Preoperative Renal Volume: A Surrogate Measure for Radical Nephrectomy-Induced Chronic Kidney Disease

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Abstract

Objectives: Surgically induced chronic kidney disease (CKD) has been found to have less impact on survival as well as function when compared to medical causes for CKD. The aim of this study is to evaluate whether preoperative remaining kidney volume correlates with renal function after nephrectomy, which represents an individual's renal reserve before surgically induced CKD.

Methods: A retrospective review of 75 consecutive patients (29.3% females) who underwent radical nephrectomy (RN) (2000–2010) was performed. Normal side kidney parenchyma, excluding renal vessels and central sinus fat, was manually outlined in each transverse slice of CT image and multiplied by slice thickness to calculate volume. Estimated glomerular filtration rate (eGFR) was determined using the Modification of Diet in Renal Disease equation. CKD is defined as eGFR <60 mL/min/1.73 m².

Results: Mean preoperative normal kidney parenchymal volume (mean age 55 [SD 13] years) is 150.7 (SD 36.4) mL. Over median follow-up of 36 months postsurgery, progression to CKD occurred in 42.6% (*n* = 32) of patients. On multivariable analysis, preoperative eGFR and preoperative renal volume <144 mL are independent predictors for postoperative CKD. On Kaplan–Meier analysis, median time to reach CKD postnephrectomy is 12.7 (range 0.03–43.66) months for renal volume <144 mL but not achieved if renal volume is >144 mL.

Conclusions: Normal kidney parenchymal volume and preoperative eGFR are independent predictive factors for postoperative CKD after RN and may represent renal reserve for both surgically and medically induced CKD, respectively. Preoperative remaining kidney volume may be an adjunct representation of renal reserve postsurgery and predict later renal function decline due to perioperative loss of nephrons.

Introduction

CHRONIC KIDNEY DISEASE (CKD) is currently defined as the glomerular filtration rate (GFR) <60 mL/min/1.73 m² for >90 days.¹ Go et al. reported that in a population study of more than 1 million individuals, CKD was associated with increased risk of death, cardiovascular event, and hospitalizations.² In addition to oncologic outcomes, CKD and its implications are now increasingly emphasized in the current era of renal function-centered care for kidney cancer patients. For example, among patients undergoing surgical treatment for kidney cancer, between 20% and 30% already have CKD before surgery.^{3,4} Although the rates of kidney surgery have increased concurrently with the rising incidence of kidney cancer over the last two decades, all-cause mortality rates

from patients with kidney cancer have not decreased. Up to one third of patients older than 70 years who are treated for kidney tumors have been found to die of other causes.⁵ Such “treatment disconnect” may be due to the potential of surgical treatment by radical nephrectomy (RN) increasing postoperative CKD morbidity, which in turn increases associated competing causes of death.

Recent reports have distinguished medical CKD (CKD-M) from surgical CKD (CKD-S). CKD-M is caused by medical renal diseases and places patients at a higher risk of progressive renal decline compared with CKD-S, which is caused by an acute insult such as surgical removal of functioning nephrons (nephrectomy or partial nephrectomy).⁶ CKD-S has been proposed to be a separate entity that impacts less on survival and long-term function in patients without

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CKD-M,⁶ but compounds the impact in patients with CKD-M already (CKD-M/S).⁷ These findings suggest that the definition and classification of CKD based solely on GFR may not accurately reflect the extent of kidney disease in patients developing CKD-S. As CKD-S results in reduced complement of nephrons, kidney volume would theoretically be an ideal anatomical representation of kidney reserve. It could better reflect the tolerability of a patient to developing CKD after the surgical insult of RN. For a patient undergoing RN, the normal side kidney before surgery would represent his or her renal reserve. Hence, the aim of this study was to measure preoperative normal kidney volume (kidney without cancer) for patients with no preoperative CKD undergoing RN and to study its association with kidney function pre- and postsurgery.

Methods

Study population

A total of 95 patients who underwent RN between September 2000 and August 2010 at our institution were evaluated for recruitment into this study. Of the patients who underwent RN, 20 (21.0%) already had CKD or end-stage kidney disease before operation and were excluded from the study. The remaining RN patients ($n=75$) were included in this analysis.

Patients undergoing RN were recorded in our kidney cancer database in accordance with the institutional review board guidelines. RN was performed by either laparoscopic or open approach, and selection was based on clinical assessments. Preoperative investigations included medical history, physical examination, laboratory studies, including serum creatinine level, and preoperative contrast-enhanced computed tomographic (CT) scans. Investigations were performed within a month before surgery. After surgery, patients were followed up at 4–6 weeks and then every 4–6 months for 2 years and annually thereafter.

At each clinical visit, all patients had a complete history and physical examination. Laboratory tests done included serum electrolytes and creatinine ($\mu\text{mol/L}$). The creatinine measurement method in our hospital laboratory was standardized to isotope dilution mass spectrometry. All preoperative, intraoperative, and postoperative data were collected retrospectively from all available computerized and medical records. The Modification of Diet in Renal Disease (MDRD) formula ($\text{GFR} [\text{mL/min/1.73 m}^2] = 186 \times [\text{serum creatinine}]^{-1.154} \times [\text{Age}]^{-0.203} \times [0.742 \text{ if female}] \times [1.212 \text{ if African American}]$) was used to calculate the estimated glomerular filtration rate (eGFR) preoperatively and at each of the postoperative clinical visits for all eGFR measurements in this study.⁸ eGFR was calculated from the NKF web-based calculator at www.kidney.org/professionals/KDOQI/gfr_calculator.cfm. The MDRD equation has also been recently validated by our institution in our local multiethnic Asian population.⁹ Sensitivity and specificity of MDRD eGFR $<60 \text{ mL/min/1.73 m}^2$ for the measured GFR $<60 \text{ mL/min/1.73 m}^2$ by Technescan DTPA nuclear scans were 90.5% and 78.4%, respectively. Positive and negative predictive values for eGFR $<60 \text{ mL/min/1.73 m}^2$ for the MDRD equation were 0.9 and 0.79, respectively. This was deemed adequate for our purposes of screening for CKD stage 3 after RN.

CKD was defined as eGFR $<60 \text{ mL/min/1.73 m}^2$ based on the two most recent serum creatinine levels, which were taken at least 3 months apart, as per KDOQI guidelines.¹ The

time to CKD was calculated in days from the time of nephrectomy to the time when the first eGFR measurement dropped below $60 \text{ mL/min/1.73 m}^2$.

Kidney volume measurements

Using contrast-enhanced CT scans performed preoperatively for all 75 patients, normal kidney volume (contralateral to the side with cancer) was measured using an adapted technique described for liver volumetry with propriety tissue segmentation software, ImageJ (NIH).¹⁰ We have previously reported this technique of kidney volume measurement in kidney donors.¹¹ CT images were obtained in the venous phase and saved in the JPEG format. With ImageJ, the functional nephron mass in the venous phase of the CT scan was manually outlined in the transverse section by a single surgeon, excluding the renal sinus fat, cysts, blood vessels, and the pelvicaliceal system. The area of the outlined functional renal mass was multiplied by slice thickness to obtain the volume. The kidney volume of the normal side was calculated by summing all volumes within the measured boundaries.

Statistical analyses

The patients were divided into two groups according to whether they eventually developed CKD after surgery. Demographic and clinical characteristics of the patients were summarized using frequencies and percentages for categorical variables, means and standard deviations for continuous variables, which were approximately normally distributed, and median and range for continuous variables with skewed distribution. The Fisher's exact test, chi-square test, independent two-sample *t*-test, and Wilcoxon rank-sum test were used to compare baseline features and postoperative outcomes.

Bivariate associations between specific risk factors and time to reach postoperative CKD were evaluated using univariate Cox regression (for continuous variables) and log-rank test (for categorical variables). Spearman's correlation regression was used to assess the relationship between preoperative normal kidney volume and eGFR. The effect of these risk factors was quantified using the hazard ratio (HR) estimate and its associated 95% confidence interval (CI). Multivariable Cox regression analysis was further implemented to account for the joint effect of risk factors that were identified to be significant predictors of time to postoperative CKD.

The area under the receiver operating characteristic (ROC) curve was estimated for preoperative normal kidney volume (contralateral to kidney cancer side), which was identified by the Cox model to be a significant risk factor of postoperative CKD. A suitable cutoff for preoperative normal kidney volume was obtained at the optimal sensitivity and specificity of the ROC curve. The Kaplan–Meier curve for the time to postoperative CKD was plotted for each subgroup of subjects defined by this cutoff.

All statistical analyses were generated using STATA software, version 11 (StataCorp. LP), assuming a two-sided test at the conventional 0.05 level of significance.

Results

The mean age of the entire study population was 55 (SD 13) years and mean parenchymal volume of the normal kidney was

150.7 (SD 36.4) mL. Mean total renal volume of both kidneys (excluding the tumor) before surgery was 246.3 (SD 62.5) mL. Preoperative mean eGFR was 84.3 (SD 18.9) mL/min/1.73 m² using the MDRD formula. There was minimal correlation of total measured preoperative kidney volume with preoperative eGFR ($r=0.287$, $p=0.0172$) by Spearman's correlation. Clear cell renal-cell carcinoma pathology accounted for 82.7% ($n=62$) of the patients undergoing nephrectomy. Patients with clinical stage T1b cancers and above accounted for 90.7% ($n=68$) of the entire population. Thirteen patients (17.3%) had metastatic renal cell carcinoma (RCC) (N1 and/or M1) at the time of surgery, but none had received preoperative chemotherapy or immunotherapy. Over a median follow-up of 36 months, progression to CKD occurred in 42.6% ($n=32$) of patients.

Table 1 shows the clinical characteristics of the patients stratified into two groups: with or without eventual postoperative CKD. The patients without postoperative CKD were younger (mean 52 ± 13 vs 61 ± 10 years, $p=0.002$) and had a greater preoperative kidney volume (161.3 ± 37.8 vs 136.5 ± 29.4 mL, $p=0.003$) than the patients with postoperative CKD. They had significantly lower preoperative creatinine level (74.9 ± 16.5 vs 87.9 ± 11.0 $\mu\text{mol/L}$, $p<0.001$) and higher preoperative eGFR (91.4 ± 20.8 vs 75.1 ± 10.9 mL/min/1.73 m², $p<0.001$). Preoperative comorbidities, including hypertension, diabetes mellitus, and ischemic heart disease, were not significantly different

between the two groups. There were two mortality rates in the group with no CKD: one patient died from metastatic lung cancer and the other from metastatic RCC. No patient in the group with CKD died during the follow-up period. There was no difference in overall survival at the end of the study ($p=0.504$) between patients with or without postoperative CKD. As expected, those with CKD had significantly higher postoperative creatinine levels (131.7 ± 28.4 vs 82.3 ± 18.3 $\mu\text{mol/L}$, $p<0.001$) and lower nadir postoperative eGFR (50 vs 73 mL/min/1.73 m², $p<0.001$).

The remaining kidney volume is >50% of the total renal volume in 96% ($n=72$) of our study population and only three patients had remaining kidney volume <50%. When the group with CKD is compared with the group without CKD (61.0 [SD 0.2] vs 63.6 [SD 0.2]%, $p=0.36$), we found that there is no statistically significant difference between the two in terms of percentage of renal volume preserved (remaining kidney volume/total viable preoperative kidney volume%).

On univariable analysis, significant risk factors for postoperative CKD are age at surgery, gender, preoperative renal volume, creatinine levels, and eGFR (Table 2). The ratio of renal volume preserved is not a significant risk factor ($p=0.36$) for postoperative CKD. Our study consists of a small number of patients, and the results may differ if a larger number of patients are analyzed. However, on

TABLE 1. COMPARISON OF DEMOGRAPHIC AND BASELINE CLINICAL FEATURES BETWEEN PATIENTS WITH AND WITHOUT POSTNEPHRECTOMY CHRONIC KIDNEY DISEASE

Characteristics	Overall (n=75)	CKD		p-Value
		Yes (n=32)	No (n=43)	
Mean age at surgery (years, SD)	55 (13)	61 (10)	52 (13)	0.002
Gender, n (%)				0.124
Female	22 (29.3)	6 (18.7)	16 (37.2)	
Male	53 (70.7)	26 (81.3)	27 (62.8)	
Race, n (%)				0.576
Chinese	65 (86.6)	29 (90.6)	36 (83.8)	
Malay	2 (2.7)	0 (0.0)	2 (4.6)	
Indian	2 (2.7)	0 (0.0)	2 (4.6)	
Others	6 (8.0)	3 (9.4)	3 (7.0)	
Surgical approach, n (%)				0.253
Laparoscopic transperitoneal	24 (32.0)	11 (34.4)	13 (30.3)	
Laparoscopic retroperitoneal	42 (56.0)	15 (46.9)	27 (62.8)	
Anterior subcostal	5 (6.7)	4 (12.5)	1 (2.3)	
Anterior rooftop	1 (1.3)	0 (0.0)	1 (2.3)	
Flank	1 (1.3)	1 (3.1)	0 (0.0)	
Midline	2 (3.7)	1 (3.1)	1 (2.3)	
Side of surgery, n (%)				0.103
Left	37 (49.3)	12 (37.5)	25 (58.1)	
Right	38 (50.7)	20 (62.5)	18 (41.9)	
Diabetes, n (%)	11 (16.4)	6 (21.4)	5 (12.8)	0.505
Hypertension, n (%)	32 (53.3)	17 (54.4)	15 (44.1)	0.123
Ischemic heart disease, n (%)	8 (15.1)	4 (17.4)	4 (13.3)	0.715
Normal kidney volume (mL, SD)	150.7 (36.4)	136.5 (29.4)	161.3 (37.8)	0.003
Normal kidney volume, n (%)				0.020
≥ 144 mL	38 (50.7)	11 (34.4)	27 (62.8)	
<144 mL	37 (49.3)	21 (65.6)	16 (37.2)	
Mean preoperative Cr ($\mu\text{mol/L}$, SD)	80.6 (15.7)	87.9 (11.0)	74.9 (16.5)	<0.001
Mean preoperative eGFR (mL/min/1.73 m ² , SD)	84.3 (18.9)	75.1 (10.9)	91.4 (20.8)	<0.001
Mean% renal volume preserved (SD)	62.5 (0.1)	61.0 (0.2)	63.6 (0.2)	0.36

CKD=chronic kidney disease; SD=standard deviation.

TABLE 2. EFFECT OF INDIVIDUAL RISK FACTORS ON TIME TO POSTNEPHRECTOMY CHRONIC KIDNEY DISEASE

<i>Risk factor</i>	<i>Number with postoperative CKD</i>	<i>Crude HR (95% CI)</i>	<i>p-Value</i>
Age at surgery (year)	—	1.05 (1.02–1.09)	0.002
Gender			
Female	6	1.00	
Male	26	2.80 (1.38–5.69)	0.016
Race			0.242
Chinese	29	1.00	
Malay	0	—	0.325
Indian	0	—	0.377
Others	3	1.64 (0.38–7.10)	0.405
Surgical approach			0.719
Laparoscopic transperitoneal	11	1.00	
Laparoscopic retroperitoneal	15	0.73 (0.33–1.64)	0.428
Anterior subcostal	4	1.36 (0.39–4.69)	0.596
Anterior rooftop	0	—	0.668
Flank	1	2.33 (0.12–45.85)	0.402
Midline	1	0.84 (0.12–5.67)	0.865
Side of surgery			
Left	12	1.00	—
Right	20	1.58 (0.79–3.16)	0.204
Diabetes	6	1.98 (0.64–6.16)	0.126
Hypertension	17	2.06 (0.95–4.44)	0.073
Ischemic heart disease	4	1.70 (0.46–6.29)	0.320
Normal kidney volume			
≥144 mL	11	1.00	—
<144 mL	21	2.77 (1.37–5.60)	0.004
Preoperative Cr ($\mu\text{mol/L}$)	—	1.04 (1.02–1.07)	0.001
Preoperative eGFR (mL/min/1.73 m^2)	—	0.96 (0.93–0.98)	0.002

HR=hazard ratio; CI=confidence interval.

multivariable Cox regression analysis, only preoperative normal renal volume (adjusted HR=2.41, 95% CI 1.14–5.09, $p=0.02$) and eGFR (adjusted HR=0.96, 95% CI 0.943–0.99, $p=0.008$) remained as independent risk factors predictive for postoperative CKD (Table 3).

On the basis of the ROC analysis, preoperative normal kidney volume individually yielded an area under the curve of 0.69 (95% CI 0.56–0.81), again suggesting its significant impact in predicting postoperative CKD (Fig. 1). An optimal sensitivity of 62.5% (95% CI 43.7%–78.9%) and specificity of 62.8% (95% CI 46.7%–77.0%) were achieved with a cutoff value of 144 mL for preoperative normal kidney volume.

Median follow-up time was 36 (range 13–51 months) months. The Kaplan–Meier curves showing the relationship between preoperative kidney volume at this cutoff and time to postoperative CKD suggest a lower survival probability for

preoperative normal kidney volume <144 mL and higher survival probability for preoperative normal kidney volume ≥144 mL (HR = 2.77; 95% CI 1.37–5.60; log rank $p=0.004$) (Fig. 2). The median time to reach CKD after nephrectomy was 12.7 (range 0.03–43.66) months for renal volume <144 mL, and for patients with renal volume >144 mL, the median time was not achieved.

For 54.7% ($n=41$) of the patients, postoperative follow-up scans from 6 months to 1 year (the time period during which compensatory hypertrophy is said to occur) after RN were

TABLE 3. ASSOCIATION BETWEEN KIDNEY VOLUME AND TIME TO POSTNEPHRECTOMY CHRONIC KIDNEY DISEASE BY MULTIVARIABLE COX PROPORTIONAL HAZARD REGRESSION

<i>Risk factor</i>	<i>Adjusted HR (95% CI)</i>	<i>p-Value</i>
Preoperative eGFR (mL/min/1.73 m^2)	0.96 (0.94–0.99)	0.008
Normal kidney volume		
≥144 mL	1.00	—
<144 mL	2.41 (1.14–5.09)	0.021

FIG. 1. Area under receiver operating characteristic (ROC) with normal kidney volume as predictor.

FIG. 2. Kaplan–Meier survival curve comparing postnephrectomy chronic kidney disease (CKD)-free survival between patients with normal kidney volume <144 mL versus ≥144 mL.

available and there was an average decrease in the size of the remaining kidney from 150.7 mL (SD 36.4) to 137.0 mL (SD 53.6), $p=0.11$. In this cohort, only 29.3% of the patients developed compensatory hypertrophy.

Discussion

In this study, preoperative volume of the normal side was an independent predictive factor for the development of CKD after surgery (CKD-S or CKD-M/S). Patients with preoperative normal kidney volume of <144 mL had a hazard risk of nearly three times that of patients with kidney volume >144 mL to develop CKD-S or CKD-M/S, even though the distribution of comorbidities was the same in both groups.

With recent reports of the difference in the implications of CKD-M and CKD-S, residual kidney volume after nephrectomy may be a better representation of renal reserve and predict later renal function decline due to perioperative loss of nephrons. This study has shown that preoperative eGFR and normal kidney volume were both independent predictive factors of postoperative CKD on multivariable analysis. Age, gender, and preoperative creatinine levels were significant risk factors on univariable analysis, but as they were parameters used to compute eGFR in the MDRD formula, it was expected that they were no longer significant on multivariable analysis. Preoperative eGFR by the MDRD formula, therefore, reflects nephron quality at the time of surgery, accounting for the negative impact of male gender and increasing age and comorbidities. The importance of preoperative eGFR on predicting surgical outcomes, such as postoperative renal function and even all-cause mortality rates, has been verified by other studies.⁶ However, it is increasingly known that using equations to estimate GFR based on serum creatinine alone may be suboptimal to predict or evaluate postsurgery kidney function in patients with kidney cancer,¹² primarily because the characteristics of the population used for the development of various equations such as MDRD differ from that of the kidney cancer population.

The volume of the normal kidney is an independent anatomical assessment of number of nephrons (quantity) remaining after surgery. Autopsy studies have verified that kidney

volume correlates with the number of functioning nephrons.¹³ In the healthy kidney donor population, Jeon et al. were able to directly correlate the kidney volume of kidney donors, as measured on contrast-enhanced CT, with nephrectomized kidney weight and various kidney function measures.¹⁴ This correlation of CT-measured kidney volumes with renal function was incorporated into a novel mathematical model to estimate GFR in potential kidney donors by Herts et al.¹⁵ By utilizing renal volume in addition to the standard parameters of age, weight, and serum creatinine, this volume-based model was found to outperform the MDRD equation in different studies.^{11,15} It is therefore expected that kidney volume is inherently related to baseline donor kidney function and this has been demonstrated in ultrasound-measured kidney sizes.¹⁶ Preoperative kidney volume has also been shown to be an important independent predictor of delayed kidney function recovery in the donors after nephrectomy.¹⁴ Preoperative transplanted donor kidney volumes have been identified as an important predictor of graft function in living donor kidney transplantation.^{17,18} Renal parenchymal volume measurements have also been shown to be accurate in estimating differential renal function in normal and urinary obstructed patients.¹⁹

For kidney cancer patients, Jeon et al. have similarly demonstrated that preoperative total kidney volume showed significant correlation with the Cockcroft–Gault formula for baseline GFR (CG-GFR) and that postoperative CG-GFR at 1 year was positively associated with preoperative volume of the normal side.²⁰ Their measurements of mean total kidney volume (265.3 mL) and preoperative normal side kidney volume (142.4 mL) were similar to the measurements in our study for RN patients, despite different techniques of kidney volumetry. Our study also adds to the findings of Jeon et al. by assessing renal function based on the more widely used MDRD equation, on which the KDOQI–CKD classification was based. Furthermore, we also evaluated renal function beyond 1 year of RN. Our study also supports the findings by the group in Cleveland Clinic of the impact of parenchymal volume preservation on renal function after partial nephrectomy for small renal masses.^{21,22} This impact may be even more important than warm ischemic time. Interestingly, kidney volumes obtained in these studies were larger in the Western population (median of 184–219 mL) than those in the Asian population^{14,20} and may be related to body size.

For patients who had postoperative CT scan ($n=41$), only 29.3% developed compensatory hypertrophy. Although the patient subset is small, for RN patients with increasing age and comorbidities, compensatory hypertrophy of the remaining kidney is not a universal phenomenon postnephrectomy.

One of the limitations of our study, when considering its applicability, is the study population size and demographics. Although the number of studies is comparable to other publications looking at kidney parenchymal volume, caution is needed when extrapolating the remaining kidney volume threshold of 144 mL to other population groups. What is increasingly clear from current publications is that the kidney volume is increasingly validated in both radical and partial nephrectomy populations as a quantitative marker of kidney reserve. Different thresholds can easily be worked up for different population groups. The risk of developing CKD with time after surgery is likely an interaction between a quantitative marker of CKD-S (normal kidney volume) and a qualitative marker of CKD-M (preoperative eGFR by MDRD

equation or proteinuria). With a larger number of patients, it would be interesting to contemplate the potential of adding preoperative kidney volume to the original MDRD equation to assess the renal function of patients undergoing surgical nephron loss and to predict the risk of CKD-M/S, just as Herts et al. have done for kidney donors.¹⁵

Conclusions

In conclusion, preoperative normal kidney volume and preoperative eGFR are independent significant predictors of risk of progression to CKD after RN. In our study population, a preoperative volume of the normal side kidney of 144 mL marks the threshold below which the median time to reach CKD is about 1 year after surgery. The clinical implication of our study is as follows: for patients with a kidney cancer and a preoperative normal kidney volume of <144 mL, a partial nephrectomy should be performed if the lesion is T1, even if they did not have CKD-M at the time of surgery. If RN is unavoidable, then they should be closely monitored for deterioration to CKD postoperation.

Author Disclosure Statement

No competing financial interests exist.

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Abbreviations Used

CI = confidence interval
CKD = chronic kidney disease
CT = computed tomographic
eGFR = estimated glomerular filtration rate
IDMS = isotope dilution mass spectrometry
MDRD = modification of diet in renal disease
RN = radical nephrectomy
ROC = receiver operating characteristic