Long-Term Renal Function Recovery following Radical Nephrectomy for Kidney Cancer: Results from a Multicenter Confirmatory Study

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Purpose: We sought to confirm the findings from a previous single institution study of 572 patients from Memorial Sloan Kettering Cancer Center in which we found that 49% of patients recovered to the preoperative estimated glomerular filtration rate within 2 years following radical nephrectomy for renal cell carcinoma.

Materials and Methods: A multicenter retrospective study was performed in 1,928 patients using data contributed from 3 independent centers. The outcome of interest was postoperative recovery to the preoperative estimated glomerular filtration rate. 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 had recovered to the preoperative estimated glomerular filtration rate by 2 years following radical nephrectomy. Furthermore, this study confirmed that recovery of renal function differed according to preoperative renal function such that patients with a lower preoperative estimated glomerular filtration rate had an increased chance of recovery. This study also suggested that larger tumor size and female gender were significantly associated with an increased chance of renal function recovery.

Conclusions: In this multicenter retrospective study we confirmed that in the long term a large proportion of patients recover to preoperative renal function following radical nephrectomy for kidney tumors. Recovery is more likely among those with a lower preoperative estimated glomerular filtration rate.

Key Words: kidney; carcinoma, renal cell; nephrectomy; creatinine; kidney function tests

Abbreviations and Acronyms

CKD = chronic kidney disease

eGFR = estimated glomerular filtration rate

MSKCC = Memorial Sloan Kettering Cancer Center

SCr = serum creatinine

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Patients who undergo radical nephrectomy for renal tumors are at risk for a postoperative reduction in renal function due to loss of renal mass. Previous studies have shown that lower preoperative eGFR, older age and higher comorbidity are associated with lower postoperative eGFR and new onset CKD following radical nephrectomy.[1–6] It is of interest to characterize the natural history of eGFR after radical nephrectomy for

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renal tumors to better understand long-term trends in renal function recovery and identify patient characteristics associated with postoperative renal function recovery.

We recently reported the results of a study investigating the postoperative natural history of eGFR in patients who underwent radical nephrectomy for kidney cancer at MSKCC and found that 49% recovered to preoperative eGFR within 2 years following surgery.[7] Additionally, we found that eGFR recovery differed according to preoperative eGFR. In patients with preoperative eGFR less than 60 ml/minute/1.73 m^2 younger age and female gender were also associated with a higher chance of eGFR recovery. In contrast, in patients with preoperative eGFR 60 ml/minute/1.73 m^2 or greater hypertension was associated with a lower chance of eGFR recovery and increased tumor size was associated with a higher chance of eGFR recovery.

To confirm these single center findings we performed a multicenter retrospective study using data from 3 centers where a high volume of kidney surgery is done.

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 period who met the same inclusion and exclusion criteria as in the previous study[7] were selected, specifically including those with nonmetastatic renal cell carcinoma who underwent radical nephrectomy between 2006 and 2013, and had not received systemic therapy. Patients were excluded due to missing preoperative creatinine in 62, race in 47, age in 1, tumor size in 45, diabetes in 9 and no postoperative creatinine in 7. This resulted in a final sample size for this analysis of 1,928 patients with a total of 24,066 serum creatinine measurements. The final sample included 323 patients from Spectrum Health, 932 from Cleveland Clinic and 673 from Mayo Clinic.

Serum creatinine values were used to calculate eGFR using the CKD-EPI (Epidemiology Collaboration) formula, eGFR (ml/minute/1.73 m^2) = $141 \times \min(SCr/k, 1)^a \times \max(SCr/k, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ if female $\times$ 1.159 if black, where SCr is serum creatinine in mg/dl, k is 0.7 in female patients and 0.9 in male patients, a is -0.329 in female patients and -0.411 in 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 mirrored those of the previous series,[7] as is common in a study attempting to confirm a previous finding. Rather than performing any variable selection or model building we simply included variables from the multivariable analysis in the prior study.

Preoperative eGFR was dichotomized as 60 or greater vs less than 60 ml/minute/1.73 m^2. We plotted the trajectory of eGFR in each patient with time from the immediate preoperative measurement through 3 years postoperatively. We used LOWESS to explore trends overall and according to dichotomous preoperative eGFR. The association of patient and disease characteristics with preoperative eGFR was analyzed by 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. Followup was calculated from the date of radical nephrectomy. Survivors without eGFR recovery were censored at the last eGFR measurement or 36 months, whichever was first.

The cumulative incidence of eGFR recovery was estimated. Between group 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 series, including age at surgery, gender, diabetes, hypertension and tumor size,[7] with additional adjustment for study center.

Statistical significance was considered at $p < 0.05$. All statistical analyses were performed with R, version 3.2.5 (https://www.r-project.org/), including the cmprsk package.

RESULTS

Of the 1,928 patients 64.6% were male. Median age at surgery was 64 years (IQR 54–72). Median preoperative eGFR was 71.9 ml/minute/1.73 m^2 (IQR 56.6–87.5). Preoperative eGFR was 60 ml/minute/1.73 m^2 or greater in 70.1% of patients and less than 60 ml/minute/1.73 m^2 in 29.9%. Patients with preoperative eGFR less than 60 ml/minute/1.73 m^2 were older (median age at surgery 70 vs 61 years) and more of them had diabetes (27.6% vs 21.4%) and hypertension (75.6% vs 59.2%, all $p < 0.001$) compared to patients with preoperative eGFR 60 ml/minute/1.73 m^2 or greater (table 1).

Line plots with LOWESS trends revealed that all patients experienced a decrease in eGFR immediately postoperatively followed by a generally flat trend with time in those with preoperative eGFR 60 ml/minute/1.73 m^2 or greater and a slightly upward trend in those with preoperative eGFR less than 60 ml/minute/1.73 m^2 (fig. 1, *A*). These trends were broadly similar to what was seen in our prior study (fig. 1, *B*),[7] although in the MSKCC data we saw a more pronounced upward trend in each group in the later part of followup.

Median survivor followup was 3.7 years (IQR 1.8–6.1). During followup 883 patients experienced recovery to preoperative eGFR and 95 died without eGFR recovery. While 499 patients recovered to within 5% of preoperative eGFR, 384 recovered to

Table 1. *Patient characteristics by preoperative eGFR*

			eGFR (ml/min/1.73 m^2)					
	Overall		60 or Greater		Less Than 60		p Value*	Original MSKCC Study
No. pts	1,928		1,351		577		—	572
Median age at surgery (IQR)	64	(54–72)	61	(53–69)	70	(61–77)	<0.001	61 (53–69)
Median cm tumor size (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)
No. gender (%):							0.731	
F	683	(35.4)	482	(35.7)	201	(34.8)		185 (32.3)
M	1,245	(64.6)	869	(64.3)	376	(65.2)		387 (67.7)
No. race (%):							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	1,757	(91.1)	1,222	(90.5)	535	(92.7)		506 (88.5)
No. diabetes (%):							<0.001	
No	1,480	(76.8)	1,062	(78.6)	418	(72.4)		476 (83.2)
Yes	448	(23.2)	289	(21.4)	159	(27.6)		96 (16.8)
No. hypertension (%):							<0.001	
No	692	(35.9)	551	(40.8)	141	(24.4)		215 (37.6)
Yes	1,236	(64.1)	800	(59.2)	436	(75.6)		357 (62.4)

*Logistic regression adjusted for study center.

eGFR greater than 5% higher than the preoperative level. In these 384 patients the median increase above the preoperative level was 8.8 ml/minute/1.73 m^2 (IQR 5.6–13.8).

To examine 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 (fig. 2). We found significant differences in eGFR recovery according to preoperative eGFR such that patients with higher preoperative eGFR were less likely to fully recover function (p <0.001). Compared to the original result in the MSKCC data the observed result was quite similar among patients with preoperative eGFR 60 ml/minute/1.73 m^2 or greater but the slope of the cumulative incidence of eGFR was less steep in those with preoperative eGFR less than 60 ml/minute/1.73 m^2 (fig. 2).

Overall 42% and 45% of patients recovered to baseline eGFR by 1 and 2 years postoperatively, respectively. The 1-year cumulative incidence of eGFR recovery was 32% and 64%, and the 2-year cumulative incidence was 36% and 67% among patients with preoperative eGFR 60 or greater and

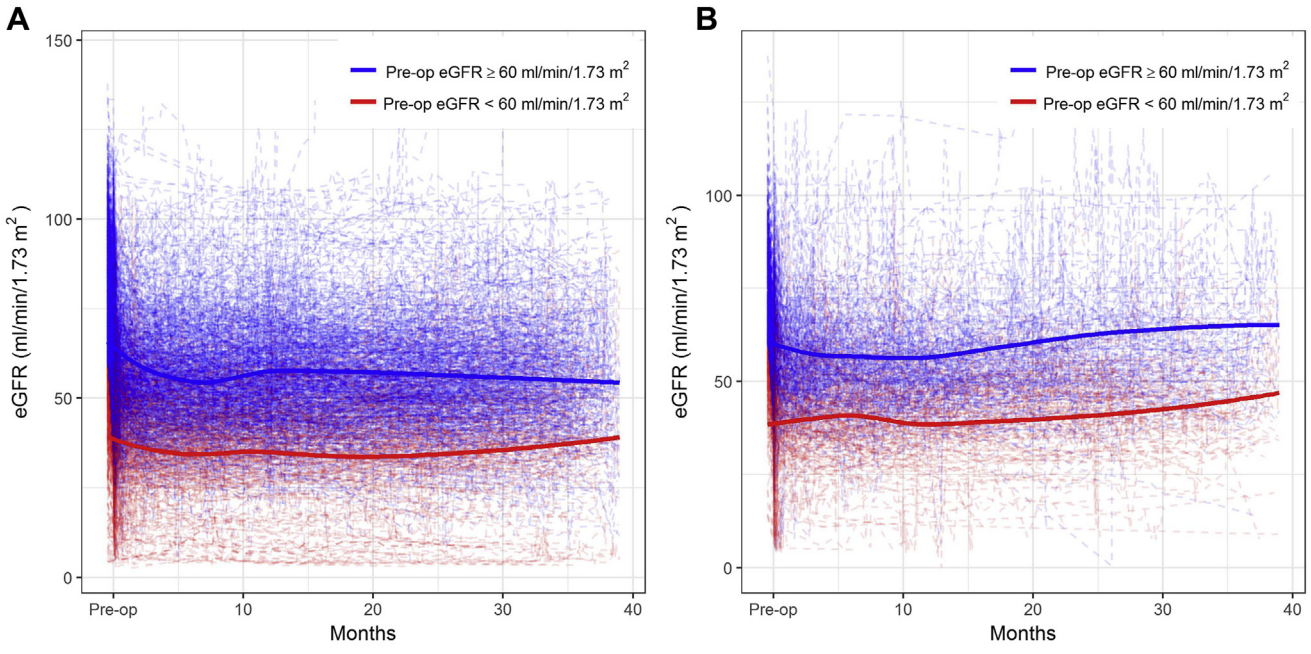

Figure 1. Postoperative eGFR trajectories according to preoperative eGFR. *A*, current multicenter study population. *B*, original MSKCC study. Dotted curves represent individual patient data. Solid curves represent LOWESS.

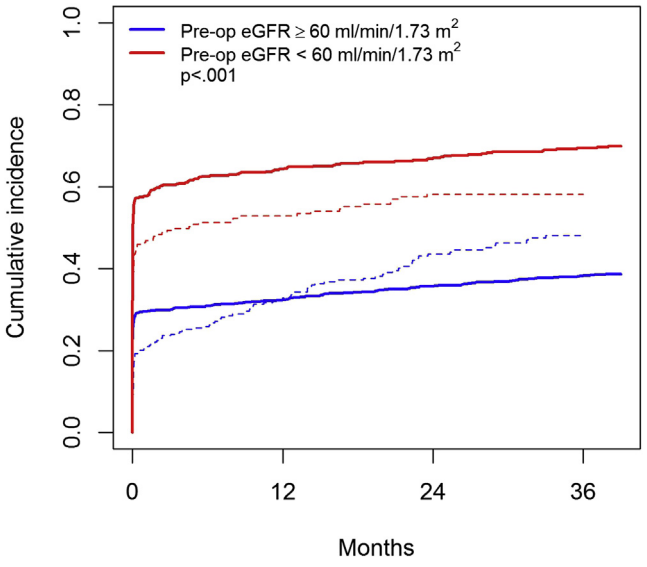

Figure 2. Cumulative incidence of eGFR recovery according to preoperative eGFR. Competing risks regression p value adjusted for study center. Solid curves represent current multicenter study results. Dashed curves represent previous study results using MSKCC data.

less than 60 ml/minute/1.73 m^2, respectively. This validates the finding in our original study that nearly half of all patients experienced eGFR recovery in the long term and the frequency of recovery differed according to preoperative eGFR.[7] Unlike the previous study, median time to eGFR recovery was not reached in the current series since those in the preoperative eGFR 60 ml/minute/1.73 m^2 or greater group did not experience as much late recovery. Thus, the cumulative incidence curve flattened off.

Multivariable competing risks regression incorporated age at surgery, gender, diabetes, hypertension and tumor size, and was stratified by preoperative eGFR and also adjusted for study center (table 2). Stratification was performed after identifying significant interaction effects with preoperative eGFR in the original study.[7] We observed

Table 2. *Multivariable competing risks regression incorporating all factors and study center*

	Preop eGFR 60 ml/min/1.73 m^2 or Greater		Preop eGFR Less Than 60 ml/min/1.73 m^2	
	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
Gender:		0.001		0.730
M	1.00		1.00	
F	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	1.06 (1.04–1.08)	<0.001	1.04 (1.02–1.06)	0.001

that female gender was associated with a significantly increased chance of eGFR recovery among patients with preoperative eGFR 60 ml/minute/1.73 m^2 or greater (HR 1.33, 95% CI 1.13–1.57). We also found that increasing tumor size was significantly associated with an increased chance of eGFR recovery among those with preoperative eGFR 60 ml/minute/1.73 m^2 or greater (HR 1.06, 95% CI 1.04–1.08) and with preoperative eGFR less than 60 ml/minute/1.73 m^2 (HR 1.04, 95% CI 1.02–1.06).

Those results differed somewhat from the original MSKCC study[7] in that we did not find that younger age or female gender were associated with an increased chance of eGFR recovery in patients with preoperative eGFR less than 60 ml/minute/1.73 m^2. We also did not find that hypertension was associated with a decreased chance of eGFR recovery in those with preoperative eGFR 60 ml/minute/1.73 m^2 or greater.

DISCUSSION

Overall this study confirms that a substantial proportion of patients experience eGFR recovery following radical nephrectomy, this recovery differs according to preoperative eGFR, and tumor size and patient gender are important factors associated with eGFR recovery. Patients with low preoperative eGFR and patients with larger tumors were more likely to experience renal function recovery. This finding suggests that low eGFR should not be seen as a contraindication to radical nephrectomy when such a procedure is otherwise indicated since in this study the 1-year cumulative incidence of recovery was 64% in patients with preoperative eGFR less than 60 ml/minute/1.73 m^2.

It is of course important to understand that renal function recovery differs between patients who undergo radical vs partial nephrectomy. This debate was initially begun by investigators comparing renal functional outcomes in patients with small renal tumors (T1a) treated with partial or radical nephrectomy. In a recent review article Li et al found that in single center retrospective studies as well as in population based studies worse renal functional outcomes in patients with small renal tumors (T1a, b) were reported in those who underwent radical vs partial nephrectomy.[9] These worse outcomes included higher postoperative mean serum creatinine, an increased cumulative incidence of renal insufficiency and an increased rate of new onset chronic kidney disease.

At the centers in our study there is a long established commitment to kidney sparing operations in 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 impact of radical nephrectomy on renal function. It was encouraging to find that many patients indeed recovered preoperative renal function and sometimes even experienced improved renal function postoperatively.

A novel finding of our previous study, which the current work confirmed, was that increased tumor size was significantly associated with an increased chance of eGFR recovery.[7] It is possible that the normal contralateral kidney is the major contributor to total eGFR in patients with large tumors and it 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 found that the median increase in eGFR in the contralateral kidney was 2.3% in patients who underwent partial nephrectomy and 21.1% in those who underwent radical nephrectomy.[10] Choi et al found that the preoperative volume of the affected and contralateral kidneys was higher among patients with a lower CKD stage.[11]

The phenomenon of hyperfiltration and recovery of renal function noted in donor nephrectomies[12,13] and 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. Further study is needed. Assuming that radical nephrectomy is 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 multicenter study as we found in our original single center study.[7] Creation of a binary time to event end point did not allow for detailed investigation of patterns with time and there was clearly intrapatient variation with time (fig. 1). Originally our interest was the time to initial recovery of renal function[7] and in the current study we simply sought to confirm the previous findings. Future studies could rather categorize the measurement at each time point as having returned or not returned to baseline and look at longitudinal trends in renal function recovery or recovery status at the last measured time point could be examined. Furthermore, we acknowledge that renal function recovery is not the only significant outcome in patients following radical nephrectomy. 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 was important to confirm our previously reported novel findings from a single institution, retrospective study.[7] We have done so in a rigorous and hypothesis driven manner, which lends strength to these results.

CONCLUSIONS

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

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EDITORIAL COMMENT

This multi-institutional study by Zabor et al confirming the findings from a previous single institution study from Memorial Sloan Kettering Cancer Center demonstrated that 45% of patients had recovered to the preoperative eGFR by 2 years following radical nephrectomy (reference 7 in article). Of these patients 43% actually recovered to an eGFR that was greater than 5% higher than the preoperative level. Importantly low preoperative renal function (eGFR less than 60 ml/minute/1.73 m^2), larger tumors and female gender were associated with an increased chance of renal function recovery.

The general trend in the management of renal tumors has been nephron sparing surgery due to the deleterious effects of CKD. The impact on overall survival of radical vs partial nephrectomy has been debated. However, radical nephrectomy may be imperative for more advanced cancers. This study provides evidence to suggest that all is not lost in these patients with almost half recovering renal function by 2 years postoperatively. As such, practicing urologists can use this information to better choose appropriate surgical intervention and counsel patients prior to surgery, especially those with low baseline CKD. The longer term impact (greater than 2 years) of radical nephrectomy on renal function is still unknown but these results are encouraging.

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