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ASSESSING RENAL FUNCTION FOLLOWING PARTIAL NEPHRECTOMY USING RENAL NUCLEAR SCINTIGRAPHY and eGFR

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Keywords

partial nephrectomy; renal scintigraphy; renal function; renal tumor

INTRODUCTION

Nephron-sparing surgery has emerged as the preferred standard of treatment for patients with small renal tumors, providing curative oncologic results while intending optimal preservation of renal function, irrespective of approach.¹⁻³ Despite the best of intentions and the most meticulous technique, however, nephron-sparing surgery often causes iatrogenic renal injury. Up to one-third of patients with a baseline estimated glomerular filtration rate (eGFR) of greater than 60 mL/min/1.73m² will progress to stage III chronic kidney disease after this procedure.⁴ The degree of change in postoperative renal function is based on a number of variables that can be broadly characterized as either modifiable or immutable. Much of what can be technically controlled relates to ischemic renal injury and the quantity of resected functional renal tissue.⁵ In order to limit the effects of renal ischemia, appropriate methods of measuring postoperative function of the affected kidney are needed.

The traditional model for quantifying kidney injury in the postoperative setting has relied on serial measurements of serum creatinine to calculate an eGFR. This model has several limitations. Serum creatinine levels are often inconsistent, dependent not only on renal function but also on overall plasma volume and the rate of creatinine biosynthesis.⁶ Further, pooled samples obtained from either serology or excreted urinary biomarkers cannot account for the compensatory influence of the contralateral kidney. In the setting of radical nephrectomy, the remaining kidney has been shown to compensate for the loss of renal units by increasing renal blood flow. This results in hyperfiltration, which is responsible for the observed 25% decrease in eGFR that is in contradistinction to the 50% drop that would be expected if the number of functional nephrons were divided in half. These changes are durable and may still be seen 10 years after surgery.^{7,8}

Dimercaptosuccinic acid (^{99m}Tc-DMSA) renal scintigraphy is a valuable tool for measuring differential kidney function.⁹ It is a safe, noninvasive test that quantifies cortical function by

detecting selective renal parenchymal perfusion.¹⁰ The utility of nuclear scans for predicting postoperative renal insufficiency of the affected kidney after radical and partial nephrectomy has previously been demonstrated.¹¹⁻¹⁴ Nuclear scans can indicate damage to the affected kidney that is not reflected in serum creatinine measurements and eGFR calculations.¹⁴ We believe long ischemia time and large tumor size predict for renal damage that will impact postoperative kidney function. A useful measure of kidney function should be sensitive to nephrogenic injury induced by these variables. We hypothesized that a combination of eGFR and renal scintigraphy would be more strongly associated with ischemia time and tumor size than eGFR alone.

MATERIAL AND METHODS

Patients

We identified 32 patients who underwent partial nephrectomy with preoperative and postoperative ^{99m}Tc-DMSA renal scans. All cases were performed using a minimally invasive surgical approach (laparoscopy or robotic-assisted laparoscopy) by the same surgeon (JC) at a single institution between 2007 and 2010, representing 20% of the series of 174 cases similarly treated. Median time from surgery for preoperative and postoperative renal scans was 9.5 days (interquartile range [IQR] 1–132) and 200 days (IQR 91–415) days, respectively. We used the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula to calculate total eGFR for each patient.¹⁵ Renal scan data was used to calculate proportional eGFR in the involved kidney as a product of the percent function of the operated kidney and total eGFR.

Surgical Technique

All surgical procedures were performed in a similar manner, and approach (transabdominal or retroperitoneal) was based on tumor location. A vascular bulldog clamp was used for complete vascular occlusion of the renal artery(s) to provide a bloodless operative field. Intraoperative ultrasound was used in all cases. Tumors were excised using a cold scissor. Any intraoperative pelvicaliceal injury was reconstructed with absorbable suture. Steps for hemostasis included suturing of cut end vessels with 3-0 absorbable sutures and use of thrombin-collagen coagulant agents secured with 0 polyglactin sutures. After removal of the vascular clamp, kidneys were observed for 20 minutes to confirm hemostasis and Doppler sonography was used to verify pulsatile flow within the central renal vasculature.

Statistical Methods

Percent function of each kidney was obtained from renal scan studies. Clamp time and tumor size were assumed to cause kidney damage. To assess whether percent function of the involved kidney and proportional eGFR are sensitive markers of renal damage, univariate linear regression models were created with clamp time and tumor size as independent variables. For comparison, two additional univariate linear regression models were included, with total postoperative eGFR as the outcome and clamp time and tumor size as the independent variables. If clamp time and tumor size were significantly associated with an outcome, that outcome was interpreted to be a sensitive marker of renal injury. Additionally, if an outcome was associated with larger R-squared values compared to the other outcomes, it was interpreted as being a more sensitive marker. The errors from the linear regression models were assessed for normality using the Shapiro-Wilk test. All analyses were conducted using Stata statistical software (version 11.1; Stata Corp, College Station, TX).

RESULTS

Characteristics of the patient cohort are summarized in Table 1. Nineteen patients (59%) were male, and 26 (81%) were white. For the involved kidney, preoperative mean eGFR and percent function were 31 mL/min/m² and 50%, respectively; postoperative eGFR and percent function were 27 mL/min/m² and 44%, respectively (Table 2). For the uninvolved kidney, preoperative mean eGFR was 31 mL/min/m² and increased to 35 mL/min/m² postoperatively. The results from the univariate linear regression models are shown in Table 3. All regression models met the normality assumption ($P > .05$) except the tumor size and percent function model ($P = .01$), where the non-normality was due to one outlying value ($P = .7$ without outlying observation). The main results of the model were not importantly changed when the observation was omitted from the analysis (eg, R^2 changed by .025, slope coefficient by .1, and the statistical significance of the model did not change), and therefore the final model utilized all observations. Decreased clamping time was significantly associated with increased postoperative percent function, postoperative involved kidney eGFR, and postoperative total eGFR. Decreased tumor size was significantly associated with increased postoperative proportional eGFR only. Additionally, proportional eGFR was the only outcome significantly associated with both tumor size and clamp time, indicating it may be a better indicator of renal damage than percent function and total eGFR (Fig. 1A-1B). These same trends are seen with respect to the R-squared: clamp time and tumor size explain more of the variation in proportional eGFR ($R^2 = .39$ and $R^2 = .17$, respectively), compared to percent function and total eGFR. These results suggest that proportional eGFR is a more sensitive marker of renal damage because it is associated with larger R-squared values and is significantly related to both clamp time and tumor size.

COMMENT

Acute kidney injury is a serious complication of partial nephrectomy. In this study, we use renal scintigraphy to identify risk factors for renal decline in patients undergoing partial nephrectomy. Our data are in concordance with a recent study by Tachikake et al, which concluded that increased intraoperative ischemic time during partial nephrectomy leads to kidney damage detectable by ^{99m}Tc-DMSA renal scintigraphy.¹⁴

In its most severe form, renal failure is associated with a 50% mortality rate in critically ill patients,¹⁶ but even mild deterioration in kidney function is associated with poor outcomes.^{17,18} Patients with kidney disease carry an increased risk for anemia, coagulopathy, electrolyte abnormalities, and infection.¹⁹ If they progress to end-stage renal disease requiring hemodialysis, they face a 20% mortality rate.²⁰ Inadequate kidney function also excludes patients with metastatic renal cell carcinoma from undergoing treatment with systemic immunomodulation therapy, including interferon-alpha, interleukin-2, and tyrosine-kinase inhibitors.^{21,22}

One problem with using eGFR to assess renal damage is that damage to one kidney can be compensated for by increasing function of the opposing kidney. This complicates estimates of damage to the operated kidney. In our study we used a noninvasive test, ^{99m}Tc-DMSA renal scintigraphy, to distinguish individual kidney function. Preoperative and postoperative ^{99m}Tc-DMSA scanning allows for proper identification of changes in differential renal function if damage to the operated kidney is present. Clamp time and tumor size are well-identified factors that effect renal damage. Using eGFR alone may mask the true damage caused by a partial nephrectomy. In our study we individualized each kidney by calculating the product of the percent function based on ^{99m}Tc-DMSA renal scintigraphy with the overall eGFR to identify the percent function of either kidney. This calculation allows for the quantification of function of each kidney as an individual entity. In

the univariate analysis, proportional eGFR was a more sensitive marker of renal damage as measured by clamp time and tumor size when compared to total eGFR.

Percent function and proportional eGFR typically decline after partial nephrectomy, although this was not the case with all patients in our study; several had an increase in percent function of the operated kidney. We hypothesize this may be due to the local toxic effect that a renal tumor has on the ipsilateral kidney.

The need for accurate detection of renal failure has lead to investigation into biochemical pathways involved in nephrogenic injury. There are currently many novel biomarkers showing promise in uncovering renal injury, including neutrophil gelatinase-associated lipocalin (NGAL), interleukin 18 (IL-18), cystatin C, and kidney injury molecule 1 (KIM-1).²³ It is unknown at this time whether these markers could play a clinically relevant role. Until a reliable marker is found, we must use our proven tools to the fullest of their capabilities in identifying renal damage secondary to surgical intervention. The data suggest that proportional eGFR may be an effective approach for measuring renal function in the postoperative setting.

Our study is limited by its retrospective design, the small cohort size, and the limiting of selection criteria to only those patients undergoing laparoscopic partial nephrectomy. Future large-scale prospective studies will be necessary to validate our findings of the feasibility of detecting kidney function separately for the affected and unaffected kidney.

CONCLUSIONS

This is the largest study to date comparing total eGFR to proportional eGFR derived from differential renal scans to assess renal function after partial nephrectomy and the impact of surgical variables. Our results suggest proportional eGFR has a stronger association with putative factors of renal dysfunction after partial nephrectomy, including clamp time and tumor size, compared to total eGFR, indicating it could be a better measure of renal function after partial nephrectomy.

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Figure 1. Plot analyses of proportional eGFR per centimeter of tumor size (1A) and minute of clamp time (1B).

Table 1

Patient characteristics (n = 32)

Characteristic	Value
Age at surgery (years)	58 (55, 69)
Male	19 (59%)
Patient race	
Asian	3 (9%)
Black	3 (9%)
White	26 (81%)
Clamp time (min)	27 (19, 36)
Preoperative eGFR	63 (52, 72)
Tumor size (cm)	3 (2, 4)
Estimated blood loss (cc)	138 (100, 300)
Pathologic stage >T2	2 (6%)

eGFR, estimated glomerular filtration rate.

All values are median (IQR) or frequency (proportion).

Table 2**Renal function**

	Mean (SD)
Preoperative renal function	
Percent function of involved kidney	50% (4.8)
Total eGFR	62 (11.2)
GFR of involved kidney	31 (6.4)
GFR of noninvolved kidney	31 (6.2)
Postoperative renal function	
Percent function of involved kidney	44% (9.0)
Total GFR	62 (14.0)
GFR of involved kidney	27 (9.0)
GFR of noninvolved kidney	35 (8.3)

SD, standard deviation; eGFR, estimated glomerular filtration rate.

eGFR calculated at mL/min/m².

Table 3

Univariate linear regression results with postoperative % function and eGFR of involved kidney as outcomes

	% Function		Involved kidney eGFR		Total GFR	
	Coefficient(95% CI)	<i>P value</i>	Coefficient(95% CI)	<i>P value</i>	Coefficient(95% CI)	<i>P value</i>
Clamp time per 10 min	-3.08 (-4.73, -1.42) $R^2 = .33$	.0007	-3.08 (-4.68, -1.49) $R^2 = .39$	.0005	-3.07 (-5.93, -.202) $R^2 = .16$	.037
Tumor size (cm)	-1.48 (-3.51, .543) $R^2 = .07$	.15	-2.24 (-4.21, -.273) $R^2 = .17$	.027	-2.54 (-5.74, .652) $R^2 = .09$	.11

eGFR, estimated glomerular filtration rate