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Long-term renal functional recovery following radical nephrectomy for kidney cancer: Results from a multi-center confirmatory study

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Abstract

Purpose—To confirm the findings from a previous single-institution study of 572 patients from Memorial Sloan Kettering Cancer Center, in which we found that a significant proportion (49%) of patients recovered to their preoperative estimated glomerular filtration rate (eGFR) within 2 years following radical nephrectomy for renal cell carcinoma.

Materials and Methods—A multi-center retrospective study was conducted among 1928 patients using data contributed by three independent centers. The outcome of interest was postoperative recovery to preoperative eGFR. Data were analyzed using cumulative incidence and competing risks regression, with death from any cause treated as a competing event.

Results—This study demonstrated that 45% of patients recovered to their preoperative eGFR by 2 years following radical nephrectomy. Furthermore, this study confirmed that recovery of renal function differs according to preoperative renal function, such that patients with lower preoperative eGFR have an increased chance of recovery. This study also suggested that larger tumor size and female sex are significantly associated with increased chance of renal functional recovery.

Conclusions—In this multi-center retrospective study, we confirmed that over the long-term, a large proportion of patients recover to their preoperative renal function following radical

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nephrectomy for kidney tumors, and that recovery is more likely among those with lower preoperative eGFR.

Keywords

creatinine; estimated glomerular filtration rate; kidney cancer; radical nephrectomy; renal cell carcinoma; renal function

Introduction

Patients undergoing radical nephrectomy for renal tumors are at risk of a postoperative reduction in renal function due to loss of renal mass. Previous studies have shown that lower preoperative estimated glomerular filtration rate (eGFR), older age, and higher comorbidity are associated with lower postoperative eGFR and new onset chronic kidney disease following radical nephrectomy[1–6]. It is of interest to characterize the natural history of eGFR following radical nephrectomy for renal tumors in order to better understand long-term trends in renal functional recovery and to identify patient characteristics associated with postoperative renal functional recovery. We recently reported results from a study investigating the postoperative natural history of eGFR in patients who underwent radical nephrectomy for kidney cancer at Memorial Sloan Kettering Cancer (MSKCC) and found that nearly half (49%) of all patients recovered to their preoperative eGFR within 2 years following surgery[7]. Additionally, we found that eGFR recovery differed according to preoperative eGFR. In patients with preoperative eGFR < 60, younger age and female sex were also associated with higher chance of eGFR recovery, whereas in patients with preoperative eGFR ≥ 60, hypertension was associated with a lower chance of eGFR recovery and increased tumor size was associated with a higher chance of eGFR recovery[7]. In order to confirm these single center findings, a multi-center retrospective study was conducted from 3 centers performing a high volume of kidney surgery.

Materials and Methods

Data were contributed by Spectrum Health, Cleveland Clinic, and Mayo Clinic after institutional review board approval for retrospective data analysis. Patients from the same contemporary time period and meeting the same inclusion and exclusion criteria as the previous study[7] were selected, specifically including patients with non-metastatic renal cell carcinoma who underwent radical nephrectomy between 2006 and 2013 and had not received systemic therapy. Patients were excluded if missing preoperative creatinine (n=62), race (n=47), age (n=1), tumor size (n=45), diabetes (n=9), or no postoperative creatinine (n=7), resulting in a final sample size for this analysis that includes 1928 patients with 24,066 serum creatinine measurements. The final sample included 323 patients from Spectrum Health, 932 patients from Cleveland Clinic, and 673 patients from Mayo Clinic. Serum creatinine values were used to calculate eGFR using the CKD-Epidemiology Collaboration formula as follows: $eGFR\ (ml/min\ per\ 1.73m^2) = 141 \times \min(SCr/k, 1)^a \times \max(SCr/k, 1)^{-1.209} \times 0.993^{Age} \times 1.018[\text{if female}] \times 1.159[\text{if black}]$, where SCr is serum creatinine (mg/dl), k is 0.7 for female patients and 0.9 for male patients, a is −0.329 for female patients and −0.411 for male patients, min indicates the minimum of SCR/k or 1, and max indicates the maximum of SCr/k or 1[8].

The statistical methods in this study mirror those of the previous study[7], as is common in a study attempting to confirm a previous finding. Rather than undertaking any variable selection or model building, we are simply including variables from the multivariable analysis from the prior study. Preoperative eGFR was dichotomized as ≥ 60 versus < 60 ml/min per 1.73 m^2. We plotted the trajectory of each patient's eGFR over time from the immediate preoperative measurement through three years postoperatively, and used locally weighted scatterplot smoothing (LOWESS) to explore trends both overall and according to dichotomous preoperative eGFR. The association between patient and disease characteristics with preoperative eGFR was analyzed using logistic regression adjusted for study center, to account for possible differences across centers.

The outcome of interest in this study was postoperative recovery to preoperative eGFR, within a 5% margin of error. A competing risks analysis framework was used, with eGFR recovery as the primary event of interest and death from any cause as the competing event. Follow-up times were calculated from the date of radical nephrectomy, and patients alive and without eGFR recovery were censored at either their last eGFR measurement or 36 months, whichever came first. The cumulative incidence of eGFR recovery was estimated. Between-groups comparisons were made using competing risks regression adjusted for study center. Multivariable competing risks regression was stratified by dichotomous preoperative eGFR and incorporated factors identified in our prior study[7], including age at surgery, sex, diabetes, hypertension, and tumor size[7], with additional adjustment for study center.

A p-value < 0.05 was considered statistically significant. All statistical analyses were conducted using R software, version 3.2.5 (R Core Development Team, Vienna, Austria) including the ‘cmprsk’ package.

Results

Among the 1928 patients, 64.6% were male and median age at surgery was 64 (interquartile range (IQR): 54-72). Median preoperative eGFR was 71.9 ml/min/1.73m^2 (IQR: 56.6 – 87.5). 70.1% of patients had preoperative eGFR ≥ 60 whereas 29.9% of patients had preoperative eGFR < 60. Patients with preoperative eGFR < 60 were older (median age at surgery 70 versus 61, p < .001) and more frequently had diabetes (27.6% versus 21.4%, p < .001) and hypertension (75.6% versus 59.2%, p < .001) as compared to patients with preoperative eGFR ≥ 60 (Table 1). Line plots with LOWESS trends revealed that all patients experienced a drop in eGFR immediately postoperatively, followed by a generally flat trend over time among those with preoperative eGFR ≥ 60 and a slightly upwards trend among those with preoperative eGFR < 60 (Figure 1A). These trends are broadly similar to what was seen in our prior study (Figure 1B), though in the MSKCC data we saw a more pronounced upward trend in both groups in the later part of follow-up[7].

Median follow-up time among survivors was 3.7 years (IQR: 1.8 – 6.1). During follow-up, 883 patients experienced recovery to preoperative eGFR whereas 95 patients died without eGFR recovery. Whereas 499 patients recovered to within 5% of their preoperative eGFR, 384 recovered to an eGFR >5% higher than their preoperative level. Among these 384 patients, the median increase above their preoperative level was 8.8 ml/min/1.73 m2 (IQR: 5.6 – 13.8). To examine the time to eGFR recovery, we estimated the cumulative incidence of eGFR recovery, with death from any cause treated as a competing event, according to preoperative eGFR (Figure 2). We find significant differences in eGFR recovery according to preoperative eGFR, such that patients with higher preoperative eGFR were less likely to fully recover function ($p < .001$). Compared to the original result in the MSK data (dashed lines), the observed result is quite similar among those with preoperative eGFR >= 60 whereas the slope of the cumulative incidence of eGFR among those with preoperative eGFR < 60 is less steep.

Overall, 42% and 45% of patients recovered to their baseline eGFR by 1 and 2 years postoperatively. The 1-year cumulative incidences of eGFR recovery were 32% and 64% and the 2-year cumulative incidences of eGFR recovery were 36% and 67%, among those with preoperative eGFR ≥ 60 and < 60, respectively. This validates the finding from our original study that nearly half of all patients have eGFR recovery long-term, and that frequency of recovery differs according to preoperative eGFR[7]. Unlike the previous study, median time to eGFR recovery was not reached in this study, as those in the preoperative eGFR ≥ 60 group did not experience as much late recovery so the cumulative incidence curve flattened off.

Multivariable competing risks regression incorporated age at surgery, sex, diabetes, hypertension, and tumor size, was stratified by preoperative eGFR, and additionally adjusted for study center (Table 2). Stratification was performed after identifying significant interaction effects with preoperative eGFR in the original study[7]. We observed that female sex is associated with a significantly increased chance of eGFR recovery among those with preoperative eGFR ≥ 60 (hazard ratio (HR): 1.33, 95% confidence interval (CI): 1.13 – 1.57). We also found that increasing tumor size is significantly associated with increased chance of eGFR recovery among both those with preoperative eGFR ≥ 60 (HR: 1.06, 95% CI: 1.04 – 1.08) and with preoperative eGFR < 60 (HR: 1.04, 95% CI: 1.02 – 1.06). These results differ somewhat from the original MSKCC study in that we did not find that younger age or female sex are associated with increased chance of eGFR recovery in those with preoperative eGFR < 60. We also did not find that hypertension is associated with decreased chance of eGFR recovery in those with preoperative eGFR ≥ 60.

Discussion

Overall this study confirms that a substantial proportion of patients experience eGFR recovery following radical nephrectomy, that this recovery differs according to preoperative eGFR, and that tumor size and patient sex are important factors associated with eGFR recovery. Patients with low preoperative eGFR and patients with larger tumors were more likely to experience renal functional recovery. This finding suggests that low eGFR should not be seen as a contraindication for a radical nephrectomy when such a procedure is otherwise indicated since the 1-year cumulative incidence of recovery was 64% in patients with preoperative eGFR < 60 in this study.

It is of course important to understand that renal functional recovery differs between patients undergoing radical nephrectomy versus partial nephrectomy, a debate that was initially begun by investigators comparing renal functional outcomes in patients with small renal tumors (T1a) undergoing partial nephrectomy to radical nephrectomy. In a recent review article, Li et al[9] found that in both single-center retrospective studies as well as population-based studies, worse renal functional outcomes in small renal tumors (T1a,b) have been reported in patients undergoing radical versus partial nephrectomy, including higher postoperative mean serum creatinine, increased cumulative incidence of renal insufficiency, and increased rates of new onset chronic kidney disease. The centers in this study have a long established commitment to kidney sparing operations for patients with small renal tumors. The situation changes when urologists are confronted with large and locally advanced tumors for which radical nephrectomy is indicated. The focus of the current confirmatory study was to understand the renal functional impact radical nephrectomy and it was encouraging to find that many patients indeed recover their preoperative renal function, and sometimes even experience improved renal function, postoperatively.

A novel finding of our previous study, confirmed here, was that increased tumor size was significantly associated with increased chance of eGFR recovery. It is possible that the normal contralateral kidney is the major contributor to total eGFR in patients with large tumors and was already in the process of enhancing its contribution to overall renal function long before the index tumor was removed by radical nephrectomy. In a study of parenchymal volume and function of the contralateral kidney, Takagi et al[10] found that the median increase in eGFR in the contralateral kidney was 2.3% in patients undergoing partial nephrectomy and 21.1% in patients undergoing radical nephrectomy. A study by Choi et al[11] found that preoperative volume of both the affected and contralateral kidneys were higher among patients with lower CKD stage. The phenomenon of hyperfiltration and recovery of renal function as shown in donor nephrectomies[12,13] as well as in animal studies[14] is due to a decrease in functional renal volume, which reduces the afferent arteriolar resistance and increases the effective plasma flow. However, the biological mechanisms underlying this renal functional compensation in the contralateral kidney, and the patient and disease factors that may affect this compensation, are not well understood and further study is needed. Assuming that radical nephrectomy is being performed at high volume centers in patients with large tumors not amenable to kidney sparing approaches, research questions regarding the degree to which contralateral kidney functional compensation occurs prior to radical nephrectomy and continues after radical nephrectomy is of great interest as are the underlying physiological mechanisms that lead to these results.

A limitation of this study is the retrospective nature of the data; however, it is promising to see a similar pattern of results in this large, multi-center study as we found in our original single-center study. Creation of a binary time-to- event endpoint does not allow for detailed investigation of patterns over time, and there is clearly intra-patient variation over time as demonstrated in Figure 1. Originally, interest was in time to initial recovery of renal function, and this current study simply sought to confirm the previous findings. Future studies could rather categorize the measurement at each time point as having returned to baseline or not and look at longitudinal trends in renal functional recovery, or could examine the recovery status at the last measured timepoint. Furthermore, we acknowledge that renal function recovery is not the only significant outcome in patients following radical nephrectomy, and treatment decisions must also consider the impact of radical nephrectomy on cardiovascular and pulmonary function, which are outside the scope of the current study. Nevertheless, it is important to confirm our previously reported novel findings from a single-institution retrospective study and we have done so in a rigorous and hypothesis-driven manner, which lends strength to these results.

Conclusions

In this multi-center retrospective study, we confirmed that over the long-term, a substantial proportion of patients recover to their preoperative renal function following radical nephrectomy for kidney tumors. Renal function recovery is more likely among patients with lower preoperative eGFR and among patients with larger tumors. The biological mechanisms underlying this affect are not well understood, and further study, especially prospective study, is needed.

Acknowledgments

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Glossary

eGFR	estimated glomerular filtration rate
MSKCC	Memorial Sloan Kettering Cancer Center
SCr	serum creatinine
IQR	interquartile range
HR	hazard ratio
CI	confidence interval
CKD	chronic kidney disease

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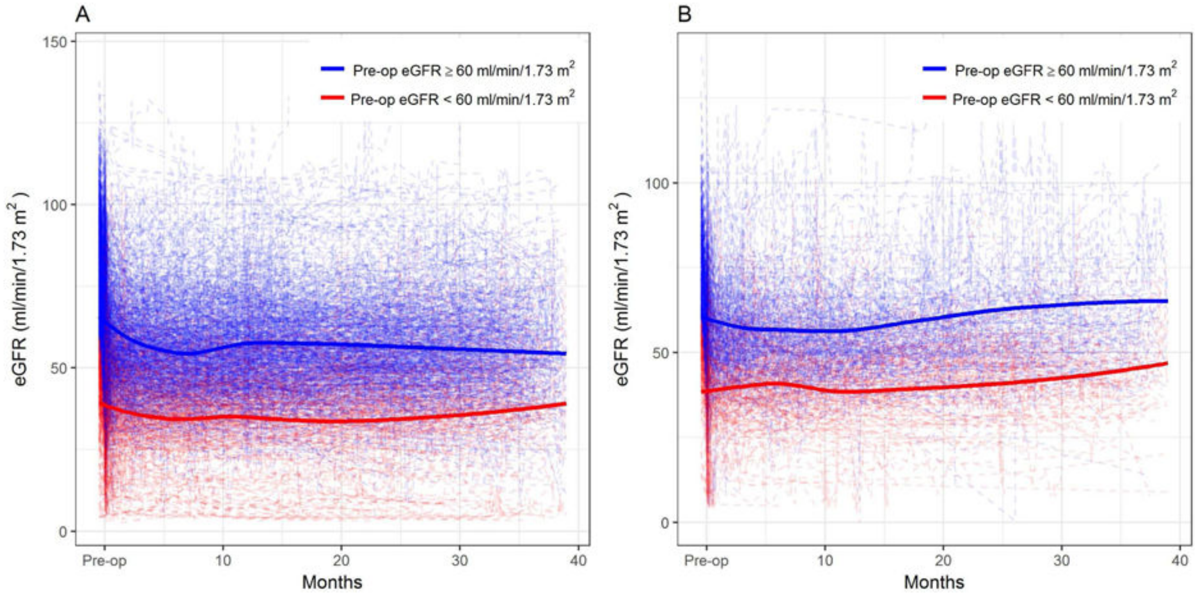

Figure 1.

Postoperative eGFR trajectories according to preoperative eGFR in (A) the current multi-center study population and (B) the original MSKCC study (dotted lines represent individual patient data whereas solid lines represent LOWESS)

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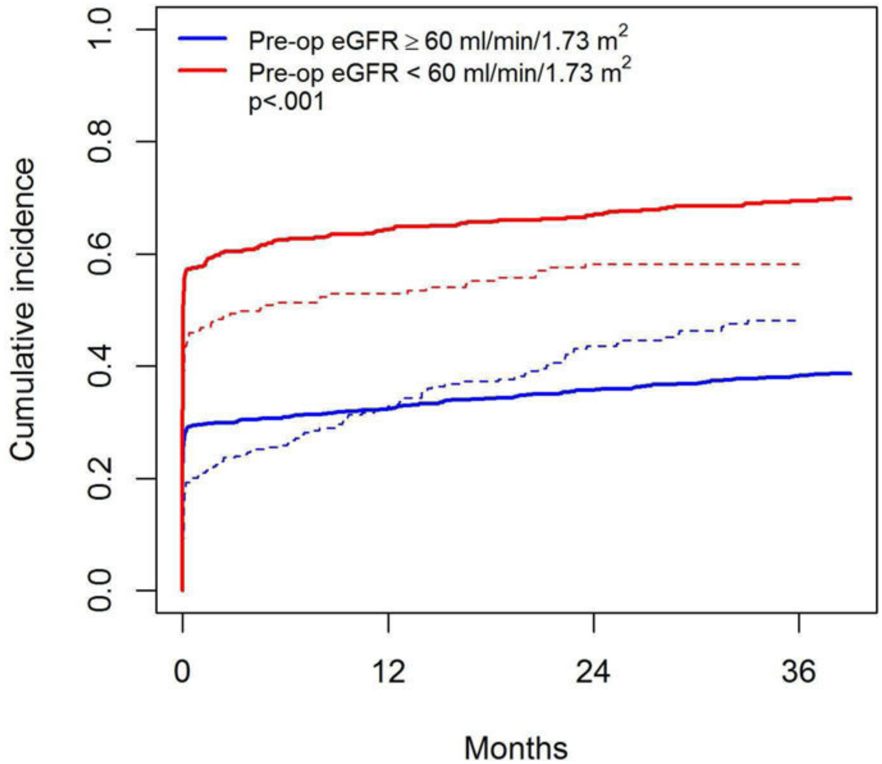

Figure 2.

Cumulative incidence of eGFR recovery according to preoperative eGFR (solid lines represent results from the current multi-center study data; dashed lines represent results from the previous study using MSKCC data). The p-value is from competing risks regression adjusted for study center.

Table 1

Patient characteristics by preoperative eGFR

	Overall (N = 1928)	eGFR≥60 (N = 1351)	eGFR<60 (N = 577)	p-value*	Orignal MSKCC study (N = 572)
Age at surgery, median (IQR)	64 (54, 72)	61 (53, 69)	70 (61, 77)	<.001	61 (53, 69)
Tumor size (cm), median (IQR)	6.9 (4.8, 9.5)	6.8 (4.7, 9.4)	7.1 (5.0, 9.8)	0.528	7.7 (5.5, 10.4)
Sex, N (%)				0.731	
Female	683 (35.4)	482 (35.7)	201 (34.8)		185 (32.3)
Male	1245 (64.6)	869 (64.3)	376 (65.2)		387 (67.7)
Race, N (%)				0.414	
Black	117 (6.1)	93 (6.9)	24 (4.2)		37 (6.5)
Other	54 (2.8)	36 (2.7)	18 (3.1)		29 (5.1)
White	1757 (91.1)	1222 (90.5)	535 (92.7)		506 (88.5)
Diabetes, N (%)				<.001	
No	1480 (76.8)	1062 (78.6)	418 (72.4)		476 (83.2)
Yes	448 (23.2)	289 (21.4)	159 (27.6)		96 (16.8)
Hypertension, N (%)				<.001	
No	692 (35.9)	551 (40.8)	141 (24.4)		215 (37.6)
Yes	1236 (64.1)	800 (59.2)	436 (75.6)		357 (62.4)

* p-value from logistic regression adjusted for study center

Table 2

Multivariable competing risks regression incorporating all factors shown in the table as well as study center

	Preoperative eGFR ≥ 60		Preoperative eGFR < 60	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age at surgery	1.00 (0.99-1.00)	0.400	0.99 (0.99-1.00)	0.170
Sex		0.001		0.730
Male	1.00		1.00	
Female	1.33 (1.13–1.57)		1.03 (0.86–1.25)	
Diabetes	0.90 (0.71–1.14)	0.390	0.95 (0.76–1.19)	0.670
Hypertension	1.09 (0.91–1.30)	0.370	1.12 (0.90–1.41)	0.310
Tumor size (cm)	1.06 (1.04–1.08)	<.001	1.04 (1.02–1.06)	0.001