Impact of renal function on eligibility for chemotherapy and survival in patients who have undergone radical nephro-ureterectomy

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What's known on the subject? and What does the study add?

- Radical nephroureterectomy (RNU), the standard of care treatment for high-risk urothelial carcinoma of the upper tract (UTUC), results in loss of a renal unit. Loss of renal function decreases eligibility for systemic chemotherapies and results in decreased overall survival in various malignancies.
- The study shows that only a small proportion of patients had a preoperative renal function that would allow cisplatin-based chemotherapy. Moreover, eGFR significantly decreased after RNU, thereby lowering the rate of cisplatin eligibility to only 16 and 52% of patients based on the thresholds of 60 and 45 mL/min/1.73 m^2, respectively. Taken together with the rest of the literature, the findings of the study support the use of cisplatin-based chemotherapy, when indicated, in the neoadjuvant rather than adjuvant setting.

Objective

- To report (i) the estimated glomerular filtration rate (eGFR) changes in patients undergoing radical nephro-ureterectomy (RNU) for upper tract urothelial carcinoma (UTUC); (ii) the rate of change in eGFR in patients eligible for cisplatin-based chemotherapy; and (iii) the association of preoperative, postoperative and rate of change of renal function variables with survival outcomes.

Patient and Methods

- We performed a retrospective analysis of 666 patients treated with RNU for UTUC at seven international institutions from 1994 to 2007.
- The eGFR was calculated at baseline and at 3–6 months (Modification of Diet in Renal Disease formula (MDRD) and Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EP) equations).

Results

- The median (interquartile range) eGFR decreased by 18.2 (8–12)% after RNU. A total of 37% of patients had a preoperative eGFR ≥ 60 mL/min/1.73 m^2, which decreased to 16% after RNU ($P < 0.001$); 72% of patients had a preoperative eGFR ≥ 45 mL/min/1.73 m^2, which decreased to 52% after RNU ($P < 0.001$). The distributions were similar when analyses were restricted to patients with locally advanced disease (pT3–pT4) and/or lymph node metastasis. Patients older than the median age of 70 years were more likely to have a decrease in eGFR after RNU ($P < 0.001$).
- None of the renal function variables was associated with clinical outcomes such as disease recurrence, cancer-specific and overall mortality; however, when analyses were restricted to patients who had no adjuvant

chemotherapy and did not experience disease recurrence ($n = 431$), a preoperative eGFR ≥ 60 mL/min/1.73 m^2 ($P = 0.03$) and a postoperative eGFR ≥ 45 mL/min/1.73 m^2 ($P = 0.04$) were associated with better overall survival in univariable analyses.

Conclusions

- In patients who had UTUC, eGFR was low and furthermore, it significantly decreased after RNU.
- Renal function did not affect cancer-specific outcomes after RNU.

Keywords

renal function, radical nephroureterectomy, upper tract urothelial carcinoma, chemotherapy

Introduction

Upper tract urothelial carcinoma (UTUC) is a relatively rare neoplasm accounting for 5–6% of all urothelial tumours. Radical nephro-ureterectomy (RNU) with excision of the bladder cuff is the standard of care treatment for high-risk UTUC [1]. Despite its durable long-term disease control in patients with early stage disease, the 5-year overall survival of patients with non-organ-confined UTUC is <50%, and for those with nodal metastasis, it is only ~35% [2–4]. In patients whose disease is detected at a point where surgical cure is possible but risk of disease recurrence remains high (≥pT3 and/or lymph node metastasis), chemotherapy has been considered as an option for adjuvant therapy [5–7]; however, the timing of chemotherapy in UTUC is in debate as surgical management of the disease, i.e. RNU, affects a patient's renal function and thereby eligibility for adjuvant chemotherapy. This strengthens the debate about neoadjuvant regimens [8,9]. Moreover, in other malignancies, such as RCC, the decrease in estimated GFR (eGFR) has been shown to negatively affect overall survival [10].

The aim of the present study was to report baseline eGFR and changes in patients undergoing RNU for UTUC. In addition, we wanted to report the effect of RNU on eligibility for cisplatin-based chemotherapy based on the change in eGFR. Finally, we evaluated the association of preoperative and postoperative renal function variables, as well as their rate of change, with oncological outcomes and overall survival.

Patients and Methods

Patients

In this institutional-review-board-approved study, all participating sites provided the necessary institutional data-sharing agreements before the initiation of the study. A total of seven centres worldwide provided data. A computerized databank was generated for data transfer. After combining the datasets, reports were generated for each variable to identify data inconsistencies and other data integrity problems. Through regular communication with all sites, resolution of all identified anomalies was achieved before analysis. Before the final analysis, the database was frozen and the final dataset was produced for the present analysis. From 1994 to 2007, 781 patients underwent RNU with bladder cuff excision for UTUC. None of patients received preoperative chemotherapy or radiotherapy. Adjuvant chemotherapy was administered at the clinicians' discretion based on tumour stage and overall health status as well as patient preference ($n = 62$). Patients in whom pre- and postoperative serum creatinine (Scr) concentration data were not available were excluded from the analyses ($n = 115$, 17.3%). These patients did not differ from the population of the study in terms of preoperative characteristics.

Pathological Evaluation

All surgical specimens were processed according to standard pathological procedures at each institution. Tumours were staged according to the 2002 American Joint Committee on Cancer/Union Internationale Contre le Cancer TNM classification [11]. Tumour grade was assessed according to the 1998 WHO/International Society of Urologic Pathology consensus classification [12]. Histopathological assessment included concomitant carcinoma *in situ*, tumour architecture (papillary or sessile based on the predominant feature of the index lesion [13]), lymphovascular invasion (defined as the presence of tumour cells within an endothelium-lined space without underlying muscular walls [14]), and tumour necrosis (defined as the presence of microscopic coagulative necrosis in >10% of the tumour [15]). Tumour location was defined as either renal pelvicalyceal or ureteric based on the index cancer [16]. Tumour multifocality was defined as the synchronous presence of two or more pathologically confirmed tumours in any location (renal pelvis or ureter) [17,18].

Follow-up

Patients were generally followed every 3–4 months for the first year after RNU, every 6 months from the second to the

fifth year, and annually thereafter. Follow-up consisted of a history, physical examination, routine blood work, urinary cytology, chest radiography, cystoscopic evaluation of the urinary bladder, and radiographic evaluation of the contralateral upper urinary tract. Elective bone scans, chest CT, or MRI were performed when clinically indicated.

Disease recurrence was defined as tumour relapse in the operative field, regional lymph nodes, and/or distant metastasis. Cause of death was determined by treating physicians, by chart review corroborated by death certificates, or by death certificates alone. To reduce bias in attribution of cause of death, only patients who had UTUC listed in the death certificate were considered to have died from UTUC for the present study [19]. All patients who were coded as dead from cancer had previous disease recurrence. Patients who died in the perioperative period (i.e. within 30 days of surgery) were censored at time of death for UTUC-specific survival analyses.

Renal Function Variables

We calculated eGFR at baseline and 3–6 months after RNU, using the MDRD (GFR [mL/min/1.73 m^2] = 175 × [Scr]-1.154 × [Age]-0.203 × [0.742 if female] × [1.212 if African]) [20] and chronic kidney disease (CKD)-EPI (GFR = 141 X_{min}[Scr/κ,1]α X_{max}[Scr/κ,1]-1.209 X 0.993Age X 1.018 [if female] X 1.159 [if black]) [21] equations. The two equations have been shown to have substantial agreement for baseline and follow-up eGFR [22]. We used the median value between the two equations (inter-equation coefficient variability of 0.94 and 0.96 for baseline and postoperative data, respectively). In addition, we calculated the absolute ($eGFR_{follow\text{-}up}$ – $eGFR_{baseline}$) and percent change in eGFR between preoperative and postoperative ([$eGFR_{follow\text{-}up}$ – $eGFR_{baseline}$] * 100/ $eGFR_{baseline}$). We also reported the preoperative and postoperative number of patients with an eGFR ≥ 60 mL/min per 1.73 m^2 and an eGFR ≥ 45 mL/min per 1.73 m^2, and also the changes in CKD stage. We chose an eGFR threshold of 60 mL/min per 1.73 m^2, which has traditionally defined eligibility for full-dose cisplatin therapy and a threshold of 45 mL/min per 1.73 m^2, which has been previously cited as a more strict definition of CKD and has been shown to be associated with a higher risk of comorbidities related to CKD. We then assessed the impact of age (using the median age of our population as the threshold) on the rate of change in renal function after RNU.

Statistical Analysis

The Mann–Whitney *U*-test was used to compare non-parametric continuous variables and a chi-squared and Fisher's exact tests to compare nominal variables. Recurrence-free and cancer-specific and overall survival curves were generated using the Kaplan–Meier method and compared using the log-rank test. Univariable and multivariable Cox regression models addressed outcomes after RNU. All reported *P*-values are two-sided, and a *P* value of 0.05 was considered to indicate statistical significance. Statistical analyses were performed with SPSS (v20.0, IBM Corp, NY, USA).

Results

Clinicopathological Characteristics and Baseline Renal Function

Overall 666 patients were included in the study. The median (interquartile range [IQR]) age at surgery was 70 (54–76) years. The clinical and pathological characteristics of the study population are shown in Table 1. The preoperative and postoperative renal function characteristics of the 666 patients are shown in Table 2; 249 patients (37%) had a preoperative eGFR ≥ 60 mL/min per 1.73 m^2 and 479 (72%) had an eGFR ≥ 45 mL/min per 1.73 m^2. The preoperative CKD stage distribution was: CKD I (*n* = 32, 5%), CKD II (*n* = 217, 32.5%), CKD III (*n* = 386, 58%), CKD IV (*n* = 28, 4%), and CKD V (*n* = 3, 0.4%).

Postoperative Renal Function and Rates of Change

After RNU, 105 patients (16%) had a postoperative eGFR ≥ 60 mL/min per 1.73 m^2 and 345 (52%) had an eGFR ≥ 45 mL/min per 1.73 m^2 (Table 2). The postoperative CKD stages distribution was: CKD I (*n* = 7, 1%), CKD II (*n* = 98, 15%), CKD III (*n* = 460, 69%), CKD IV (*n* = 91, 13.5%) and CKD V (*n* = 10, 1.5%). Comparison of preoperative and postoperative Scr levels for each patient showed a mean difference of 0.32 mg/dL (*P* < 0.001; Table 2), which represents a median (IQR) increase of 24.8 (10–34)%. On similar analysis performed for eGFR, we found a mean difference between preoperative and postoperative eGFR of 10.2 mL/min per 1.73 m^2 (*P* < 0.001), which represents a median (IQR) decrease of 18.2 (8–12)%.

Preoperative, Postoperative and Rates of Change of Renal Function Stratified by pT Stage and Lymph Node Status

There was no difference either in terms of preoperative eGFR between organ-confined and non-organ-confined UTUC (57.3 vs 55.4, *P* = 0.73), nor in terms of postoperative eGFR (46.3 vs 46.5, *P* = 0.19). The same was true for lymph node status (*P* = 0.43 and *P* = 0.53, respectively). 27.5% of patients with locally advanced disease (pT3–pT4) and 32% of patients with pN+ stage had a preoperative eGFR ≥ 60 mL/min per 1.73 m^2, a proportion that fell to 15 and 25%, respectively, after RNU.

Table 1 Clinicopathological characteristics of 666 patients treated with RNU for UTUC.

Median, IQR age, years	69.6 (54–76)
Gender, *n* (%)	
Male	441 (66)
Female	225 (34)
Body mass index, kg/m^2	
Mean (SD)	28.5 (5.5)
Median (IQR)	28.2 (24–32)
ECOG performance status, *n* (%)	
0	445 (67)
1–3	221 (33)
Previous bladder cancer, *n* (%)	
Yes	244 (37)
No	422 (63)
Primary tumour location, *n* (%)	
Renal pelvis	420 (63)
Ureteral	246 (37)
Multifocality, *n* (%)	
Yes	164 (25)
No	502 (75)
Surgical approach, *n* (%)	
Open	519 (78)
Laparoscopic	147 (22)
pT stage, *n* (%)	
pT0-pTa-pTis-pT1	326 (49)
pT2	118 (18)
pT3	182 (27)
pT4	40 (6)
Grade, *n* (%)	
No Tumour	12 (2)
Low	121 (18)
High	533 (80)
Lymph node status, *n* (%)	
pN0	291 (44)
pNx	291 (44)
pN+	84 (12)
Concomitant carcinoma *in situ*, *n* (%)	
Present	229 (34)
Absent	437 (66)
Lymphovascular invasion*, *n* (%)	
Present	171 (31)
Absent	380 (69)
Adjuvant chemotherapy, *n* (%)	
Yes	62 (9)
No	604 (91)

*ECOG, European Cooperative Oncology Group. *Lymphovascular invasion information was available only in 551 patients (83%).*

Similarly, 69% patients with locally advanced disease (pT3–pT4) and 66% of patients with pN+ stage disease had a preoperative eGFR ≥ 45 mL/min per 1.73 m^2, falling to 52 and 61%, respectively, after RNU. Finally, when combining patients with pT3–pT4 and/or pN+ disease (n = 238), only 17.5% had a postoperative eGFR ≥ 60 and 54.5% had a postoperative eGFR ≥ 45 mL/min per 1.73 m^2.

Preoperative, postoperative and rates of change of renal function stratified by patient's age at surgery

The median age at surgery was 70 years and was chosen as a threshold to stratify renal function (Table 2). Younger patients (<70 years) were more likely to have a preoperative eGFR ≥ 60 (44 vs 31%; $P < 0.001$) and ≥45 mL/min per 1.73 m^2 (79 vs 66%; $P < 0.001$) compared with patients ≥ 70 years. eGFR decreased significantly after surgery in both age groups; however, younger patients were also more likely to maintain an eGFR ≥ 60 (21 vs 11%, $P < 0.001$) and ≥45 mL/min per 1.73 m^2 (61 vs 43%, $P < 0.001$).

Association of eGFR (Preoperative and Postoperative) and Rates of Change with Clinical Outcomes

At a median (IQR) follow-up of 45.5 (24–67) months, 212 patients (32%) experienced disease recurrence, 163 (24.5%) died from UTUC and 104 (15.5%) from other causes. We addressed the association between renal function variables (preoperative and postoperative eGFR as a continuous variable or using thresholds of 60 and 45 mL/min per 1.73 m^2, and the rates of change either continuous or change in categorization) with disease recurrence, cancer-specific and overall mortality. None of these variables was associated with outcomes in univariable analyses. Similarly, when restricting the analyses to patients who did not experience disease recurrence, none of the renal function variables was associated with overall survival. The same was true when patients were stratified by an age threshold of 70 years, but when analyses were restricted to patients who had no adjuvant chemotherapy and who did not experience disease recurrence (n = 431), a preoperative eGFR ≥ 60 mL/min per 1.73 m^2 (P = 0.03, hazard ratio [HR]: 0.64, CI: 0.42–0.97) and a postoperative eGFR ≥ 45 mL/min per 1.73 m^2 (P = 0.04, HR: 0.67, CI: 0.45–0.99) were associated with better overall survival in univariable analyses (Fig. 1A and B). These factors were not independently associated with overall survival in multivariable analyses which adjusted for standard clinico-pathological features (P = 0.72, HR: 1.11, CI: 0.59–2.10 and P = 0.11, HR: 0.61, CI: 0.33–1.13).

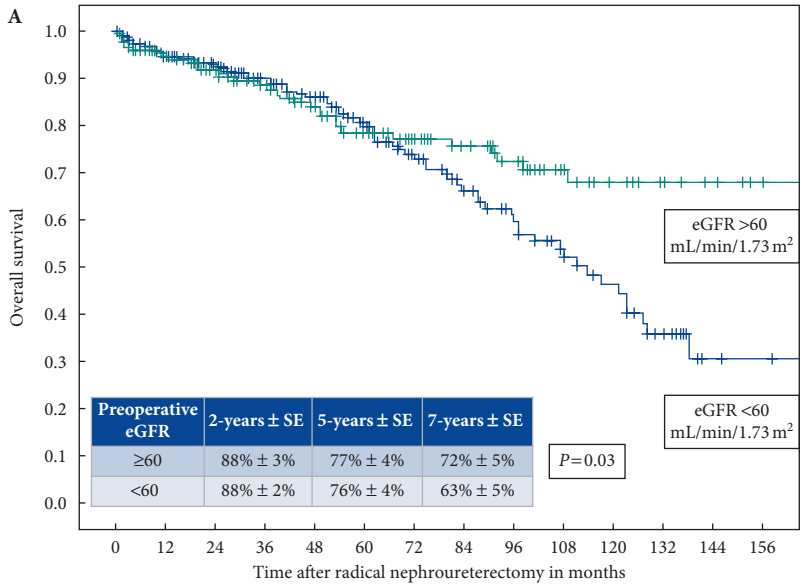
Discussion

We confirmed that eGFR decreases significantly after RNU [8,9]. We found an 18% decrease in eGFR after RNU, which was similar to the rates reported in previous studies (22–24%) [8,9]. This rate of decrease was independent of the pathological features. Younger patients (<70 years) were more likely to have a better preoperative eGFR and to maintain it postoperatively than older patients (≥70 years). This is in contrast to the findings of Kaag et al. [9] who did not find a statistically significant difference between age categories. The differences between that and the present study are probably attributable to differences in samples size and patient characteristics such as age distribution.

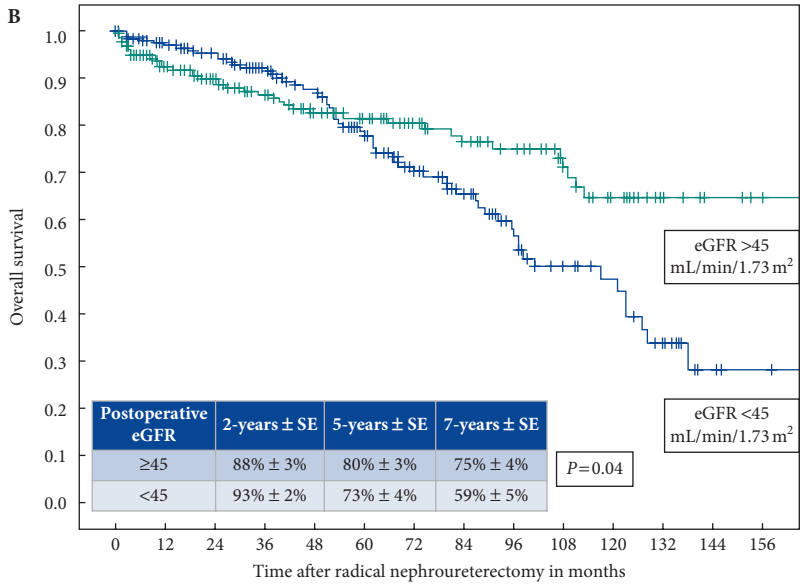
Table 2 Baseline and postoperative renal function of the 666 patients treated with RNU for UTUC.

	Preoperative	Postoperative	*P*
SCr, mg/dL			<0.001
Mean (SD)	1.29 (0.48)	1.61 (1.2)	
Median (IQR)	1.20 (1–1.5)	1.3 (1–2)	
eGFR mL/min per 1.73 m^2			
MDRD			<0.001
Mean (SD)	56.1 (18.4)	45.9 (15.8)	
Median (IQR)	54.8 (43–66)	45.5 (35–54)	
CDK-EPI			<0.001
Mean (SD)	57.2 (18.4)	46.8 (16.9)	
Median (IQR)	55 (44–69)	46 (35–57)	
eGFR(MDRD+CDK-EPI)/2			<0.001
Mean (SD)	56.6 (18)	46.3 (16.3)	
Median (IQR)	56.1 (43–68)	45.9 (35–55)	
eGFR ≥ 60 mL/min per 1.73 m2 pT stage, *n* (%)	249 (37)	105 (16)	<0.001
pT stage, *n* (%)			<0.001
pT0-pTis-pTa-pT1	138 (56)	60 (57)	
pT2	40 (16)	12 (11)	
pT3	53 (21)	25 (24)	
pT4	18 (7)	8 (8)	
Lymph node status, *n* (%)			<0.001
pNx	119 (48)	45 (43)	
pN0	103 (41)	39 (37)	
pN+	27 (11)	21 (20)	
eGFR ≥ 45 mL/min per 1.73 m^2, *n* (%)	479 (72)	345 (52)	<0.001
pT stage, *n* (%)			<0.001
pT0-pTis-pTa-pT1	240 (50)	172 (50)	
pT2	87 (18)	57 (16)	
pT3	124 (26)	92 (27)	
pT4	28 (6)	24 (7)	
Lymph node status			<0.001
pNx	216 (45)	141 (41)	
pN0	208 (43)	153 (44)	
pN+	55 (12)	51 (15)	
≥70 years old			
SCr, mg/dL			<0.001
Mean (SD)	1.29 (0.42)	1.61 (1.15)	
eGFR mL/min per 1.73 m^2			<0.001
Mean (SD)	52.9 (16.9)	43.5 (15.2)	
eGFR ≥ 60 mL/min per 1.73 m^2, *n* (%)	107 (31)	36 (11)	<0.001
eGFR ≥ 45 mL/min per 1.73 m^2, *n* (%)	225 (66)	148 (43)	<0.001
<70 years old			
SCr, mg/dL			<0.001
Mean (SD)	1.29 (0.55)	1.61 (1.26)	
Median (IQR)			
eGFR mL/min per 1.73 m^2			<0.001
Mean (SD)	60.6 (19)	49.4 (16.8)	
Median (IQR)			
eGFR ≥ 60 mL/min per 1.73 m^2, *n* (%)	142 (44)	69 (21)	<0.001
eGFR ≥ 45 mL/min per 1.73 m^2, *n* (%)	255 (79)	198 (61)	<0.001

We found that only a small proportion of patients with high-risk UTUC were eligible for adjuvant chemotherapy based on eGFR. Moreover, the rate of eligibility decreased dramatically after RNU. The role and benefit of adjuvant chemotherapy for locally advanced and/or lymph-node-positive UTUC remains controversial [23]. Although a small single-centre retrospective series reported a benefit in overall survival in 32 patients [5], two retrospective international studies could not confirm these results ($n = 121$ and $n = 143$) [6,7]. By contrast, two retrospective studies using systemic chemotherapy in the neoadjuvant setting ($n = 107$ and $n = 82$) found a 14–15% complete remission (pT0) rate [24,25]. Extrapolating from lower tract urothelial carcinoma, and based on cumulative evidence, the neoadjuvant setting seems the most effective way of administrating systemic cisplatin-based chemotherapy in UTUC [26,27]. This is even more important in UTUC because eligibility for cisplatin-based chemotherapy is heavily based on renal function, which decreases after RNU [8,9]. We chose an eGFR threshold of 60 mL/min per 1.73 m^2, which has traditionally defined eligibility for full-dose cisplatin therapy and also represents



Patient numbers at risk for overall survival														
Months	0	12	24	36	48	60	72	84	96	108	120	132	144	156
Preoperative eGFR ≥60 mL/min/1.73 m²	175	140	118	101	82	67	56	50	42	28	20	14	10	6
Preoperative eGFR <60 mL/min/1.73 m²	256	218	180	143	122	100	74	56	44	31	23	13	4	3



Patient numbers at risk for overall survival														
Months	0	12	24	36	48	60	72	84	96	108	120	132	144	156
Postoperative eGFR ≥45 mL/min/1.73 m²	217	175	142	117	93	77	64	56	49	36	25	16	10	7
Postoperative eGFR <45 mL/min/1.73 m²	214	183	156	127	111	90	66	50	37	23	18	11	4	2

Fig. 1 **A**, Overall survival in patients without adjuvant chemotherapy and who did not experience disease recurrence. **B**, Overall survival in patients without adjuvant chemotherapy and who did not experience disease recurrence.

the transition into stage III CKD, and a threshold of 45 mL/min per 1.73 m^2, which has been previously cited as a more strict definition of CKD and has been shown to be associated with a higher risk of comorbidities related to CKD [28]. Based on the eGFR threshold of 60 mL/min per 1.73 m^2, 37% of patients were eligible for neoadjuvant cisplatin-based chemotherapy and only 16% were candidates for adjuvant chemotherapy. With the threshold

of 45 mL/min per 1.73 m^2, 72% of patients were eligible for neoadjuvant cisplatin-based chemotherapy while only 52% were candidates for adjuvant chemotherapy. Thus, in addition to possible associated reasons, the decrease in eGFR after RNU supports the use of cisplatin-based chemotherapy for high-risk UTUC in a neoadjuvant rather than adjuvant setting. The pertinent and remaining question is the identification of candidates for systemic chemotherapy [2] but, even more so than in bladder urothelial carcinoma, deficiencies in clinical staging make the accurate identification of patients who have advanced disease and are therefore the best candidates for systemic chemotherapy extremely difficult.

We did not find any association between eGFR, irrespective of categorization of the data, with oncological outcomes and overall survival. CKD has been associated with a significant increase in cardiovascular events and death from any cause, independently of competing comorbidities [28]. In RCC, a decrease in eGFR has been associated with overall survival [10,29,30], but in the present study, renal function features (preoperative, postoperative and rate of change) were not associated with recurrence-free and cancer-specific survival, probably owing to the fact that cancer features had a stronger effect on outcomes. The lack of association with overall survival could be attributable to the short follow-up (45 months) of patients who did not succumb to their UTUC; however, when excluding from the analyses patients who experienced disease recurrence and those who underwent adjuvant chemotherapy, a preoperative eGFR $\geq$ 60 and a postoperative eGFR $\geq$ 45 mL/min per 1.73 m^2 were associated with overall survival. Larger cohorts with longer follow-up in patients who do not succumb to their disease are necessary to fully assess the association of eGFR with overall survival in patients who underwent RNU.

The present study has several limitations, including those inherent to a retrospective multicentre study design. We did not perform a centralized pathological review, which could have led to misinterpretations of pathological features. We used eGFR rather than creatinine clearance. Although patients with CKD stage 5 were present in the study, patients with comorbidities and/or CKD preoperatively may have been preferentially selected for conservative management. We acknowledge that medical comorbidities (e.g. hypertension and diabetes mellitus) could affect the renal function of these patients. Unfortunately, information on comorbidities was not available in our database, so we were unable to include this in the present analyses. In addition, the short follow-up and low number of non-cancer-specific events may have limited the statistical significance of some analyses.

In conclusion, only a small proportion of patients had a preoperative renal function that would allow cisplatin-based chemotherapy. Furthermore, eGFR significantly decreased after RNU, thereby lowering the rate of cisplatin eligibility to only 16 and 52% of patients, based on the thresholds of 60 and 45 mL/min per 1.73 m^2, respectively. Older patients ($\geq$70 years) had a lower baseline eGFR than younger patients and older patients ($\geq$70 years) had a proportionally higher rate of decrease in eGFR after RNU. Neither preoperative nor postoperative eGFR variables affected cancer-specific and overall survival outcomes after RNU. Taken together with the rest of the literature, the present findings support the use of cisplatin-based chemotherapy, when indicated, in the neoadjuvant rather than adjuvant setting.

Conflict of Interest

None declared.

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Abbreviations: eGFR, estimated GFR; RNU, radical nephro-ureterectomy; UTUC, upper tract urothelial carcinoma; Scr, serum creatinine; MDRD, modification of diet in renal disease formula; CKD, chronic kidney disease; EPI, chronic kidney disease epidemiology collaboration formula; IQR, interquartile range; HR, hazard ratio.