Factors That Affect Proportional Glomerular Filtration Rate After Minimally Invasive Partial Nephrectomy

A. Ari Hakimi, MD,¹ Reza Ghavamian, MD,² Steven K. Williams, MD,² Philip H. Kim, MD,¹ Ling Chen, MPH,³ John P. Sfakianos, MD,¹ Gal E. Keren-Paz, MD,¹ Alexander Sankin, MD,¹ Natasha Ginzburg, MD,² and Jonathan A. Coleman, MD^{1,4}

Abstract

Background and Purpose: Several factors have been shown to impact the overall glomerular filtration (GFR) rate after partial nephrectomy. Change in overall GFR, however, does not necessarily reflect the impact of these factors on the operated kidney. Using preoperative and postoperative renal scintigraphy, we sought to assess the impact of patient, tumor, and operative factors on GFR of the affected kidney (proportional GFR).

Patients and Methods: We identified 73 patients who underwent minimally invasive partial nephrectomy with preoperative and postoperative renal scans from two institutions. Patient, tumor, and operative characteristics were recorded. We used multiple linear regression to determine the patient and clinical factors predictive of postoperative proportional GFR in the operated kidney. We tested for an interaction between preoperative proportional GFR and nephrometry score and ischemia. We further fitted two separate linear models to compare the proportion of variance (R^2) explained by ischemia time in change in renal function in the operated kidney with the change in renal function in both kidneys.

Results: Surgical parameters (procedure approach, ischemia time, and estimated blood loss) and preoperative proportional GFR were significantly associated with postoperative proportional GFR. Preoperative proportional GFR ($\beta=5.93$, 95% confidence interval [CI]: 3.88, 7.97, $P<0.0005$) and procedure approach ($\beta=8.67$, 95% CI: 4.50, 12.80, $P<0.0005$) were strongly associated with outcome while ischemia time ($\beta=-1.80$, 95% CI: -3.48 , -0.11 , $P=0.04$) and estimated blood loss ($\beta=-1.15$, 95% CI: -0.29 , -0.01 , $P=0.04$) just reached statistical significance. The interaction term between preoperative proportional GFR and nephrometry score or ischemia time was not statistically significant (nephrometry, $P=0.2$ continuous or $P=0.6$ categorical, and ischemia, $P=0.7$, respectively).

Conclusion: Lower preoperative proportional GFR, longer ischemia times, and higher blood loss all negatively impact postoperative proportional GFR while tumor complexity as gauged by morphometry scoring does not. Larger studies are needed to determine whether renal scintigraphy is a more accurate method of measuring the impact of the ischemia time on postoperative proportional GFR.

Introduction

PARTIAL NEPHRECTOMY IS NOW CONSIDERED the standard of care for most localized renal masses <7 cm, because it offers the best chance of achieving both oncologic control and preservation of renal function.¹ Several factors have been shown to impact overall glomerular filtration rate (GFR) after partial nephrectomy.² These risk factors can be grouped into three categories: Patient-related (comorbidities, renal function), tumor-related (size, location, nephrometry score), and surgery-related (blood loss, ischemia time, surgical approach). A reliable and standardized means of evaluating

iatrogenic loss of renal function is critical to understanding the impact of controllable surgical factors on kidney function. Global measures of function such as overall GFR do not account for compensation from the opposite kidney, and assessment of urinary enzymology is confounded by mixing of urine in the bladder.

To interrogate the factors most closely associated with functional change in proportional GFR in the operated kidney in patients undergoing minimally invasive partial nephrectomy—whether laparoscopic or robot-assisted—we used preoperative and postoperative renal scintigraphy to develop a composite functional assessment.

¹Department of Surgery, Urology Service, Memorial Sloan-Kettering Cancer Center, New York, New York.

²Department of Urology, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, New York.

³Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, New York.

⁴Department of Urology, Weill Cornell Medical College of Cornell University, New York, New York.

Patients and Methods

Our analysis included 79 patients from two academic institutions (Institutions A and B) who underwent partial nephrectomy for the treatment of solid renal masses between February 2007 and March 2011. Preoperative and postoperative renal scans were obtained using either technetium-99m mercaptoacetyltriglycine (99mTc-MAG3) or diethylene triamine pentaacetic acid (99mTc-DTPA). Excluded from all analyses were one patient who had the postoperative scan more than 2 years after surgery, and one patient who experienced renal loss from postoperative renal vein thrombosis. We also excluded four patients whose procedures did not include renal hilar control, leaving data from 73 patients available for analysis. Postoperative renal scans were performed at a median of 6.9 months (interquartile range [IQR] 5.8, 7.4) after surgery for patients from Institution A and a median of 2.7 months (IQR 2.4, 3.2) after surgery for patients from Institution B.

We sought to identify factors that may be useful in predicting proportional GFR in the operated kidney after partial nephrectomy. Using multiple linear regression models, we evaluated the following potential predictors: Patient features (age, race [white *vs* nonwhite], body mass index, American Society of Anesthesiologists score, and preoperative proportional GFR), tumor characteristics (using the R.E.N.A.L. [radius; exophytic/endophytic; nearness; anterior/posterior; location] nephrometry score,³ which quantifies the anatomic characteristics of renal masses), and surgical parameters (ischemia time, estimated blood loss, and approach [robot-assisted *vs* laparoscopic]). To determine the relationship between lower proportional GFR and complex tumors, we examined whether there was an interaction between preoperative proportional GFR and nephrometry score (with ≥ 8 *vs* < 8 as the cutoff). We also tested for an interaction effect between preoperative proportional GFR and ischemia time to evaluate if patients with preexisting renal dysfunction were more sensitive to ischemia.

A secondary aim of the study was to determine whether the effects of ischemia time could be better assessed by the change

in postoperative renal function (as measured by GFR) of the operated kidney or of both kidneys. We fitted two separate linear models to compare the proportion of variance (explained by ischemia time) in change in renal function in the operated kidney with the change in renal function in both kidneys. The difference between these models and corresponding 95% CI were calculated by bootstrapping methods. All analyses were conducted using Stata 11.1 (StataCorp, College Station, TX).

Results

Baseline demographic, tumor, and surgical characteristics are summarized in Table 1. Patients from both institutions had largely similar characteristics. There was a marked difference in race (87% white at Institution A *vs* 14% at Institution B), and a higher proportion of robotic procedures were performed at Institution A (66% *vs* 31%), however.

Table 2 summarizes the results of the multivariable regression analyses for the overall cohort. Surgical parameters (procedure approach, ischemia time, and estimated blood loss) and preoperative proportional GFR were significantly associated with postoperative proportional GFR. Preoperative proportional GFR ($\beta = 5.93$, 95% CI: 3.88, 7.97, $P < 0.0005$) and procedure approach ($\beta = 8.67$, 95% CI: 4.50, 12.80, $P < 0.0005$) were strongly associated with outcome. Ischemia time ($\beta = -1.80$, 95% CI: -3.48 , -0.11 , $P = 0.04$) and estimated blood loss ($\beta = -1.15$, 95% CI: -0.29 , -0.01 , $P = 0.04$) were also significantly associated with outcome. Given the large number of predictors we wanted to explore and only 73 patients, we were concerned the model may be overfitting the data. As a sensitivity analysis, we removed all nonsignificant predictors from the model, but this had no important effect on either the regression coefficients or statistical significance.

The interaction term between preoperative proportional GFR and nephrometry score was not statistically significant ($P = 0.6$). There was, therefore, no evidence of a synergistic effect on postoperative proportional GFR. There was also no significant interaction effect between preoperative

TABLE 1. PATIENT, TUMOR, AND SURGICAL CHARACTERISTICS

	Overall	Institution A	Institution B
N	73	38	35
Age at surgery (years)	58 (52, 65)	58 (49, 64)	60 (52, 67)
Male	35 (48%)	21 (55%)	14 (40%)
Patient race			
Asian	3 (4%)	3 (8%)	0 (0%)
Black	17 (23%)	2 (5%)	15 (43%)
Hispanic	15 (21%)	0 (0%)	15 (43%)
White	38 (52%)	33 (87%)	5 (14%)
Body mass index (kg/m ²)	30 (26, 34)	28 (26, 34)	32 (26, 36)
ASA score (3 and 4)	33 (45%)	19 (50%)	14 (40%)
Preoperative proportional GFR (mL/min/1.73 m ²)	34 (28, 42)	32 (27, 39)	37 (29, 48)
Nephrometry score	7 (6, 9)	8 (6, 9)	7 (5, 8)
Pathologic stage $>T_2$	2 (3%)	2 (5%)	0 (0%)
Ischemia time (min)	24 (19, 30)	25 (19, 34)	24 (20, 30)
Estimated blood loss (mL)	100 (50, 200)	150 (100, 250)	50 (50, 125)
Robotic approach	36 (49%)	25 (66%)	11 (31%)

All values presented are median (interquartile range) or frequency (percent).

ASA = American Society of Anesthesiologists; GFR = glomerular filtration rate.

TABLE 2. MULTIVARIABLE REGRESSION ANALYSES OF FACTORS PREDICTIVE OF CHANGE IN PROPORTIONAL GLOMERULAR FILTRATION RATE IN THE OPERATED KIDNEY AFTER PARTIAL NEPHRECTOMY AMONG ALL PATIENTS

Predictive factors	Estimate*	95% CI	P value
Preoperative proportional GFR per 10 mL/min/1.73 m ²	5.93	3.88, 7.97	<0.0005
ASA score (3 and 4)	-1.49	-5.98, 3.00	0.5
Age per 10 years	-0.09	-2.20, 2.02	0.9
Body mass index (kg/m ²)	-0.13	-0.45, 0.19	0.4
Estimated blood loss per 10 mL	-0.15	-0.29, -0.01	0.04
Ischemia time per 10 minutes	-1.80	-3.48, -0.11	0.04
White race	0.44	-3.74, 4.62	0.8
Robotic approach	8.67	4.50, 12.80	<0.0005
Nephrometry score	-0.15	-1.22, 0.92	0.8

*The estimates give the change in postoperative proportional GFR (mL/min/1.73 m²) for a 1 unit increase in the predictor.
CI=confidence interval; GFR=glomerular filtration rate; ASA=American Society of Anesthesiologists.

proportional GFR and ischemia time ($P=0.7$). Patients with low preoperative GFR in the operated kidney were not more sensitive to ischemia time in this analysis.

Given the large difference in rate of robot-assisted surgery between the two study sites, it seemed plausible that the association between robot-assisted surgery and outcome may reflect differences between institutions rather than surgical approaches. To examine this question, we conducted a sensitivity analysis by adding institution to the model as a covariate. Institution was not found to be significant ($P=0.1$), and the estimate for the effect of robot-assisted surgery was not importantly affected ($\beta=7.84$, 95% CI: 3.59, 12.10, $P<0.0005$). We are, therefore, confident that the association between robotic approach and postoperative proportional GFR was not simply from an institutional effect.

To assess if tumor size is predictive of postoperative proportional GFR, we conducted a sensitivity analyses and replaced nephrometry score with tumor size in the model. Tumor size was a significant predictor of postoperative GFR on multivariable analyses ($\beta=-1.36$, 95% CI: -2.57, -0.15, $P=0.028$). Tumor size, however, did not affect the significance of preoperative proportional GFR and procedure approach. The regression coefficients and statistical significance of preoperative proportional GFR and procedure approach were not importantly affected after adjusting for tumor size ($\beta=5.93$, $P<0.001$ and $\beta=8.60$, $P<0.0001$, respectively).

With respect to our secondary aim, the proportion of variance explained by ischemia time was slightly higher for the change in GFR in the operated kidney (11%) than the change in GFR in both kidneys (6%), although the difference was not statistically significant ($P=0.3$). Given the relatively wide confidence interval (95% CI, -4% to 15%), however, it may be that larger numbers of patients are required to test this hypothesis adequately.

Discussion

Accumulating evidence supports the benefit of partial nephrectomy, regardless of approach, for clinically localized tumors for both cancer specific and overall survival.^{1,4,5} The understanding of increased risk of chronic kidney disease (CKD) with radical nephrectomy as well as recent data highlighting the association between CKD and cardiovascular morbidity and mortality have led to the desire to preserve as much normal renal parenchyma as possible.⁶

Several factors are thought to impact postoperative renal function, including patient-related factors such as age, comorbidities, and preoperative renal function.⁷ Other factors include intrinsic tumor characteristics such as tumor size and location, the categorization of which can be standardized using validated scoring systems such as the R.E.N.A.L. nephrometry score.³ Finally, surgical factors including surgical approach, blood loss, volume of normal resected renal parenchyma, and most importantly, renal ischemia (generally warm ischemia in most minimally invasive series) have been shown to impact postoperative renal function.^{2,8,9}

Despite the well-documented factors impacting postoperative renal function, several important shortcomings remain. Historically, renal function was assessed by measuring serum creatinine, a crude method that often used arbitrary cutoffs such as 1.5 or 2.0 mg/dL and vastly underestimated renal functional decline. A growing awareness among the urologic community of better mechanisms for defining GFR, such as the Modification of Diet in Renal Disease (MDRD) equation and, more recently, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, helped to better measure the impact of treatment. Nevertheless, even the most sophisticated formulas only provide information on overall renal function, factoring in the compensation of the non-operated kidney.

This limits our ability to understand the impact the above-mentioned risk factors have on individual renal GFR or proportional GFR. This becomes critical when determining the best surgical approach for a suspicious renal mass, which includes balancing the value of renal preservation with the increased risk of complications associated with nephron-sparing and other minimally invasive surgery.¹⁰ The best decision-making model should incorporate as many of these factors as possible and determine their individual and multivariable effect on proportional GFR. Several institutions now use renal scintigraphy (nuclear renal scans) both before and after surgery to best determine the impact on the individual renal unit.

DTPA and MAG3 are radionuclide agents that may be more accurate markers of renal damage after partial nephrectomy than serum creatinine or the MDRD or CKD-EPI equations.¹¹ Radionuclide scans eliminate the need for 24-hour urine collection—as well as concerns for possible confounders in the urinary constituents—while conveniently providing an ability to estimate the GFR of individual renal

units. Because the DTPA or MAG3 scans provide comparable absolute estimates of each renal unit function in GFR instead of relative percent of the two kidneys, each kidney with the tumor may serve as a control for itself, for comparison after excision for future analysis. Thus, repeating the scan during the postoperative period can help discriminate immediate postoperative effects from any other possible confounders affecting renal function in the long term.

Several small, recent studies have analyzed the association between many of these factors and renal functional changes using GFR in combination with relative function on radio-nuclide scans. Song and associates¹² used DTPA scans to assess individual renal function before and after both open and laparoscopic partial nephrectomy. In all 117 patients, GFR uniformly decreased after surgery. The degree of GFR reduction, however, was similar regardless of surgical approach (29.9% *vs* 33.2%, respectively). The authors found on multivariate analysis that renal volume reduction was the most significant, independent prognosticator for GFR reduction, followed by polar location of the tumor (upper *vs* midpolar-lower pole) and increasing age. Interestingly, the authors found that increases in warm ischemia time (WIT) did not significantly affect GFR.

Choi and colleagues¹³ evaluated the association between WIT and percent change in GFR using 99mTc-DTPA at two postoperative points (3 and 12 months). They examined whether a kidney damaged by warm ischemia during laparoscopic and robot-assisted partial nephrectomy could recover over time. The authors reported that the GFR of the affected kidney was consistently and significantly reduced at 3 and 12 months postoperatively in patients with a WIT greater than 28 minutes. In contrast, no significant GFR change was seen in patients with a WIT of 28 minutes or less. On multivariate analysis, WIT was a strong independent predictor of GFR reduction even 12 months after surgery, and no other parameters were significantly associated with functional reduction at 12 months after surgery.

Porpiglia and coworkers¹⁴ used MAG3 renal scans to assess kidney damage in 18 patients with a normal contralateral kidney 1 year after laparoscopic partial nephrectomy.¹⁴ WIT for these patients ranged between 31 and 60 minutes. The authors reported that the operated kidney showed mild recovery 1 year after surgery, even after a prolonged WIT, despite an initial significant decrease of approximately 11% in the operated kidney's contribution to overall function. This was followed by constant and progressive recovery, but the differential ratio never reached the preoperative value (42.8% at 1 year *vs* 48.3% before surgery).

The authors recently reported on a follow-up study of the long-term effect of WIT on renal function.¹⁵ The study included only patients with tumors <4 cm, estimated GFR (eGFR) >60 mL/min/1.73 m², with split renal function (SRF) of the affected kidney in the 45% to 55% range. Measures of renal function were evaluated at 3 months and 1 year and then yearly after surgery. Renal scans were conducted preoperatively, at the third and twelfth postoperative months, and then yearly for a minimum of 4 years. The authors found that serum creatinine and eGFR did not significantly change after surgery, whereas measurements derived from MAG3 renal scans (SRF and effective renal plasma flow [ERPF]) were significantly worse as early as 3 months after surgery and remained stable during the subsequent four years after sur-

gery. The authors found that duration of warm ischemia was correlated with decline in renal function as measured by MAG3 renal scan. Age, body mass index, tumor size, R.E.N.A.L. nephrometry score, peritumoral healthy tissue thickness, and comorbidities measured by the Charlson Comorbidity Index were not correlated with decline in renal function. The authors suggested that these results confirmed that serum creatinine and derived measures have low sensitivity for evaluating kidney damage in patients presenting normal or moderately reduced kidney function (CKD stage I/II) at follow-up. In contrast, by using SRF and ERPF as estimated by renal scan, loss of renal function was recorded at the third post-operative month with respect to baseline. This loss remained stable over time as confirmed by follow-up measurements of SRF and ERPF.

The studies using renal scintigraphy to facilitate determination of proportional GFR have been small, with very few using multivariable modeling and standardized tumor assessments such as nephrometry scores. Our study of 73 patients enabled us to do so. We found that higher preoperative proportional GFR ($\beta=5.93$, 95% CI: 3.88, 7.97, $P<0.0005$) and robotic approach ($\beta=8.67$, 95% CI: 4.50, 12.80, $P<0.0005$) were strongly associated with improved proportional GFR, while longer ischemia time ($\beta=-1.80$, 95% CI: -3.48, -0.11, $P=0.04$) and estimated blood loss ($\beta=-1.15$, 95% CI: -0.29, -0.01, $P=0.04$) also led to worse function. We did not see an interaction between decline in proportional GFR and tumor complexity as determined by nephrometry scores ($P=0.6$). We also found no significant interaction effect between preoperative proportional GFR and ischemia time ($P=0.7$), suggesting that patients with low preoperative GFR are not more sensitive to ischemia time.

We were unable to achieve our secondary aim—to determine whether proportional GFR better captures the effects of ischemia time on the operated kidney when compared with conventional calculations. We found that proportion of variance explained by ischemia time was slightly higher for the change in GFR in the operated kidney (11%) than the change in GFR in both kidneys (6%) ($P=0.3$). Given the relatively wide CI (95% CI, -4% to 15%) and small sample sizes, a larger number of patients is needed to test this hypothesis adequately.

We believe that our study furthers the understanding of the interplay between patient, tumor, and surgical factors in renal function loss after partial nephrectomy and suggests that renal scintigraphy provides the best available marker to gauge the iatrogenic change in proportional GFR in the affected kidney resulting from renal surgical interventions. Larger multi-institutional studies can help improve these models further, with the intention to more accurately predict the impact of our surgery on individual renal function, and the goal of optimizing renal functional outcomes with appropriately applied therapies and interventions.

One limitation of our study is that different agents were used for renal scintigraphy, although this is not considered a problem for comparative purposes (according to personal communication with several nuclear medicine specialists). Further limitations include relatively small sample size, and time for postoperative renal scan. Porpiglia and associates,¹⁵ however, did not find significant differences in SRF recovery following the 3-month renal scan (in a series with multiple postoperative scans extending out to 4 years).

Conclusion

Lower preoperative proportional GFR, longer ischemia times, and higher blood loss all negatively impact postoperative proportional GFR while tumor complexity does not. Larger studies are needed to determine whether renal scintigraphy is a more accurate method of measuring the impact of the ischemia time on postoperative proportional GFR, which will help determine a more personalized approach to the management of suspicious renal masses.

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Disclosure Statement

No competing financial interests exist.

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Address correspondence to:

A. Ari Hakimi, MD

Sidney Kimmel Center for Prostate and Urologic Cancers

Memorial Sloan-Kettering Cancer Center

353 East 68th Street

New York, NY 10065

E-mail: hakimia@mskcc.org

Abbreviations Used

CKD = chronic kidney disease
 CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration
 DTPA = diethylene triamine pentaacetic acid
 eGFR = estimated glomerular filtration rate
 ERPF = effective renal plasma flow
 GFR = glomerular filtration rate
 IQR = interquartile range
 MAG3 = mercaptoacetyltriglycine 3
 MDRD = Modification of Diet in Renal Disease
 R.E.N.A.L. = radius; exophytic/endophytic; nearness; anterior/posterior; location
 SRF = split renal function
 WIT = warm ischemia time