

Segmental Ureterectomy Versus Radical Nephroureterectomy in Older Patients Treated for Upper Tract Urothelial Carcinoma

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Abstract

Surgery in older patients is associated with higher perioperative morbidity and mortality rates. We compared radical nephroureterectomy and segmental ureterectomy (less invasive) in patients older than 75 years of age with upper tract urothelial carcinoma. Segmental ureterectomy showed lower rates of post-operative complications, without affecting survival; it could be safely indicated in selected older patients with upper tract urothelial carcinoma.

Introduction: The world population is ageing and surgical procedures for older patients are associated with higher perioperative morbidity and mortality rates than in younger patients. Segmental ureterectomy (SU) has been proposed as an alternative to radical nephroureterectomy (RNU) for selected upper tract urothelial carcinomas (UTUC), to reduce post-operative morbidity, and preserve renal function. The aim of this study was to compare RNU and SU in terms of post-operative complications, functional outcomes, and overall survival (OS) in older patients treated for UTUC.

Materials and Methods: Data of patients aged 75 years or older and treated for UTUC were included. The primary outcome was to compare RNU versus SU according to post-operative complications, the estimated glomerular filtration rate (eGFR) variation, and OS. Complications were defined according to the Clavien-Dindo classification. eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Un-adjusted OS curves were plotted using the Kaplan–Meier method. **Results:** Overall, 177 patients (150 RNU and 27 SU) were eligible for the analysis. Pre- and post-operative characteristics were similar between the 2 groups. RNU patients showed higher incidence of post-operative complications (34.0% vs. 7.4%, $P = .011$). The mean post-operative serum creatinine was lower in SU patients in comparison with the RNU ones (1.23 vs. 1.69 mg/dL, $P = .046$), but no differences were found in terms of eGFR variation ($P = .258$). At 3 years of follow-up, the OS was comparable between the two surgical techniques ($P = .129$). **Conclusion:** In older patients diagnosed with UTUC, SU could offer lower rates of post-operative complications without affecting survival.

Clinical Genitourinary Cancer, Vol. 20, No. 4, 381–387 © 2022 Elsevier Inc. All rights reserved.

Keywords: Aged, Postoperative complications, Kidney sparing surgery, Survival, Renal function

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Submitted: Apr 28, 2021; Revised: Dec 27, 2021; Accepted: Jan 8, 2022; Epub: 13 January 2022

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Introduction

While the population is ageing all over the world,¹ it has been already shown that upper tract urothelial carcinoma (UTUC) is a rare condition accounting for 5%-10% of urothelial carcinomas² with a peak incidence in the 7th-9th decades. It is known that UTUC affects the quality of life of older patients especially regarding general health, social functioning, and vitality.³

The primary treatment for UTUC is radical nephroureterectomy (RNU). However, surgical procedures for older patients are generally associated with higher perioperative morbidity, and mortality rates than in younger patients⁴. Segmental ureterectomy (SU) has been proposed as an alternative to RNU for selected cases, to reduce post-operative morbidity, and to preserve renal function. It has been shown that the operation time of SU and, more importantly, the length of hospital stay for UTUC patients treated with SU can be significantly reduced in comparison with RNU (141 vs. 288 mins, $P < .001$; 17.5 vs. 21 days, $P = .045$; respectively)⁵. However there is no clear benefit for SU in reducing serious surgical complication occurrence (Clavien–Dindo classification grade > 2 : 25.0 vs. 38.5%, $P = .271$) and pain control (mean pain score: 2.06 vs. 1.93, $P = .864$) in comparison with RNU⁶. SU has been associated with preservation of estimated glomerular filtration rate (eGFR),^{7,8} although recent findings questioned this point in particular in case of preoperative renal function impairment.⁹ Additionally, SU can offer overall (OS), cancer-specific, recurrence-free, and intravesical recurrence-free survival similar to RNU.^{7,8}

To the best of our knowledge, evidence is scarce on post-operative complications, renal function, and survival of older patients treated with SU in comparison with RNU for UTUC. Consequently, this study aims at overcoming this gap in knowledge.

Materials and Methods

This is a multicenter study including data of patients treated for UTUC from January 2003 to December 2013 in six Italian tertiary referral centers (Bologna, Genoa, Milan, Palermo, Trieste, and Turin).

All patients aged 75 years or older having undergone SU or RNU for UTUC were eligible for the analysis. Patients with a history of other malignancies, metastatic disease, and radical cystectomy were excluded from the analysis. All patients were diagnosed using computed tomography or magnetic resonance imaging; preoperative ureteroscopy with biopsy was performed in case of diagnostic uncertainty. Patients were treated with RNU or SU according to tumor location and surgeon preference. Similarly, SU was performed as a complete distal ureterectomy with bladder cuff removal and ureteric re-implantation, or as a segmental resection with ureteric termino-terminal anastomosis, according to tumor location, and intra-operative choice. Thirty-day post-operative complications were recorded and classified according to the Clavien-Dindo classification.¹⁰ Subsequent follow-up was performed according to the most recent international guidelines.

The primary outcome of the present study was to compare post-operative complications, eGFR variation, and OS according to the

Table 1 Pre-operative Clinical and Oncological Characteristics of the Study Population

Variable	Total	RNU	SU	P-value
Patients	177	150 (84.7)	27 (15.3)	
Age, yr	80.0 ± 3.6	80.0 ± 3.7	80.1 ± 3.2	.883
Gender				
Male	125 (70.6)	108 (72.0)	17 (63.0)	.472
Female	52 (29.4)	42 (28.0)	10 (37.0)	
Smoking status – 80 patients				
No	48 (60.0)	42 (60.0)	6 (60.0)	1.000
Yes	32 (40.0)	28 (40.0)	4 (40.0)	
Symptoms – 134 patients				
No	41 (30.6)	33 (27.5)	8 (57.1)	.049
Yes	93 (69.4)	87 (72.5)	6 (42.9)	
Tumor localization				
Renal pelvis	80 (45.2)	80 (53.3)	0 (0.0)	< 0.001
Ureter	75 (42.4)	48 (32.0)	27 (100.0)	
Proximal	10 (5.6)	9 (6.0)	1 (3.7)	
Middle	23 (13.0)	18 (12.0)	5 (18.5)	
Distal	42 (23.7)	21 (14.0)	21 (77.8)	
Both	22 (12.4)	22 (14.7)	0 (0.0)	
Focality				
Unifocal	118 (66.7)	96 (64.0)	22 (81.5)	.121
Multifocal	59 (33.3)	54 (36.0)	5 (18.5)	
Side				
Right	76 (42.9)	66 (44.0)	10 (37.0)	0.638
Left	99 (55.9)	82 (54.7)	17 (63.0)	
Bilateral	2 (1.2)	2 (1.3)	0 (0.0)	
Hydronephrosis – 136 patients				
No	54 (39.7)	50 (41.0)	4 (28.6)	.541
Yes	82 (60.3)	72 (59.0)	10 (71.4)	
Biopsy				
No	150 (84.7)	127 (84.7)	23 (85.2)	1.000
Yes	27 (15.3)	23 (15.3)	4 (14.8)	
Negative	7 (25.9)	6 (26.1)	1 (25.0)	1.000
Positive	20 (74.1)	17 (73.9)	3 (75.0)	
History of bladder cancer				
No	113 (63.8)	96 (64.0)	17 (63.0)	1.000
Yes	64 (36.2)	54 (36.0)	10 (37.0)	

Continuous variables are expressed as mean ± SD; Nominal variables are expressed as No. (%).

surgical technique chosen (RNU vs. SU) in older patients (age ≥ 75 years). The pre- and post-operative eGFR was calculated through the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula that considers serum creatinine levels, patient age, and race.

Pre- and post-operative characteristics were compared using t test or Mann-Whitney U test for continuous variables and χ^2 test for categorical variables. Un-adjusted OS curves in the 2 subgroups were plotted using the Kaplan–Meier method. Log-rank test was used to test statistical significant deviation of survival curves. The hazard

ratio (HR) for OS at 36 months was calculated through a bivariate Cox regression analysis comparing the types of surgery (SU vs. RNU). For the multivariate analysis, the propensity score of being in the SU group rather than RNU group was computed using a logistic regression model based on age, gender, pre-operative eGFR, and tumor localization. The HR for OS at 36 months was also calculated through a multivariate Cox regression analysis considering type of surgery and the propensity score as independent variables. CSS was not calculated due to the small number of events. Statistical analyses were performed with R software v. 3.3.3 (R Foundation, Vienna, Austria). A P value $< .05$ was considered as statistically significant.

Results

Clinical Characteristics of the Study Population

One hundred seventy-seven patients aged 75 years or older were eligible for the analysis. Eighty (45.2%), 75 (42.4%) and 22 (12.4%) patients were diagnosed with renal pelvis, ureteral and both tumors, respectively. Overall, 150 patients underwent RNU and 27 SU. Pre-operative clinical characteristics (*Table 1*) were similar between the 2 groups except for the presence of symptoms ($P = .049$). Pre-operative oncological characteristics were also similar between RNU and SU groups except for tumor localization ($P < .001$): renal pelvis tumors were not eligible for SU, while out of the 27 patients treated with SU, 1 (3.7%), 5 (18.5%) and 21 (77.8%) patients had a tumor of the proximal, middle and distal ureter, respectively. In the same group, 7 (25.9%) patients (1, 4 and 2 patients with proximal, middle and distal ureteral tumor) were treated with SU and ureteric termino-terminal anastomosis; the other 20 (74.1%) patients were treated with distal ureterectomy with bladder cuff removal and ureteric re-implantation. Furthermore there was no difference in focality ($P = .121$), presence of hydronephrosis ($P = .541$), and history of previous bladder cancer ($P = 1.000$).

A similar distribution of post-operative pathologic diagnosis was found (*Table 2*). In particular, 78 (44.1%) patients were diagnosed with non-invasive UTUC at final pathologic examination (42% vs. 51.8% in RNU and SU groups, respectively). Pathologic grade was similar in the two groups ($P = .335$), with nearly 2/3 of patients being diagnosed with high grade disease. Although lymph node dissection was performed in a similar percentage of cases (26.7 vs. 22.2% in RNU and SU patients, respectively) the number of lymph nodes dissected was lower in the SU group, but not significantly ($P = .195$).

Post-operative Complications

RNU patients showed a higher incidence of post-operative complications (34.0% vs 7.4%, $P = .011$). In particular, 5 patients within the RNU group were reoperated for bleeding: laparotomy with hemostatic revision was performed in 3 cases and adrenalectomy in 2 cases. One patient was operated for wound dehiscence and one other patient underwent contralateral nephrostomy placement. Seven other patients experienced a Clavien-Dindo grade 4 complication (respiratory failure in 3 cases, severe renal failure in 3 other cases, cardiac arrhythmia in 1 case). Finally, 5 patients treated with RNU died of severe acute renal failure (1 patient), respiratory failure

(1 patient), sepsis (1 patient), and unknown causes (2 patients) after admission to the intensive care unit (*Table 3*).

eGFR Variation

Preoperative renal function, in terms of serum creatinine levels and eGFR was similar in both groups (*Table 4*). Conversely, although the mean post-operative serum creatinine was lower in patients treated with SU in comparison with those with RNU (1.23 vs. 1.69 mg/dL, $P = .046$), no differences were noted in terms of post-operative eGFR (51.0 vs. 42.6 mL/min/1.73m², $P = .101$). Indeed, the variation of renal function after surgery did not significantly differ between the groups both in terms of serum creatinine, and eGFR.

Overall Survival and Oncological Outcomes

Given the observed survival rates, a probability of Type I error (α) of 0.05, a β of 0.8, and a ratio of sample size between groups of 5, the sample size needed for achieving a statistical power of 80% for the log-rank test (2 tails) was 129 and 26 patients for RSU and SU, respectively. At 3 years of follow-up, the OS was not significantly different between the two surgical techniques (65.6 vs. 86.6% for RNU and SU, respectively, $P = .129$; *Figure 1*). In the crude analysis for OS at 36 months, when compared to RNU, SU showed a HR of 0.35 (95%CI 0.08-1.45; $P = .147$). At the multivariate analysis for OS at 36 months, when compared to RNU, SU showed a HR 0.03 (95%CI 0.01-1.25; $P = .065$). At a median follow-up of 25.5 months, no significant differences were shown in terms of local recurrence, and metastasis (*Table 5*). In the SU group there was only one case of cancer related death (pT3NxR1). In the RNU group there were 26 cases of cancer related deaths: 7 (25.9%) patients were diagnosed with a non-invasive UTUC, while 19 (74.1%) had an invasive UTUC.

Discussion

In the current study, we assessed the surgical, functional and survival outcomes of SU in comparison with RNU in patients aged 75 years and older diagnosed with UTUC. For the first time we reported no differences in terms of post-operative eGFR and OS, but lower rates of post-operative complications after SU in these patients.

While the world population is aging,¹ overall health status, and functional independence in older people has improved in the last decades. In fact a large longitudinal study¹¹ revealed that at age 70 the overall health profile is now favorable, but it reported rising comorbidity and declining cognitive status at age 78 and even more at 85. All these data suggest that a cut-off point beyond age 70 years could better define entry into old age. Indeed Orimo et al. already suggested that the cut-off age to define "older" should change from 65 years to 75 years.¹² According to these findings, we chose 75 as a cut-off age to define older patients to be included in the analysis for the aims of the current study.

Age has been already recognized as an independent predictor of overall and cancer-specific mortality in UTUC patients treated with RNU. In a recent study¹³ including data of 454 UTUC patients (86% \geq pT1) who received surgery between 1995 and 2014, an age older than 70 years independently and adversely predicted

Table 2 Post-operative Pathological Characteristics

Variable	Total	RNU	SU	P-value
Pathological T-stage				
T0/Ta/T1/CIS	79 (44.6)	64 (42.7)	15 (55.6)	.499
T2	41 (23.2)	34 (22.7)	7 (25.9)	
T3	49 (27.7)	44 (29.3)	5 (18.5)	
T4	6 (3.4)	6 (4.0)	0 (0.0)	
Tx	2 (1.1)	2 (1.3)	0 (0.0)	
CIS associated				
No	157 (88.7)	134 (89.3)	23 (85.2)	.767
Yes	20 (11.3)	16 (10.7)	4 (14.8)	
Pathological N-stage				
N0	37 (20.9)	31 (20.7)	6 (22.2)	.789
N1	3 (1.7)	3 (2.0)	0 (0.0)	
N2	5 (2.8)	5 (3.3)	0 (0.0)	
N3	1 (0.6)	1 (0.7)	0 (0.0)	
Nx	131 (74.0)	110 (73.3)	21 (77.8)	
No. Lymph nodes dissected	6.5 (4.7 - 8.3)	7.5 (5.0 - 10.8)	4.5 (1.4 - 7.8)	.195
Grade – 174 patients				
G1	5 (2.9)	4 (2.7)	1 (3.8)	.335
G2	55 (31.6)	50 (33.8)	5 (19.2)	
G3	114 (65.5)	94 (63.5)	20 (76.9)	
Lymph vascular invasion – 138 patients				
No	117 (84.8)	105 (84.7)	12 (85.7)	1.000
Yes	21 (15.2)	19 (15.3)	2 (14.3)	
Necrosis				
No	153 (86.4)	128 (85.3)	25 (92.6)	.478
Yes	24 (13.6)	22 (14.7)	2 (7.4)	
Bladder cuff removal				
No	72 (40.7)	65 (43.3)	7 (25.9)	.138
Yes	105 (59.3)	85 (56.7)	20 (74.1)	
Surgical margins				
Positive	17 (9.6)	13 (8.7)	4 (14.8)	.520
Negative	160 (90.4)	137 (91.3)	23 (85.2)	
Concomitant bladder cancer				
No	140 (79.1)	121 (80.7)	19 (70.4)	.340
Yes	37 (20.9)	29 (19.3)	8 (29.6)	

Continuous variables are expressed as median (95%CI); Nominal variables are expressed as No. (%).

progression-free survival (HR 1.82; 95%CI 1.24 - 2.66; $P = .004$) and OS (HR 1.96; 95%CI 1.28 - 2.74; $P = .002$). Furthermore Shariat et al.¹⁴ had already shown that patients older than 70 years were also less likely to undergo lymphadenectomy and to receive adjuvant chemotherapy ($P = .026$).

Increasing comorbidity is indeed the main limitation to surgical practice in older patients: in fact, conservative treatment and adjuvant topical therapy could be proposed in very selected UTUC cases.¹⁵ According to previous literature,^{7,8} we reported comparable OS after SU, and RNU also in the subgroup of patients older than 75 years of age. Hamel et al.⁴ showed that in older patients, who had one or more complications in 20% of cases, 30-day mortality rates

were higher for those suffering post-operative complications when compared to those without complications (26% vs. 4%). However, urological surgeries in older patients are generally effective and safe, and complications occur mainly during emergency procedures and major operations such as cystectomy and nephrectomy (together with RNU).¹⁶ Our data showed a higher incidence of post-operative complications in the RNU group, with 5 (3.3%) patients dying after RNU in comparison with none among those treated with SU. This result has high societal impact considering that post-operative complications may represent a clinical burden on the long-term and affect survival.

Table 3 Clavien-Dindo Classification of 30-Day Post-operative Complications

Variable	Total	RNU	SU	P-value
Post-operative complications				
No	124 (70.1)	99 (66.0)	25 (92.6)	.011
Yes	53 (29.9)	51 (34.0)	2 (7.4)	
Clavien-Dindo classification – 53 patients				
1	10 (18.9)	8 (15.7)	2 (100.0)	.063
2	24 (45.3)	24 (47.1)	0 (0.0)	
3	7 (13.2)	7 (13.7)	0 (0.0)	
4	7 (13.2)	7 (13.7)	0 (0.0)	
5	5 (9.4)	5 (9.8)	0 (0.0)	

Nominal variables are expressed as No. (%).

Table 4 Pre- and Post-Operative Renal Function

Variable	Total	RNU	SU	P-value
Serum creatinine, mg/mL				
Pre-operative	1.31 ± 0.45	1.33 ± 0.44	1.16 ± 0.50	.225
Post-operative	1.64 ± 0.79	1.69 ± 0.82	1.23 ± 0.42	.046
Variation	0.32 ± 0.71	0.37 ± 0.73	-0.04 ± 0.29	.075
eGFR, mL/min/1.73m ²				
Pre-operative	52.6 ± 18.5	52.1 ± 18.3	56.6 ± 20.5	.452
Post-operative	43.5 ± 17.4	42.6 ± 17.5	51.0 ± 15.1	.101
Variation	-8.8 ± 18.2	-9.5 ± 18.6	-2.9 ± 14.2	.258

Continuous variables are expressed as mean ± SD; eGFR = estimated glomerular filtration rate.

Figure 1 Comparison between SU and RNU in terms of overall survival.

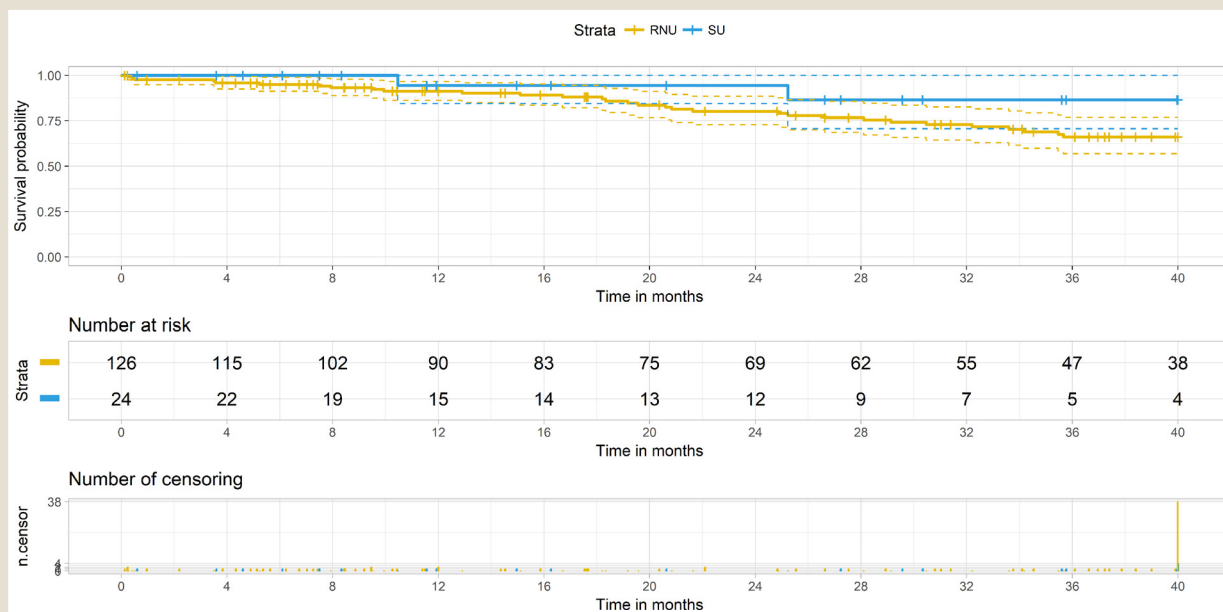


Table 5 Post-operative Oncological Follow-up

Variable	Total	RNU	SU	P-value
Follow-up period, mo	25.5 (19.5 - 30.8)	26.6 (19.5 - 33.6)	22.9 (11.3 - 31.7)	.273
Local recurrence - 146 patients				
No	78 (53.4)	64 (52.5)	14 (58.3)	.632
Ipsilateral	3 (2.1)	3 (2.4)	0 (0.0)	
Contralateral	1 (0.7)	1 (0.8)	0 (0.0)	
Vesical	56 (38.4)	46 (37.7)	10 (41.7)	
Lymph Nodes	8 (5.5)	8 (6.6)	0 (0.0)	
Metastasis - 156 patients				
No	135 (86.5)	112 (84.8)	23 (95.8)	.260
Yes	21 (13.5)	20 (15.2)	1 (4.2)	
Systemic chemotherapy - 154 patients				
No	144 (93.5)	122 (93.8)	22 (91.7)	.958
Yes	10 (6.5)	8 (6.2)	2 (8.3)	

Continuous variables are expressed as median (95%CI); Nominal variables are expressed as No. (%).

Finally, a recent meta-analysis showed that patients treated with SU had a lower probability of pre-operative hydronephrosis (OR 0.52; 95%CI 0.31 - 0.88, $P = .02$) and consequently a higher post-operative eGFR ($+10.97$ mL/min/ 1.73m^2 ; 95%CI 2.97 - 18.98, $P = .007$).⁸ However, in cases with pre-operative hydronephrosis and impaired renal function no differences were found between SU and RNU in terms of post-operative eGFR.⁹ In line with these results, in this study including patients older than 75 years of age with a pre-operative impaired renal function (mean pre-operative eGFR 52.6 ± 18.5 mL/min/ 1.73m^2), we did not find any significant post-operative variation of renal function in the two groups. eGFR, calculated with the CKD-EPI formula, can better estimate renal function due to accounting for age, sex and race; this may reflect the differences reported for the surgical technique impact on renal function according to creatinine levels and eGFR.

The main limitations of this study are its retrospective design and the relatively limited population (especially within the SU subgroup), that depend primarily on the rarity of the disease. Data on the dimensions of the disease at CT scan or previous intravesical chemotherapy were not available. Additionally, data on comorbidities were not available in our retrospective dataset, and thus a precise analysis on patient frailty was not possible. However, this limitation can be partially overcome by the fact that age is an already recognized independent and negative prognostic factor for UTUC and older patients are at high surgical risk, being characterized by multiple comorbidities in general. Finally, no data on postoperative bladder instillations early after surgery or adjuvant chemotherapy protocol were reported. On the other hand, the main strength of our study is its multicenter approach with a validated and shared follow-up scheme.

Conclusion

In the current retrospective study, we investigated the role of SU versus RNU in older patients (aged 75 years or older) with UTUC. Interestingly, we found that SU could offer lower rates of post-operative complications without affecting survival. No differ-

ences were reported in terms of post-operative variation of renal function. If confirmed in further and hopefully prospective studies, our current results may suggest that SU could be safely indicated, and preferred for its lower rate of complications in selected older patients with UTUC.

Clinical Practice Points

While the population is ageing all over the world, it has been already shown that upper tract urothelial carcinoma (UTUC) especially affects patients in the 7th - 9th decades. The primary treatment for UTUC is radical nephroureterectomy (RNU), but invasive surgical procedures in older patients are generally associated with higher perioperative morbidity and mortality. Kidney sparing surgery (eg segmental ureterectomy, SU) was proposed and has been demonstrated a valid alternative to RNU in selected UTUC cases, reducing post-operative morbidity, preserving renal function, and guaranteeing the same oncological results. In the current retrospective study, we compared SU and RNU in terms of oncological, functional, and morbidity in 177 patients older than 75 years of age diagnosed with UTUC. A hundred and fifty patients underwent RNU, while 27 underwent SU, according to tumor location, and surgeon preference. Interestingly, we found that SU could offer lower rates of post-operative complications (7.4% vs. 34.0%, $P = .011$). SU did not better preserve renal function in this population: indeed, a similar variation of post-operative renal function was found in the 2 groups ($P = .258$), probably depending on the presence of an overall median pre-operative estimated glomerular filtration rate of 52.6 ± 18.5 mL/min/ 1.73m^2 . Together with the evidence of similar pathologic results and oncological follow-up, no differences were also found in terms of overall survival ($P = .129$). Our results could change clinical practice suggesting that SU could be safely indicated and preferred for its lower rate of complications in selected older patients with UTUC.

Disclosure

The authors declare that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Author contributions

Alberto Abrate: Conceptualization, Investigation, Methodology, Writing - original draft, Francesco Sessa: Investigation, Methodology, Writing - original draft, Maurizio Sessa: Methodology, Formal analysis, Writing - original draft, Riccardo Campi: Investigation, Arcangelo Sebastianelli: Investigation, Virginia Varca: Investigation, Carlo Pavone: Investigation, Marco Vella: Investigation, Riccardo Bartoletti: Writing - review & editing, Vincenzo Ficarra: Writing - review & editing, Sergio Serni: Investigation, Eugenio Brunocilla: Investigation, Andrea Gregori: Investigation, Carlo Trombetta: Investigation, Andrea Lissiani: Investigation, Carlo Terrone: Investigation, Paolo Gontero: Investigation, Riccardo Schiavina: Investigation, Mauro Gacci: Writing - review & editing, Supervision, Alchiede Simonato: Conceptualization, Writing - review & editing, Supervision.

Funding

The authors report no involvement in the research by the sponsor that could have influenced the outcome of this work.

Acknowledgments

Special thanks to Lisa Marie Terzariol for the linguistic revision.

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