# Segmental ureterectomy vs. radical nephroureterectomy for ureteral carcinoma in patients with a preoperative glomerular filtration rate less than 90 ml/min/1.73 $m^2$: A multicenter study

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## Abstract

**Objectives:** To compare segmental ureterectomy (SU) and radical nephroureterectomy (RNU) in terms of overall survival (OS) and impact on postoperative renal function in patients treated for upper tract urothelial carcinoma (UTUC) of the ureter with preoperatively reduced estimated glomerular filtration rate (eGFR).

**Materials and methods:** We retrospectively collected the data of consecutive patients treated for UTUC, in 6 Italian tertiary referral centers, from 2003 to 2013, and analyzed those treated with RNU or SU for ureteral cancer and with a preoperative eGFR <90 ml/min/1.73$m^2$. The primary outcome was to compare the postoperative eGFR variation and the OS according to the surgical technique chosen.

**Results:** Out of 521 patients with UTUC, 228 patients had preoperative reduced eGFR. Out of these patients, 93 had ureteral cancer and were included in the primary analyses − 67 (72.0%) treated with RNU and 26 (28.0%) with SU. Preoperative characteristics were similar in the 2 groups. The overall median follow-up period was 26.5 months. A nonsignificant postoperative eGFR decrease of 3.0 ml/min/1.73$m^2$ was found overall ($P = 0.094$), with nonsignificant difference between the 2 groups ($P = 0.735$). A comparable 5-year OS was calculated for RNU and SU patients ($P = 0.99$).

**Conclusions:** The type of surgery (SU vs. RNU) has a low impact on postoperative renal function and OS in patients with ureteral cancer and preoperative eGFR <90 ml/min/1.73$m^2$. The indications for kidney sparing surgery for UTUC should be based on the surgical and oncological risks in these patients. 

*Keywords:* Glomerular filtration rate; Radical nephroureterectomy; Segmental ureterectomy; Survival; Upper tract urothelial carcinoma

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## 1. Introduction

Upper tract urothelial carcinoma (UTUC) is a quite rare condition accounting for 5% to 10% of urothelial carcinomas [1,2]. Although UTUC can be located both in the pyelocaliceal cavities and the ureter [3], radical nephroureterectomy (RNU) is still considered the gold standard treatment for UTUC, regardless of tumor location [4]. However, due to its morbidity, in particular in patients with impaired renal function, and the consequently increased risk of noncancer related death, kidney-sparing surgery (KSS) has been proposed as an alternative to RNU in particular cases of UTUC. In fact KSS and RNU were shown to guarantee similar survival for low-grade and noninvasive UTUC, but it has been also shown that selected patients with high-grade and invasive ureteral cancer could safely benefit from segmental ureterectomy (SU) when feasible [5].

Moreover, SU has been associated with a better preservation of renal function [6,7]. Recently, it has been shown that impaired renal function could be related to worse overall (OS), cancer-specific (CSS) and recurrence-free survival after RNU [8]. However, to our knowledge, to date there are no published studies comparing SU with RNU for UTUC in terms of impact on postoperative renal function and survival in patients with preoperatively reduced estimated glomerular filtration rate (eGFR).

The aim of our study was to evaluate the OS of patients with preoperatively reduced eGFR and electively treated with SU or RNU for UTUC, and determine whether the type of surgery affects postoperative renal function in this subgroup of patients.

## 2. Material and methods

### 2.1. Study design

The data of patients treated for UTUC were retrospectively collected in 6 Italian tertiary referral centers (Bologna, Genoa, Milan, Palermo, Trieste, Turin), from 2003 to 2013. All patients with complete data about pre- and postoperative renal function and preoperative reduced eGFR, who underwent SU or RNU for ureteral cancer, were included in the analysis. Patients with history of other malignancies, metastatic disease, and radical cystectomy were excluded from the analysis. The pre- and postoperative eGFR was calculated through the Chronic Kidney Disease Epidemiology Collaboration formula that considers serum creatinine levels, patient age, and race. A reduced eGFR was defined as <90 ml/min/1.73m$^2$. The stages of eGFR reduction were defined as follows: mild eGFR reduction (eGFR 60.0−89.9 ml/min/1.73m$^2$), mild-moderate eGFR reduction (eGFR 45.0−59.9 ml/min/1.73m$^2$), moderate-severe eGFR reduction (eGFR 30.0−44.9 ml/min/1.73m$^2$), severe eGFR reduction (eGFR 15.0−29.9 ml/min/1.73m$^2$), and kidney failure (eGFR <15 ml/min/1.73m$^2$).

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 surgeon preference and tumor location. Subsequent follow-up took place every 3 months the first year after surgery, every 4 months the second year, every 6 months from the third to the fifth year, and then annually according to the most recent international guidelines [9].

### 2.2. Statistical analysis

Statistical analysis was performed by one of the authors (M.S.). Pre- and postoperative characteristics were compared using $t$ tests for continuous variables and $\chi^2$ for categorical variables. The primary outcome of the present study was to compare eGFR variation and survival according to the surgical technique chosen (RNU vs. SU) in patients with preoperatively reduced eGFR. In order to better standardize the population taken into account, and with the aim to strengthen the impact of our results in clinical practice, we primarily focused the analyses on those patients with ureteral cancer. Unadjusted OS curves in the 2 subgroups were compared through the Kaplan−Meier method for all-causes mortality. 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 <0.05 was considered as statistically significant.

## 3. Results

Overall, we collected the data of 521 patients treated for UTUC. The renal function data of 256 patients were available; 228 patients had a preoperative eGFR <90 ml/min/1.73m$^2$. Ninety-three patients of them had ureteral cancer and were eligible for the analysis - 67 (72.0%) treated with RNU and 26 (28.0%) with SU. Preoperative clinical characteristics were similar between the 2 groups, except for tumor localization ($P = 0.032$) and side ($P = 0.023$; Table 1). The overall median follow-up period was 26.5 months.

Pre- and postoperative renal function data are shown in Table 2. Preoperative and postoperative creatinine levels were significantly lower in the SU group in comparison with the RNU group ($P = 0.001$ and $P = 0.002$, respectively). However a nonsignificant difference between the 2 groups in terms of postoperative worsening of serum creatinine levels ($P = 0.230$) was found, although RNU patients showed a significant postoperative increase of creatinine levels of 0.2 ± 0.7 mg/dl ($P = 0.028$), in comparison with a nonsignificant change of the creatinine levels in SU patients ($P = 0.734$). On the other hand, SU patients had a significantly higher preoperative eGFR (66.8 ± 19.7 vs. 50.3 ± 14.7 ml/min/1.73m$^2$, respectively; $P < 0.001$) and also postoperative eGFR (62.9 ± 16.6 vs. 47.7 ± 18.9 ml/min/1.73m$^2$, respectively; $P < 0.001$). Interestingly, a nonsignificant worsening of the eGFR was found in RNU

Table 1
Preoperative clinical and demographic characteristics of the study population

| Variable | Total | RNU | SU | *P*-value |
|---|---|---|---|---|
| Patients | 93 | 67 (72.0) | 26 (28.0) | |
| Age, yr | 72.4 ± 9.0 | 72.7 ± 8.9 | 71.7 ± 9.3 | 0.656 |
| Gender | | | | |
| Female | 25 (26.9) | 16 (23.9) | 9 (34.6) | 0.431 |
| Male | 68 (73.1) | 51 (76.1) | 17 (65.4) | |
| Smoking status | | | | |
| No | 57 (61.3) | 42 (62.7) | 15 (57.7) | 0.836 |
| Yes | 36 (38.7) | 25 (37.3) | 11 (42.3) | |
| Preoperative endoscopic biopsy | | | | |
| No | 63 (67.7) | 48 (71.6) | 15 (57.7) | 0.296 |
| Yes | 30 (32.3) | 19 (28.4) | 11 (42.3) | |
| Negative | 5 (16.7) | 5 (26.3) | 0 (0.0) | 0.175 |
| Positive | 25 (83.3) | 14 (73.7) | 11 (100.0) | |
| G1 | 10 (40.0) | 5 (35.7) | 5 (45.5) | 0.293 |
| G2 | 6 (24.0) | 5 (35.7) | 1 (9.1) | |
| G3 | 9 (36.0) | 4 (28.6) | 5 (45.5) | |
| Tumor localization | | | | |
| Distal ureter | 59 (63.4) | 37 (55.2) | 22 (84.6) | 0.032 |
| Middle ureter | 19 (20.4) | 15 (22.4) | 4 (15.4) | |
| Proximal ureter | 11 (11.8) | 11 (16.4) | 0 (0.0) | |
| Multiple | 4 (4.3) | 4 (6.0) | 0 (0.0) | |
| Focality | | | | |
| Single | 67 (72.0) | 47 (70.1) | 20 (76.9) | 0.692 |
| Multiple | 26 (28.0) | 20 (29.9) | 6 (23.1) | |
| Side | | | | |
| Right | 48 (51.6) | 40 (59.7) | 8 (30.8) | 0.023 |
| Left | 45 (48.4) | 27 (40.3) | 18 (69.2) | |
| Hydronephrosis grade | | | | |
| No | 13 (14.0) | 7 (10.4) | 6 (23.1) | 0.113 |
| 1 | 18 (19.4) | 13 (19.4) | 5 (19.2) | |
| 2 | 32 (34.4) | 21 (31.3) | 11 (42.3) | |
| 3 | 30 (32.3) | 26 (38.8) | 4 (15.4) | |
| History of bladder carcinoma | | | | |
| No | 56 (60.2) | 42 (62.7) | 14 (53.8) | 0.585 |
| Yes | 37 (39.8) | 25 (37.3) | 12 (46.2) | |

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

Table 2
Preoperative and postoperative renal function in the overall population and in the two subgroups

| Variable | Total | RNU | SU | *P*-value |
|---|---|---|---|---|
| Patients | 93 | 67 (72.0) | 26 (28.0) | |
| Creatinine, mg/dl | | | | |
| Preoperative | 1.3 ± 0.4 | 1.4 ± 0.4 | 1.1 ± 0.4 | 0.001 |
| Postoperative | 1.5 ± 0.7 | 1.6 ± 0.8 | 1.1 ± 0.3 | 0.002 |
| Delta | 0.1 ± 0.6 | 0.2 ± 0.7 | 0.0 ± 0.3 | 0.230 |
| eGFR, ml/min/1.73m$^2$ | | | | |
| Preoperative | 54.9 ± 17.8 | 50.3 ± 14.7 | 66.8 ± 19.7 | < 0.001 |
| Postoperative | 51.9 ± 19.5 | 47.7 ± 18.9 | 62.9 ± 16.6 | < 0.001 |
| Delta | -3.0 ± 17.0 | -2.6 ± 17.3 | -4.0 ± 16.8 | 0.735 |
| Preoperative eGFR-reduction stage | | | | |
| Mild | 31 (33.3) | 13 (19.4) | 18 (69.2) | <0.001 |
| Mild-moderate | 34 (36.6) | 31 (46.3) | 3 (11.5) | |
| Moderate-severe | 21 (22.6) | 18 (26.9) | 3 (11.5) | |
| Severe | 7 (7.5) | 5 (7.5) | 2 (7.7) | |
| Kidney failure | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| Postoperative eGFR-reduction stage | | | | |
| Normal renal function | 2 (2.2) | 1 (1.5) | 1 (3.8) | 0.059 |
| Mild | 28 (30.1) | 15 (22.4) | 13 (50.0) | |
| Mild-moderate | 29 (31.2) | 21 (31.3) | 8 (30.8) | |
| Moderate-severe | 24 (25.8) | 20 (29.9) | 4 (15.4) | |
| Severe | 8 (8.6) | 8 (11.9) | 0 (0.0) | |
| Kidney failure | 2 (2.2) | 2 (3.0) | 0 (0.0) | |
| Postoperative change of eGFR-reduction stage | | | | |
| Downstaging | 21 (22.6) | 14 (20.9) | 7 (26.9) | 0.803 |
| Same stage | 47 (50.5) | 35 (52.2) | 12 (46.2) | |
| Upstaging | 25 (26.9) | 18 (26.9) | 7 (26.9) | |

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

patients (-2.6 ± 17.3ml/min/1.73m$^2$, $P = 0.219$) and SU patients (-4.0 ± 16.8 ml/min/1.73m$^2$, $P = 0.239$) after surgery, and no significant differences were observed in terms of delta eGFR between the 2 groups ($P = 0.735$).

Pathological examination showed a higher incidence of higher stage and grade cancers in patients undergone RNU (Table 3). However, at the end of follow-up, no differences were found in terms of overall recurrences between the 2 groups ($P = 1.000$), although with a different localization of recurrence ($P = 0.032$). Notably 4 patients within the SU group were found with ipsilateral recurrence at follow-up, but only one needed RNU. Only 2 (7.7%) cancer-related deaths were reported in SU group in comparison with 18 (26.9%) in RNU group ($P = 0.129$).

A 5-year OS of 52.0% (95%CI 38.1−71.1) and 46.8% (95% CI 22.8−95.9) was calculated for RNU and SU patients, respectively ($P = 0.99$; Fig. 1).

## 4. Discussion

In the current study, we investigated 93 patients with preoperative eGFR <90 ml/min/1.73m$^2$ and treated with RNU or SU for ureteral cancer − we reported a nonsignificant postoperative worsening of renal function in patients who had undergone RNU and SU. Moreover a comparable OS was found in the 2 groups.

RNU is still indicated as the standard treatment for UTUC [4]. However, KSS is considered acceptable to avoid subsequent morbidities following RNU in case of anatomical or functional solitary kidney, bilateral disease or severe renal insufficiency [10]. Much effort has been spent in trying to preoperatively identify which patients and which tumors could be managed conservatively with KSS. Flexible ureterorenoscopy with biopsy/cytology and CT scan or MR imaging are suggested to accurately evaluate the upper tract, helping the surgeon in the decision-making process. However, the choice of the surgical technique mainly depends on tumor size and location. Some preoperative variables such as smoking, hydronephrosis, ureteroscopic biopsy grade, urine cytology grade [11], tumor size [12], and previous bladder-urothelial carcinoma [13] proved to

Table 3
Pathological characteristics and follow-up

| Variable | Total | RNU | SU | *P*-value |
|---|---|---|---|---|
| Patients | 93 | 67 (72.0) | 26 (28.0) | |
| Pathological T-stage | | | | |
| Ta | 25 (26.9) | 12 (17.9) | 13 (50.0) | 0.021 |
| T1 | 22 (23.7) | 18 (26.9) | 4 (15.4) | |
| T2 | 22 (23.7) | 16 (23.9) | 6 (23.1) | |
| T3 | 13 (14.0) | 11 (16.4) | 2 (7.7) | |
| T4 | 9 (9.7) | 9 (13.4) | 0 (0.0) | |
| T0 | 2 (2.2) | 1 (1.5) | 1 (3.8) | |
| Tis associated | | | | |
| No | 78 (83.9) | 56 (83.6) | 22 (84.6) | 1.000 |
| Yes | 15 (16.1) | 11 (16.4) | 4 (15.4) | |
| Lymph node dissection | | | | |
| No | 53 (57.0) | 34 (50.7) | 19 (73.1) | 0.086 |
| Yes | 40 (43.0) | 33 (49.3) | 7 (26.9) | |
| No. Lymph nodes dissected | 10.3 ± 8.7 | 11.9 ± 9.2 | 4.9 ± 2.0 | 0.048 |
| Pathological N-stage | | | | |
| N0 | 36 (38.7) | 29 (43.3) | 7 (26.9) | 0.214 |
| N1 | 2 (2.2) | 2 (3.0) | 0 (0.0) | |
| N2 | 2 (2.2) | 2 (3.0) | 0 (0.0) | |
| Nx | 53 (57.0) | 34 (50.7) | 19 (73.1) | |
| Grade | | | | |
| G1 | 6 (6.5) | 2 (3.0) | 4 (15.4) | 0.047 |
| G2 | 38 (40.9) | 26 (38.8) | 12 (46.2) | |
| G3 | 49 (52.7) | 39 (58.2) | 10 (38.5) | |
| Lymph vascular invasion | | | | |
| No | 75 (80.6) | 53 (79.1) | 22 (84.6) | 0.756 |
| Yes | 18 (19.4) | 14 (20.9) | 4 (15.4) | |
| Necrosis | | | | |
| No | 81 (87.1) | 58 (86.6) | 23 (88.5) | 1.000 |
| **Yes** | 12 (12.9) | 9 (13.4) | 3 (11.5) | |
| Surgical margins | | | | |
| Negative | 73 (78.5) | 55 (82.1) | 18 (69.2) | 0.283 |
| Positive | 20 (21.5) | 12 (17.9) | 8 (30.8) | |
| Concomitant bladder cancer | | | | |
| No | 74 (79.6) | 53 (79.1) | 21 (80.8) | 1.000 |
| Yes | 19 (20.4) | 14 (20.9) | 5 (19.2) | |
| Follow-up period, mo | 26.5 (21.0−35.4) | 27.4 (17.4−37.6) | 25.8 (13.2−35.8) | 0.400 |
| Recurrence | | | | |
| No | 41 (44.1) | 30 (44.8) | 11 (42.3) | 1.000 |
| Yes | 52 (55.9) | 37 (55.2) | 15 (57.7) | |
| Local recurrence − 42 patients | | | | |
| Ipsilateral | 4 (9.5) | 0 (0.0) | 4 (26.7) | 0.032 |
| Contralateral | 1 (2.4) | 1 (3.7) | 0 (0.0) | |
| Bilateral | 1 (2.4) | 0 (0.0) | 1 (6.7) | |
| Vesical | 32 (76.2) | 23 (85.2) | 9 (60.0) | |
| Lymph nodes | 4 (9.5) | 3 (11.1) | 1 (6.7) | |
| Metastasis | | | | |
| No | 75 (80.6) | 50 (74.6) | 25 (96.2) | 0.039 |
| Yes | 18 (19.4) | 17 (25.4) | 1 (3.8) | |
| Adjuvant systemic chemotherapy | | | | |
| No | 85 (91.4) | 61 (91.0) | 24 (92.3) | 1.000 |
| Yes | 8 (8.6) | 6 (9.0) | 2 (7.7) | |
| Death at the end of follow-up | | | | |
| No | 60 (64.5) | 41 (61.2) | 19 (73.1) | 0.405 |
| Yes | 33 (35.5) | 26 (38.8) | 7 (26.9) | |
| Other causes | 13 (39.4) | 8 (30.8) | 5 (71.4) | 0.129 |
| Cancer related | 20 (60.6) | 18 (69.2) | 2 (28.6) | |

Continuous variables are expressed as mean ± SD or median (95% CI); Nominal variables are expressed as No. (%).

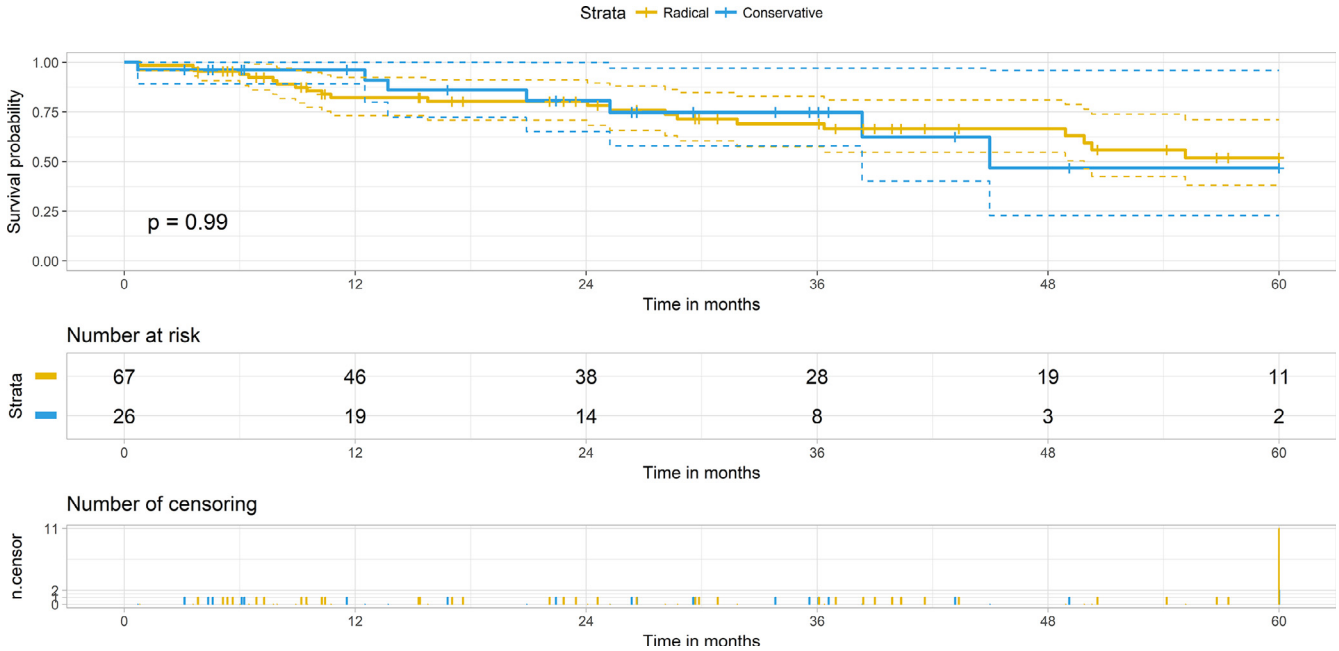


Fig. 1. Comparison between SU and RNU in terms of 5-year OS.

be related with adverse outcome for UTUC. On the contrary, tumor localization is a controversial risk factor – in fact some authors reported better prognoses for renal pelvis tumors compared to ureteral tumors [14], but others reported worst prognoses for proximal ureteral and renal pelvis tumors instead [15]. SU (open or laparoscopic), endoscopic and percutaneous procedures can be all considered KSS [5] and they have been often analyzed in heterogeneous populations with variable results [16]. For this reason, in the current study only SU was considered as KSS for the purposes of the study and no comparison between different surgical, endoscopic, or percutaneous KSS techniques was performed.

Colin et al. [17] reported no significant differences in terms of CSS between SU and RNU in patients with unifocal, <2 cm and ≤ pT2 UTUC in a subgroup analysis of a multicenter study. On the other hand, Bagrodia et al. [18] in 2013 demonstrated that SU and RNU ensured equivalent CSS for high-grade tumors as well.

In a recent meta-analysis, showing no significant difference between SU and RNU in terms of OS and CSS, Fang et al. [19] investigated renal function before and after surgery, finding a significant perioperative eGFR decrease of 9.32 ml/min/1.73 $m^2$ ($P = 0.007$) in RNU patients in comparison with the KSS ones.

Furthermore, Yu et al. [8] investigated the effect of a preoperative eGFR <60 ml/min/1.73$m^2$ on the prognosis of patients treated with RNU for UTUC. The authors reported a significantly shorter OS, CSS, and recurrence-free survival for patients with preoperative renal failure in comparison to those with "normal" renal function ($P = 0.001$). Moreover, the multivariable Cox regression analysis, showed that preoperative renal failure was related to worse OS (hazard ratio [HR]: 1.66, 95% confidence interval [CI]: 1.15–2.40; $P = 0.007$), CSS (HR: 2.44, 95% CI: 1.44–4.14, $P = 0.001$), and recurrence-free survival (HR: 1.81, 95% CI: 1.15–2.86, $P = 0.011$). Interestingly, Zhang et al. [20] recently confirmed a nonsignificantly different OS for RNU and SU ($P = 0.694$) in a retrospective cohort study including patients with a preoperative eGFR of 65.1 ± 26.9 and 65.8 ± 25.5 ml/min/1.73$m^2$, respectively ($P = 0.878$). In the same study, the postoperative eGFR was higher in SU group in comparison with the RNU group (61.6 ± 25.7 vs. 50.01 ± 20.36 ml/min/1.73$m^2$, respectively; $P = 0.010$) and a higher percentage of patients with postoperative moderate or higher eGFR reduction was reported in the RNU group in comparison with SU group (53.2% vs. 25.0% $P = 0.008$).

In the current study, we investigated the impact of RNU vs. SU over postoperative renal function and OS specifically in patients with a preoperative eGFR <90 ml/min/1.73$m^2$. Although there was a statistically significant serum creatinine increase of 0.2 mg/dl after RNU ($P = 0.028$), we found a non-significant postoperative eGFR decrease in both groups (Table 2). This probably depended on the high prevalence of preoperative hydronephrosis in both the groups (Table 1) which could suggest a poor pre-existing function in the operated renal unit and therefore preserving it made no difference in the global eGFR. Interestingly, also a comparable OS was found in RNU and SU patients. All these data could suggest that the type of surgery (conservative vs. radical) has a low impact on postoperative renal function and OS in patients with preoperatively reduced eGFR, which should be instead considered as a condition affecting the outcomes by itself.

The main limitation of the current study is its retrospective design and relatively few SU patients, which could be seen as a limit for the analyses, but that is due to the

infrequency of the disease. Although the use of the WHO1973 grading system should not reduce the scientific impact of the current study, future studies using the updated grading system are needed to confirm our findings. On the contrary, the main strength of our study is its multicenter approach with a validated and shared follow-up scheme.

## 5. Conclusions

In the current retrospective study, we investigated the role of SU vs. RNU in patients with UTUC and preoperative eGFR <90 ml/min/1.73m$^2$. A nonsignificant eGFR decrease was found and a comparable OS was calculated in the 2 groups. If confirmed in further and hopefully prospective studies, our current results may suggest that the role of KSS should be reconsidered in patients with preoperatively reduced eGFR. Therefore, the indication for KSS should not be based on preoperative renal function, but primarily on surgical feasibility and oncological risk factors, as the surgical technique has limited impact on postoperative eGFR.

## Conflicts of interests

The authors declare that they have no conflict of interest.


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