

Segmental ureterectomy can be performed safely in patients with urothelial carcinoma of distal ureter

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Cite as: *Can Urol Assoc J* 2019;13(7):E202-9. <http://dx.doi.org/10.5489/cuaj.5555>

Published online November 20, 2018

Abstract

Introduction: We aimed to compare oncological outcomes by surgery type (segmental ureterectomy [SU] vs. radical nephroureterectomy [RNU]) in a large cohort of patients with upper tract urothelial carcinoma (UTUC) of the distal ureter.

Methods: We performed a retrospective analysis of 219 patients with UTUC of the distal ureter among 931 patients with UTUC who underwent SU and RNU. Clinicopathological outcomes were evaluated. Cancer-specific survival (CSS), overall survival (OS), local recurrence-free survival (RFS), intravesical recurrence-free survival (IVRFS), contralateral recurrence-free survival, and distant metastasis-free survival were assessed by the Kaplan-Meier method and Cox regression, estimating hazard ratios (HR) and 95% confidence intervals (CIs).

Results: A total of 179 (81.7%) patients underwent RNU and 40 (18.3%) underwent SU: 85 males (47.5%) with RNU and 17 (42.5%) with SU ($p=0.568$). The median age with RNU and SU was 71 years (range 31–86) and 70 years (range 46–90), respectively ($p=0.499$). The T stage of the two groups did not differ ($p=0.122$), nor did mean tumor length (3.35 ± 2.62 vs. 3.25 ± 2.14 ; $p=0.953$), grade ($p=0.075$), tumor necrosis ($p=0.634$), or followup time (months) (58.1 ± 8.1 vs. 63.7 ± 3.4 ; $p=0.462$). The two groups did not differ in CSS ($p=0.358$) or OS ($p=0.206$), and surgery type did not predict CSS (HR 0.862; 95% CI 0.469–1.585; $p=0.633$) or OS (HR 0.764; 95% CI 0.419–1.392; $p=0.379$). Local RFS was higher with RNU than SU (96.2% vs. 86.0%; $p=0.02$), but the groups did not differ in IVRFS ($p=0.661$), contralateral RFS ($p=0.183$), or distant metastasis-free survival ($p=0.078$). On multivariate analysis, SU was associated with local RFS (HR 5.069; 95% CI 1.029–24.968; $p=0.046$) and distant metastasis-free survival (HR 6.497; 95% CI 1.196–35.283; $p=0.03$). Local RFS was lower with SU than RNU for patients with pT3–4 stage ($p=0.006$).

Conclusions: Long-term oncological outcomes were equivalent with SU and RNU in patients with UTUC of the distal ureter. SU affected local recurrence survival, especially with advanced tumor stage, and distant metastasis survival.

Introduction

Upper tract urothelial carcinoma (UTUC) is an uncommon disease and accounts for 7–8% of all renal tumors and 5–10% of all urothelial carcinomas.^{1–2} The standard option for UTUC treatment remains radical nephroureterectomy (RNU) because of the aggressiveness of the disease. However, segmental ureterectomy (SU) is increasingly being chosen for better preservation of postoperative renal function, especially for patients with chronic renal insufficiency, solitary kidney, or bilateral synchronous disease.^{3–5} To our knowledge, cancer-specific survival (CSS) and recurrence-free survival (RFS) after SU is not clear, and the indication of SU is debatable.

Here, we compared oncological outcomes by surgery type (SU vs. RNU) in a large cohort of patients with UTUC of the distal ureter, which could be meaningful for management of UTUC.

Methods

Patients

A series of 931 UTUC patients who had undergone surgery at our institution from January 2000 to April 2014 was retrospectively analyzed. We included 248 patients with tumors localized at the distal ureter (defined as below the level of iliac vessels) and who underwent SU or RNU. We excluded patients with evidence of metastatic disease at the time of diagnosis, other malignancies, or incomplete followup data. Patients were preoperatively evaluated by imaging (ultrasonography, computed tomography [CT], magnetic resonance imaging [MRI], or intravenous urography) and urine cytology and cystoscopy. Preoperative ureteroscopy with biopsy was not routinely assessed in case of inconclusive diagnosis.

For patients who were followed at our institution, the followup regimen included cystoscopy every three months for the first two years. The followup intervals were extended

to half a year up to five years after surgery and one year thereafter. Chest x-ray, urine cytology, serum creatine measurement, and abdominal ultrasonography or CT/MRI were performed at the same time.

Statistical analysis

Patients were divided into two groups by surgery type: SU or RNU. The following clinical and pathological variables were reviewed: sex, age/body mass index (BMI), previous history of UTUC and bladder carcinoma, surgical procedure, tumor length and side, tumor stage and grade, lymphovascular invasion (LVI), and necrosis. Clinical and pathological characteristics were compared by Wilcoxon test, Chi-square test, or Fisher exact test. CSS, overall survival (OS), local RFS, intravesical recurrence-free survival (IVRFS), contralateral recurrence-free survival, and distant metastasis-free survival were analyzed by the Kaplan-Meier method with the log-rank test. Univariable analysis with the log-rank test and multivariable analysis with the Cox proportional hazards regression model were used, estimating hazard ratios (HRs) and 95% confidence intervals (CIs). Two-tailed $p < 0.05$ was considered statistically significant.

Results

Clinicopathological characteristics

The clinical and pathological characteristics of the 219 patients included are in Tables 1 and 2; 179 (81.7%) underwent RNU and 40 (18.3%) underwent SU. The RNU group had 85 males (47.5%) and the SU group 17 males (42.5%) ($p = 0.568$). The median age was 71 years (range 31–86) and 70 years (range 46–90), respectively ($p = 0.499$). Also, the mean BMI was similar ($p = 0.485$). The two groups did not differ in history of UTUC and bladder carcinoma (6.1% vs 7.5%, $p = 0.724$; 14.0% vs 12.5%, $p = 0.806$). Surgery was

performed by laparoscopy for 71 RNU patients (39.7%) and 12 SU patients (30.0%) ($p = 0.255$). Surgery was performed in retroperitoneal approach in 145 RNU patients (81.0%) and 34 SU patients (85.0%) ($p = 0.554$). There were two patients (5.0%) who had undergone lymph node dissection in the SU group and 24 patients (13.4%) in the RNU group ($p = 0.137$). The T stage of the two groups did not differ ($p = 0.122$) and no lymph node metastasis was found in any patient. The groups did not differ in mean tumor length (3.35 ± 2.62 vs. 3.25 ± 2.14 ; $p = 0.953$), tumor grade ($p = 0.075$), or rate of necrosis ($p = 0.634$).

CSS and OS

The mean followup time (months) did not differ between the RNU and SU groups (58.1 ± 8.1 vs. 63.7 ± 3.4 ; $p = 0.462$), and CSS and OS did not differ ($p = 0.358$ and $p = 0.206$) (Fig. 1).

On multivariable analysis, age, history of UTUC; and tumor length were significantly associated with both CSS and OS (Table 3). However, the surgery type, RNU or SU, did not predict CSS (HR 0.862; 95% CI 0.469–1.585; $p = 0.633$) or OS (HR 0.764; 95% CI 0.419–1.392; $p = 0.379$).

Recurrence and distant metastasis

The five-year local RFS was 96.2% and 86.0% with RNU and SU, respectively ($p = 0.02$) (Fig. 2A). On multivariable analysis, local RFS was associated with SU (HR 5.069; 95% CI 1.029–24.968; $p = 0.046$) (Table 4). The five-year IVRFS was 45.4% and 46.4% with RNU and SU, respectively ($p = 0.661$) (Fig. 2B). On multivariable analysis, IVRFS was associated with history of bladder carcinoma (HR 2.129; 95% CI 1.385–3.273; $p = 0.001$) and tumor necrosis (HR 2.12; 95% CI 1.212–3.708; $p = 0.008$). The five-year contralateral RFS with RNU and SU was 89.6% and 92.9%, respectively ($p = 0.183$) (Fig. 2C). On multivariable analysis, contralateral RFS was associated with age and BMI of patients and tumor length. The five-year distant metastasis-free survival with RNU and SU was 96.0%

Table 1. Association between surgery type (radical nephroureterectomy [RNU] and segmental ureterectomy [SU]) and preoperative clinical characteristics of patients with upper tract urothelial carcinoma (UTUC) of the distal ureter

	RNU n=179	SU n=40	Chi-square or Z	p
Male (%)	85 (47.5%)	17 (42.5%)	0.327	0.568
Median age (range)	71 (31–86)	70 (46–90)	-0.677	0.499
BMI, mean \pm SD	24.38 \pm 3.43	24.98 \pm 3.83	-0.698	0.485
History of UTUC	11 (6.1%)	3 (7.5%)		0.724
History of bladder carcinoma	25 (14.0%)	5 (12.5%)	0.432	0.806
Surgical procedure, laparoscopy	71 (39.7%)	12 (30.0%)	1.298	0.255
Surgical approach, retroperitoneal	145 (81.0%)	34 (85.0%)	0.349	0.554
Tumor side, left	88 (49.2%)	16 (40.0%)	2.737	0.254
Lymph node dissection	24 (13.5%)	2 (5.0%)	2.209	0.137

BMI: body mass index; SD: standard deviation.

Table 2. Association between surgery type (radical nephroureterectomy [RNU] and segmental ureterectomy [SU]) and postoperative clinicopathological characteristics of patients with upper tract urothelial carcinoma (UTUC) of the distal ureter

	RNU n=179	SU n=40	Chi-square or Z	p
T stage			7.268	0.122
Ta	7 (3.9%)	0		
T1	53 (29.6%)	18 (45%)		
T2	79 (44.1%)	12 (30.0%)		
T3	39 (21.8%)	10 (25%)		
T4	1 (0.6%)	0		
N stage				
N0	179	40		
N1	0	0		
Grade			5.186	0.075
1	10 (5.6%)	0		
2	82 (45.8%)	23 (57.5%)		
3	87 (48.6%)	17 (42.5%)		
LVI	10 (5.6%)	2(5.0%)		1
Tumour length	3.35±2.62	3.25±2.14	0.059	0.953
Necrosis	26 (14.5%)	7 (17.5%)	0.226	0.634
eGFR difference	25.09±18.45	20.14±16.29	-0.249	0.840
Local recurrence	10 (5.6%)	3 (7.5%)		0.71
Bladder recurrence	102 (57.0%)	22 (55.0%)	0.052	0.819
Contralateral recurrence	13 (7.3%)	1 (2.5%)		0.474
Metastasis	6 (3.4%)	4 (10.0%)		0.087

eGFR: estimated glomerular filtration rate; LVI: lymphovascular invasion.

and 90.3%, respectively ($p=0.078$) (Fig. 2D). On multivariable analysis, distant metastasis-free survival was associated with SU (HR 6.497; 95% CI 1.196–35.283; $p=0.03$).

On stratification by T stage (pTa–T2 vs. pT3–T4), CSS, OS, contralateral RFS, IVRFS, and distant metastasis-free survival did not differ by RNU or SU (data not shown). For patients with pTa–T2, local RFS did not differ by surgery type ($p=0.296$) (Fig. 3). However, for patients with pT3–T4, local RFS was shorter with SU than with RNU ($p=0.006$) (Fig. 3). The site of local recurrence after SU in the three patients was ureteral residue. Two of the three patients had further surgery and one took chemotherapy for treatment.

Discussion

We aimed to compare oncological outcomes by surgery type (SU vs. RNU) in a large cohort of patients with UTUC of the distal ureter. Long-term oncological outcomes were equivalent with SU and RNU in patients with UTUC of the distal ureter. SU affected local RFS and distant metastasis survival. Local RFS was lower with SU than with RNU for patients with advanced-disease stage.

In the 2017 European Association of Urology guidelines, RNU is the standard for high-risk UTUC, regardless of tumor location.⁶ In low-risk cancers, which are unifocal, small, low-grade, and with no infiltration seen on CT or urography, sur-

vival with kidney-sparing surgery (i.e., ureteroscopy or SU) is similar to that with RNU.⁷ In high-risk cancers, kidney-sparing surgery can also be considered with renal insufficiency or solitary functional kidney.^{3,8} As compared with SU, ureteroscopy has several drawbacks: there is a lack of pathological specimens if treated by laser generator and lymphadenectomy is not possible, which is important in evaluating the stage and grade.^{8,9} Thus, SU is favored over RNU in some situations. However, CSS and RSS was unknown with SU.

A retrospective study of more than 2000 patients with UTUC showed no significant difference in CSS with SU vs. RNU.⁸ Another study revealed that SU or RNU were not predictors of CSS on multivariable analysis and CSS or RFS did not differ on Kaplan-Meier analyses.¹⁰ Few studies of survival and recurrence for tumors at the distal ureter have been reported. Whether SU could be used in high-risk tumors is still controversial. Bin et al showed no significant difference in CSS with proximal, middle, or distal tumor location of the ureter in UTUC.¹¹

In our study, the clinicopathological characteristics of patients with SU and RNU, including TNM stage and tumor grade, did not differ, so the results of CSS, OS, and RFS were less influenced. The surgery type, SU vs. RNU, did not affect CSS or OS. Several studies also found CSS and OS comparable with SU and RNU in patients with UTUC of the distal ureter.^{7,12,13} Furthermore, we found that older

Table 3. Univariable and multivariable analysis of the association of surgery type with cancer-free survival (CSS) and overall survival (OS)

Variables	CSS				OS			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Sex	1.437 (0.941–2.193)	0.093	1.088 (0.688–1.721)	0.717	1.451 (0.97–2.17)	0.07	1.167 (0.758–1.799)	0.483
Age	1.037 (1.011–1.065)	0.005*	1.03 (1.003–1.057)	0.028*	1.037 (1.012–1.063)	0.004*	1.03 (1.005–1.056)	0.019*
BMI	0.972 (0.917–1.031)	0.35	0.982 (0.922–1.047)	0.585	0.969 (0.916–1.023)	0.275	0.978 (0.921–1.038)	0.457
Side, left vs. right	0.958 (0.635–1.445)	0.837	0.998 (0.656–1.517)	0.991	0.935 (0.632–1.383)	0.737	0.986 (0.661–1.471)	0.945
History of UTUC, yes vs. no	11.377 (6.119–21.150)	<0.001*	9.416 (4.689–18.907)	<0.001*	10.463 (5.677–19.284)	<0.001*	9.022 (4.577–17.784)	<0.001*
History of bladder carcinoma, yes vs. no	1.148 (0.616–2.138)	0.664	1.403 (0.728–2.703)	0.312	1.029 (0.554–1.912)	0.927	1.228 (0.642–2.35)	0.535
Surgery type, reference SU	0.722 (0.4–1.303)	0.279	0.862 (0.469–1.585)	0.633	0.644 (0.359–1.156)	0.14	0.764 (0.419–1.392)	0.379
Surgery approach, reference laparoscopy	0.917 (0.581–1.449)	0.711	1.048 (0.646–1.689)	0.85	1.02 (0.665–1.563)	0.928	1.165 (0.742–1.831)	0.506
T stage	1.607 (1.214–2.127)	0.001*	1.474 (1.027–2.115)	0.035*	1.53 (1.174–1.995)	0.002*	1.341 (0.974–1.847)	0.072
Grade	1.882 (1.264–2.803)	0.2	1.098 (0.662–1.824)	0.717	1.865 (1.277–2.724)	0.001*	1.132 (0.7–1.832)	0.613
LVI	1.039 (0.453–2.386)	0.927	0.772 (0.307–1.945)	0.584	1.099 (0.508–2.376)	0.81	0.806 (0.339–1.919)	0.626
Tumour length	1.126 (1.055–1.201)	<0.001*	1.089 (1.014–1.169)	0.018*	1.127 (1.06–1.199)	<0.001*	1.083 (1.013–1.159)	0.019*
Necrosis	1.184 (0.678–2.066)	0.552	0.947 (0.51–1.759)	0.863	1.309 (0.784–2.186)	0.304	1.104 (0.62–1.968)	0.626

*Statistically significant. BMI: body mass index; CI: confidence interval; HR: hazard ratio; LVI: lymphovascular invasion. SU: segmental ureterectomy; UTUC: upper tract urothelial carcinoma.

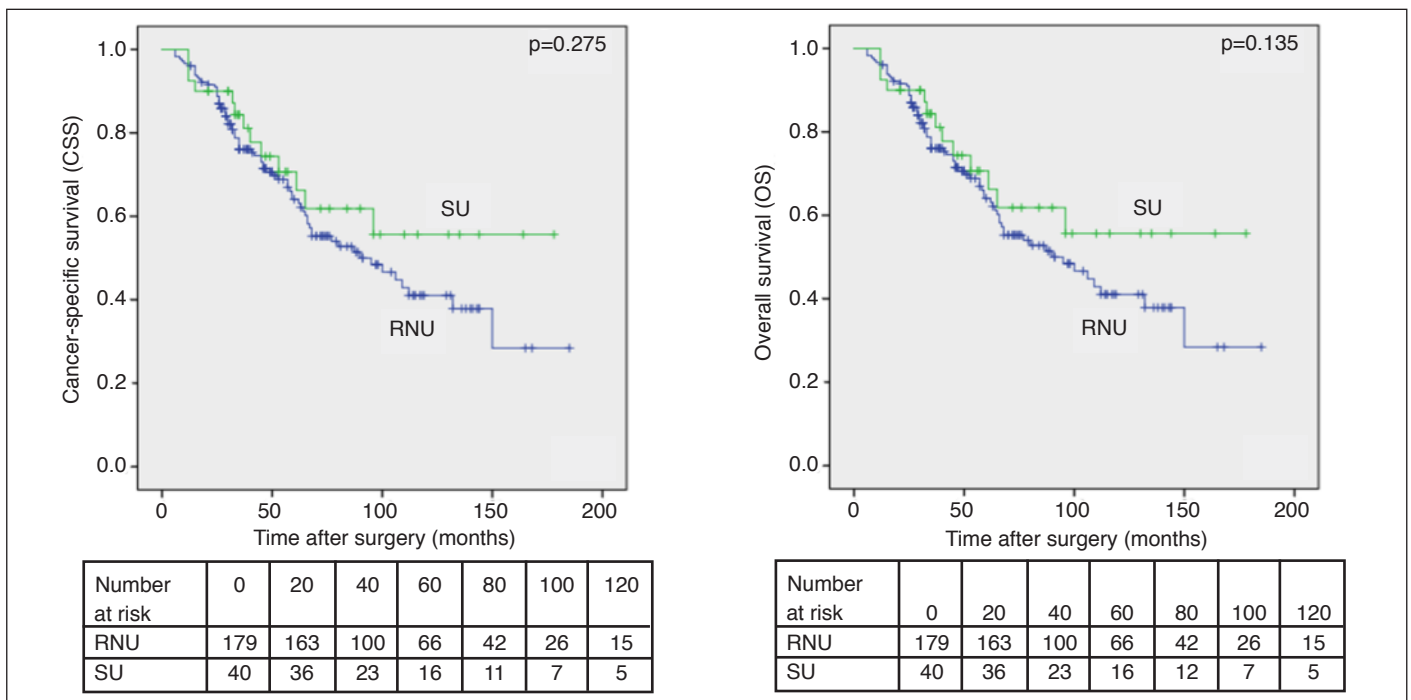


Fig. 1. Survival curves in patients by surgery type. The dots represent censored observations. RNU: radical nephroureterectomy; SU: segmental ureterectomy.

Table 4. Univariable and multivariable analysis of factors associated with recurrence-free survival and distant metastasis-free survival

Variables	Local recurrence-free survival			Intravesicular recurrence-free survival			Contralateral recurrence-free survival			Distant metastasis-free survival		
	Univariable	Multivariable	P	Univariable	Multivariable	P	Univariable	Multivariable	P	Univariable	Multivariable	P
Sex	0.109		0.068	0.197	0.158	0.505	0.122	0.14	0.177			
Age	0.351		0.066	0.028*	0.157	0.089	0.903 (0.848–0.962)	0.139	0.03*	1.126 (1.012–1.254)		
BMI	0.505		0.212	0.414	0.704	0.313	0.816 (0.675–0.985)	0.975	0.488			
Side, left vs. right	0.604		0.693	0.379	0.148	0.687		0.828	0.667			
History of UTUC, yes vs. no	0.745		0.988	0.415	0.572	0.158		0.738	0.991			
History of bladder carcinoma, yes vs. no	0.511		0.98	<0.001*	0.001*	0.823		0.454	0.204			
Surgery type, reference SU	0.033*	5.069 (1.029–24.968)	0.046*	0.665	0.94	0.214		0.093	0.03*	6.497 (1.196–35.283)		
Surgery approach, reference laparoscopy	0.211		0.149	0.164	0.256	0.768		0.292	0.796			
T stage	0.801		0.947	0.41	0.107	0.164		0.055	0.139			
Grade	0.862		0.448	0.667	0.127	0.167		0.88	0.922			
LVI	0.063		0.692	0.704	0.682	0.5		0.983	0.015*	8.943 (1.518–52.685)		
Tumor length	0.363		0.515	0.043*	0.061	0.013*	1.287 (1.045–1.584)	0.461	0.313			
Necrosis	0.455		0.933	0.13	0.008*	0.198	2.12 (1.212–3.708)	0.212	0.616			

*Statistically significant. BMI: body mass index; CI: confidence interval; HR: hazard ratio; LVI: lymphovascular invasion; SU: segmental ureterectomy; UTUC: upper tract urothelial carcinoma.

age, advanced T stage, and length of tumor were associated with CSS and OS in UTUC, which agreed with results from the literature.

The two groups did not differ in rate of local recurrence, bladder recurrence, contralateral recurrence, and distant metastasis. The rate of bladder recurrence after RNU for UTUC is 22–47%.^{7,14} However, we found a bladder recurrence rate of 57.0% with RNU and 55.0% with SU. Lower ureter lesion was previously found an independent predictor of bladder recurrence in patients with UTUC treated with RNU,¹⁵ which may explain why we found a higher rate of bladder recurrence. A systematic review and meta-analysis of bladder recurrence after RNU found ureteral location, necrosis, a laparoscopic approach, intravesical bladder-cuff removal, and positive surgical margins linked to bladder recurrence. Ureteral tumor location was a significant predictor of bladder recurrence (HR 1.27; 95% CI 1.14–1.42; $p < 0.001$).⁷ Fradet et al showed tumors located at both the renal pelvis and ureter, older age, and laparoscopic surgery as risk factors for bladder recurrence after RNU.¹⁴ Our study found that surgery type, SU or RNU, was not associated with IVRFS, but IVRFS could be predicted by history of bladder carcinoma and tumor necrosis, which agreed with the literature. Furthermore, Liu et al, in a retrospective analysis of 664 UTUC patients who underwent RNU, found diagnostic ureteroscopy to be an independent risk factor for IVRFS.¹⁶ A study by Sung et al had a similar conclusion.¹⁷

Few studies have investigated local recurrence-free, contralateral-free and distant metastasis-free survival. Hung et al showed no significant differences in local RFS ($p = 0.302$) and distant metastasis-free survival ($p = 0.219$) with SU and RNU.¹⁸ In our study, local RFS was lower with SU than RNU, and SU was associated with reduced distant metastasis-free survival. The two groups did not differ in contralateral RFS. The tumors investigated in the Hung et al study were in the whole ureter, whereas our tumors were at the distal ureter, which may explain the differences in results.

Local RFS was lower with SU than RNU for patients with pT3–4 stage, but with no

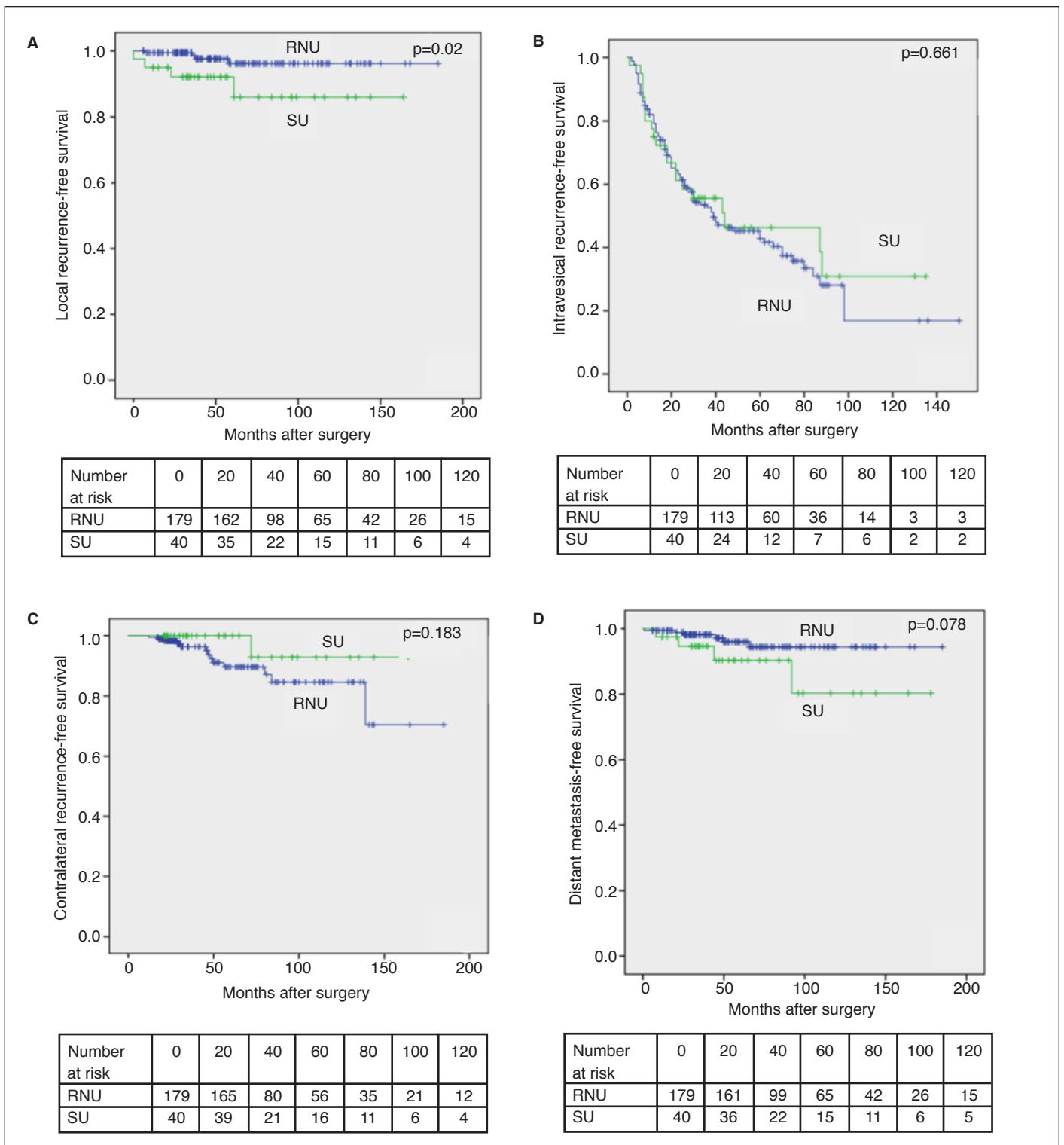


Fig. 2. Survival curves in patients by surgery type. **(A)** Local recurrence-free survival (RFS); **(B)** intravesical RFS; **(C)** contralateral recurrence-free survival; and **(D)** distant metastasis-free survival. The dots represent censored observations. RNU: radical nephroureterectomy; SU: segmental ureterectomy.

effect on CSS, OS, IVRFS, contralateral-free survival, or distant metastasis-free survival vs. RNU. The Jeldres et al study showed no difference in CSS with RNU vs. SU in patients

with pT1–2N0M0 and pT3–4N0M0.⁸ Other researchers have implied that patients with locally advanced-stage disease should not be excluded from consideration for SU.^{8,13}

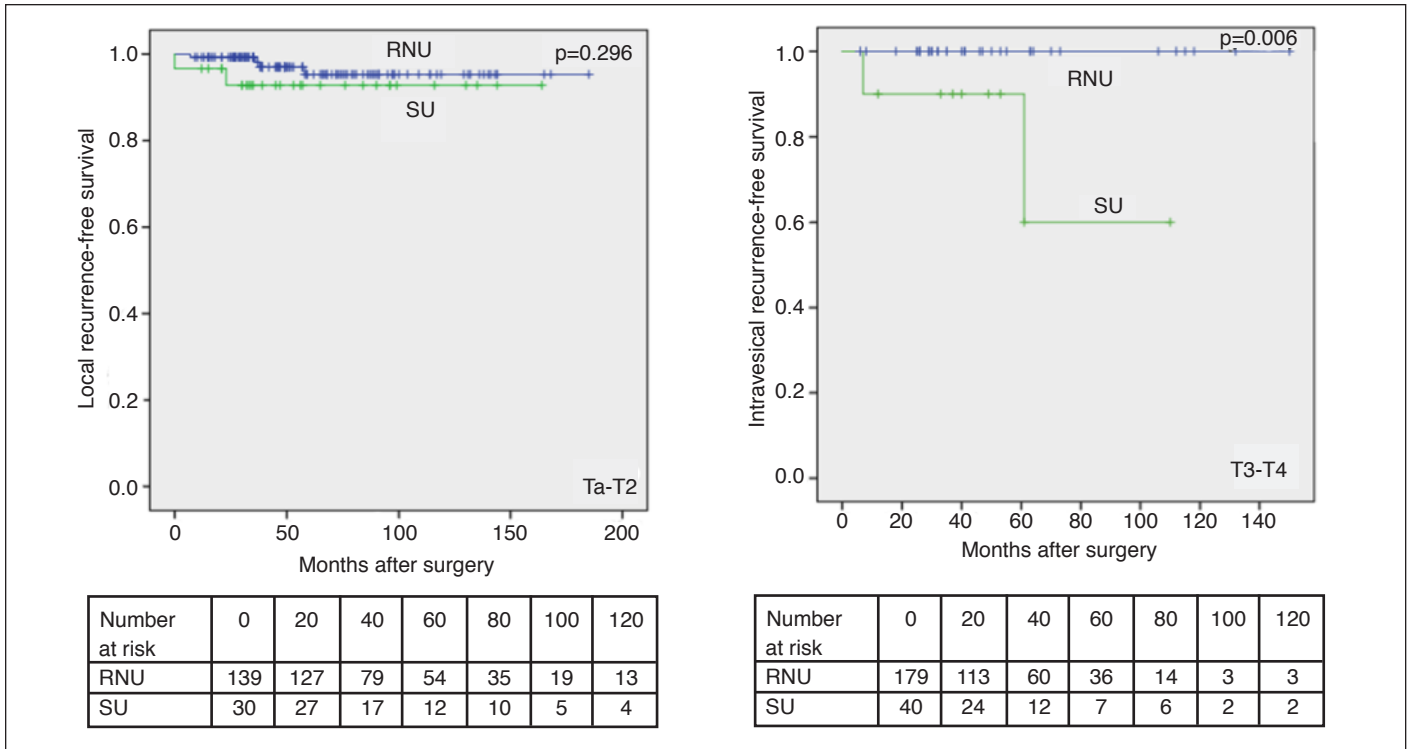


Fig. 3. Local recurrence-free survival curves by surgery type. The dots represent censored observations. RNU: radical nephroureterectomy; SU: segmental ureterectomy.

The most important advantage of SU might be its better protection of postoperative renal function. SU could contribute to good preservation of renal function.¹⁹ We have few studies about the relation between renal function and prognostic outcomes of patients with UTUC. One study showed decreased glomerular filtration rate after RNU, and renal function was not associated with disease recurrence, CSS, or OS. Furthermore, the results were similar when restricted to patients with locally advanced disease (pT3–pT4).²⁰

A systematic review and meta-analysis showed that cisplatin-based adjuvant systemic chemotherapy was beneficial for OS and disease-free survival with UTUC; non-cisplatin-based chemotherapy had no benefit.²¹ However, not all patients could receive cisplatin-based adjuvant chemotherapy because of impaired renal function. Thus, more patients could receive chemotherapy for better preservation of renal function with SU. However, we have insufficient data and still need further prospective studies. Furthermore, Xylinas et al found that in patients without adjuvant chemotherapy and disease recurrence, better renal function was associated with better OS.²⁰

This advantage of this study was its comprehensive inclusion of the prognostic outcomes of patients with UTUC in the distal ureter treated with SU and RNU, as we investigated CSS, OS, local recurrence-free survival, IVRFS, contralateral RFS, and distal metastasis-free survival and in different tumor stages. The major limitation of our study was its single-center,

retrospective design. A multicenter, randomized controlled trial is needed to investigate the prognostic difference of SU and RNU and the proper indications of SU.

Conclusions

Our study suggests that SU and RNU have equivalent long-term prognostic outcomes for patients with UTUC of the distal ureter. However, SU can affect local recurrence survival and distant metastasis survival. With advanced T stage, local RFS is lower with SU than with RNU. Thus, SU could be used for low-risk tumors and should not be excluded in patients with advanced disease. Patients who undergo SU need to be followed up carefully.

Competing interests: The authors report no competing personal or financial interests related to this work.

Funding: This work was supported by the Clinical Features Research of Capital (No. Z151100004015173) and the Capital Health Research and Development of Special (No. 2016-1-4077).

This paper has been peer-reviewed.

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