0.62-1.57; P=0.95) and multivariate IRFS reported in one study [20] showed (HR: 1.07; 95% CI: 0.76-1.51; P=0.70) (**Figure 4**). The RFS was (HR: 1.21; 95% CI: 0.92-1.60; P=0.17) in univariate group [15-17] and (HR: 1.03; 95% CI: 0.79-1.34; P=0.83) in multivariate group [15, 17, 20] respectively (**Figure 5**). MFS was (HR: 0.70; 95% CI: 0.39-1.25; P=0.23) in univariate analysis in two studies [15, 19] and (HR: 1.25; 95% CI: 0.61-2.56; P=0.54) in multivariate analysis in one study [15] (**Figure 6**). There were no significant differences in all the survival outcomes except multivariate OS, however, it was only reported in one study, it was reasonable to pass over.

Sensitivity analysis and publication bias

Sensitivity analysis was performed by removing one certain study each time. No significance of the pooled comparison between the two groups was influenced by removing any single study, indicating that the results of our meta-analysis were stable. The funnel plots were used to assess the publication bias of the included studies, and no palpable publication bias was noted (**Figure 7**).

Discussion

Due to invasive character of upper tract urothelial carcinomas, and according to the study of Park, ureteric urothelial cancer seemed to be associated with a worse prognosis compared with that of the renal pelvis [12]. Radical nephroureterectomy (RNU) with bladder cuff removal is considered as the standard management. However, in our meta-analysis and previous population studies [8, 14], segmental ureterecomy (SU) also provided feasible efficacy on the oncological outcomes. The hazard ratios for overall survival (OS), cancer specific survival (CSS), intravesical recurrence free survival (IRFS), recurrence free survival (RFS) and metastasis free survival (MFS) all had no significant difference between RNU group and SU group. In addition, RNU is an independent risk factor of postoperative chronic kidney disease [24-26], and SU, which preserves ipsilateral renal function, definitely decreases the incidence of renal inadequacy [24]. In the study of Hiroshi, the rate of change in estimated glomerular filtration rate 2% vs -20% in SU and RNU group respectively [17]. And in another study of Shih, the postoperative eGFR improved in SU group by relieving the obstruction, and contrarily, the postoperative eGFR decreased significantly in RNU group [19].

In our meta-analysis, although all included trials involved high-grade, invasive urothelial cancer, the survival outcomes showed no significant differences between SU and RNU, which indicated that it was valid to perform SU for patients with high-grade ureteric urothelial cancer. Managements for the patients with upper tract urothelial carcinomas have developed dramatically over the past two decades. Besides open or mini-invasive partial ureterectomy, endoscopic managements including percutaneous and ureteroscopic resection, fulguration or ablation have been widely applied. Results showed that some patients with low-risk disease may benefit from conservative approach. In a number of case control studies, endoscopic managements can be recommended as an alternative to nephroureterectomy for low-grade or superficial upper urinary tract transitional cell carcinoma, and the surgical method did not influence the survival [27, 28]. But on the other side, nephron sparing endoscopic approaches are often associated with higher local and bladder recurrence in low-grade upper tract urothelial carcinomas [29]. Moreover, RNU was significantly superior to endoscopic managements in high-grade disease in terms of CSS and OS [30, 31], while there was no significant difference between RNU and SU despite the tumor grades [28]. Unlike endoscopic approach, SU could possibly achieve en bloc resection of the ureter tumor with surrounding tissue. For higher-grade tumors, SU was more feasible for patients with more promising prognosis. But preoperative accurate diagnosis is difficult to differentiate between muscle invasive and non-muscle invasive tumors. So, for patients who needed to preserve the ipsilateral kidney, SU was preferred by urologists in some institutions, although endoscopic approach caused fewer lesions [19].

The postoperative progression and survival of upper tract urothelial carcinomas could be predicted by clinical factors for example age, tumor architecture, cytology, biopsy tumor grade, and presence of hydronephrosis, tissue and urinary markers and pathologic factors [5]. Ureteric cancer accounts for about one fourth of all upper tract urothelial carcinomas [32]. Pathologic factors including tumor stage, grade, carcinoma in situ and lymph node invasion may be more accurate prognosis predictive factors [5, 9, 19, 27]. SU could provide complete remove of tumor, lymph nodes and possibly invaded tissues. Based on that, there was no difference in terms of postoperative survival between SU and RNU theoretically. In a population-based study, tumor stage as well as grade achieved independent predictor status, rather than tumor location and type of surgery [8]. However, positive surgical margins often led to quick recurrence [15], which means SU could be validly applied only in tumors located in distal or middle ureter.

To our knowledge, our meta-analysis is the first one to compare SU with RNU for ureteric urothelial cancer. Although we drew delighting results, there were several limitations in our study. First, only studies published in English and Chinese were pooled in our meta-analysis, some related studies published in other languages might be missed. Second, although the funnel plots only showed publication bias in the comparison of hospital stay and catheterization time, the influence of bias in the our study could not be completely excluded. Third, until now, there are still no randomized studies, due to the low incidence of ureteric cancer. Forth, the sample size in some studies was relatively small that had limited impact on the outcomes. Multivariate HRs of OS, IRFS and MFS were reported only in one study, so we pooled our results according to univariate analysis, although the former was considered to be more accurate. Lastly, the included studies lacked criteria on the follow-up time and the surgical processes of SU and RNU, which might enlarge the heterogeneities. In the future, more multicenter randomized control studies with large sample size and high quality are required, in which, more accurate data including tumor size, location, stage and grade is available.

Conclusion

Our meta-analysis demonstrated the efficacy of SU in terms of oncological outcomes for ure-

teric urothelial cancer. We compared SU and RNU on OS, IRFS, RFS, MFS and CSS based on 8 retrospective trials, the results indicated that patients who underwent SU had similar prognosis as those who underwent standard RNU. Given the renal function preservation, SU may be a priority option to RNU for selected patients.

Disclosure of conflict of interest

None.

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