Postoperative risk of chronic kidney disease in radical nephrectomy and donor nephrectomy patients: a comparison and analysis of predictive factors

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Introduction: *To compare baseline renal function and identify predictive factors in patients undergoing radical nephrectomy (RN) or donor nephrectomy (DN) and their risk of subsequent chronic kidney disease (CKD) after surgery.*

Materials and methods: *A retrospective review of patients with no baseline CKD undergoing RN (n = 88) and DN (n = 58) from 2000 to 2008 was performed. Baseline and postoperative renal function (eGFR) was determined using the Modification of Diet in Renal Disease (MDRD) formula. CKD was defined as eGFR < 60 mL/min/1.73 m^2 according to the National Kidney Foundation guidelines.*

Results: *Before surgery, patients undergoing RN and DN had a mean eGFR (± SD) of 83.5 ± 17.4 and 92.9 ± 17.0 mL/min/1.73 m^2 respectively (p = 0.002). Patients with RN had significantly greater morbidities including hypertension (47.7%), diabetes (14.8%) and ischemic heart disease (12.5%) than DN (5.2%, 0% and 1.7% respectively) (all p < 0.05). Median follow up was 3.5 years. The relative hazard of developing CKD post RN compared with DN was 1.91 (95% CI 1.01 to 3.61, p = 0.040). The median time to CKD was 77 months (range 2-107) for RN and 100 months (range 11-105) for DN. Age, gender, comorbidities, radical nephrectomy and baseline kidney function were individual risk factors for CKD post nephrectomy. However, preoperative eGFR was the only independent prognostic factor on multi-variable analysis.*

Conclusions: *Patients undergoing RN are distinctly different from kidney donors in terms of age, renal function and comorbidities. RN is not an independent predictive factor for CKD but the lower baseline renal function in RN patients significantly accelerates renal senescence in the uninephrectomy state.*

Key Words: baseline renal function, postoperative risk, chronic kidney disease, radical nephrectomy, donor nephrectomy

Introduction

With widespread use of imaging, the incidence of renal cell carcinoma is rising, led by the increased pickup of small enhancing renal masses (less than 4 cm). The American Urological Association (AUA) guidelines on the management of a clinical T1 renal mass advocates the use of partial nephrectomy (PN) for these masses,[1] with published data showing equivalent long term oncological efficacy[2] and better renal function preservation[3] to radical nephrectomy (RN). Despite this, in the United States, the use of PN for small renal masses was reported to be less than 30%.[4] Hence, RN remains a common treatment in patients with renal cell carcinoma (RCC), particularly for larger masses and those not amenable to PN.

On the other hand, a large body of evidence indicates that both the short and long term risks of living kidney donation are minimal and the ensuing uninephric state is safe of the living donor.[5-7] These data may be extrapolated to patients undergoing RN with apparently

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normal baseline creatinine levels and contralateral kidney imaging to assure physicians and patients alike that RN patients will have limited long term morbidity and mortality from chronic kidney disease (CKD) in the post nephrectomy state. The aim of this study is to compare the baseline renal function and identify the risk factors for CKD after surgery in patients undergoing RN or DN.

Materials and methods

A total of 117 patients who underwent RN and 58 patients who underwent DN for transplantation between January 2000 to September 2008 at our institution were recruited. Of the patients who underwent RN, 29 (24.8%) already had CKD before operation and were therefore excluded from the subsequent analysis for development of CKD after nephrectomy. The remaining RN patients (n = 88) 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 approaches and the selection was based on clinical assessments. Preoperative investigations included medical history, physical examination, laboratory studies including serum creatinine level, and preoperative contrast enhanced computer tomographic (CT) scans. After surgery, patients were followed up at 4-6 weeks and then 4 to 6 months for 2 years and annually thereafter.

A multidisciplinary team rigorously assessed all living kidney donors preoperatively, and they proceeded to donation after review and approval by the institutional ethics review committee. Preoperative imaging included an abdominal pelvic CT angiogram with three-dimensional reconstruction of the renal hilum. DN was performed either using an open technique via a flank incision, or hand-assisted laparoscopic donor nephrectomy (HALDN) technique via a midline handport as described previously. Postoperatively, all living donors were followed up long term at a post transplant kidney donor clinic. Donors were seen 6 weeks after surgery, then 6 months later, and annually thereafter, unless otherwise clinically indicated.

At each clinic visit, both groups of patients had a complete history and physical examination. Laboratory tests done were serum electrolytes including serum creatinine (umol/L). The creatinine measurement method in our hospital laboratory was standardized to isotope dilution mass spectrometry (IDMS). For the purposes of this study, an institutional review board approved database was established. 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 (GFR (mL/min/1.73 m^2) = 186 x (serum creatinine)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.212 if African American), was used to calculate the estimated glomerular filtration rate (eGFR) preoperatively and at each of the postoperative clinic visits for all eGFR measurements in the study. eGFR was calculated from the NKF web-based calculator at http://www.kidney.org/professionals/KDOQI/gfr_calculator.cfm. For this study, only the calculated eGFR values using MDRD formula were used for analysis. We have elected to use MDRD formula because MDRD estimated GFRs are used to stratify and prognosticate patients with CKD as per KDOQI guidelines and in the paper by Go et al.[8] In addition, other centers have reported eGFR results estimated by MDRD after nephrectomy and therefore would better facilitate comparison. The MDRD equation has also been recently validated by our institution in our local multiethnic Asian population.[9] Sensitivity and specificity of MDRD eGFR < 60mL/min/1.73 m^2 for measured GFR < 60 mL/min/1.73 m^2 by Technescan DTPA nuclear scans were 90.5% and 78.4%. Positive and negative predictive values for eGFR < 60 mL/min/1.73 m^2 for MDRD equation were 0.9 and 0.79 respectively. This was deemed adequate for our purposes of screening for CKD stage III after radical or donor nephrectomy.

Chronic kidney disease was defined as eGFR less than 60 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. The time to CKD was calculated in days from the time of nephrectomy to the time when the first eGFR measurement dropped below 60 mL/min/1.73 m^2.

Statistical analysis

The demographic and clinical characteristics of both cohorts were summarized using frequencies and percentages for categorical variables, and means and standard deviations for continuous covariates which were all approximately normally distributed. The χ^2 test was used to compare difference in proportions for categorical variables. We compared the renal function parameters in both groups at the time of nephrectomy using the Student's t-test.

The Kaplan-Meier curve for the time to postoperative CKD was plotted for both groups of RN and DN subjects who had no baseline CKD. The bivariate associations between specific risk factors and time to postoperative CKD were also compared using the log rank test. The risk factors analyzed included DN or RN surgery; gender, ethnicity, age at surgery, hypertension, hyperlipidemia and ischemic heart disease. The effect of these risk factors

was quantified using the hazard ratio (HR) estimate and its associated 95% confidence interval. The Cox proportional hazard 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 via the log rank test.

All statistical analyses were generated using STATA software, version 11 (StataCorp LP, College Station, TX, USA). Statistical evaluations were assessed assuming a 2-sided test at the conventional 0.05 level of significance.

Results

Table 1 shows the baseline characteristics of both RN and DN groups at the time of surgery and their postoperative outcomes and renal functions. The mean eGFR ± SD by MDRD equation of RN and DN patients before surgery was 83.5 ± 17.4 and 92.9 ± 17.0 mL/min/1.73 m^2 respectively (p = 0.002). Patients from RN had significantly greater morbidities including hypertension (47.7%), diabetes (14.8%) and ischemic heart disease (12.5%) than DN group (5.2%, 0% and 1.7% respectively) (all $p < 0.05$).

The median follow up for both groups was 3.5 years. At the end of the study, the proportion of patients who developed CKD post nephrectomy was 38.6% in RN and 25.9% in DN respectively (p = 0.152). The mean eGFR of RN patients was lower than that of DN patients but the difference is not statistically significant (65.5 and 70.7 mL/min/1.73 m^2

TABLE 1. **Comparison of demographic and baseline clinical features between donor nephrectomy and radical nephrectomy patients**

	Donor nephrectomy (n = 58)	**Radical nephrectomy (n = 88)**	**p value**
Characteristics			
Mean age at surgery (yrs, SD)	40.8 (10.2)	56.3 (11.3)	< 0.001
Gender, n (%)			0.018
Male	22 (37.9)	52 (59.1)	
Female	36 (62.1)	36 (40.9)	
Race, n (%)			0.003
Chinese	38 (65.5)	74 (84.1)	
Malay	17 (29.3)	7 (8.0)	
Indian	2 (3.5)	2 (2.2)	
Others	1 (1.7)	5 (5.7)	
Diabetes, n (%)	0 (0.0)	13 (14.8)	0.002
Hypertension, n (%)	3 (5.2)	42 (47.7)	< 0.001
Ischemic heart disease, n (%)	1 (1.7)	11 (12.5)	0.028
Nephrolithiasis, n (%)	1 (1.7)	2 (2.3)	1.000
Mean preop Cr (umol/L, SD)	74.1 (16.9)	82.2 (16.3)	0.006
Mean preop eGFR (mL/min/1.73 m^2, SD)	92.9 (17.0)	83.5 (17.4)	0.002
Post-operative outcomes			
Survival status, n (%)			0.146
Alive	57 (98.3)	81 (92.1)	
Dead	1 (1.7)	7 (7.9)	
Postop CKD, n (%)	15 (25.9)	34 (38.6)	0.152
Mean latest eGFR (mL/min/1.73 m^2, SD)	70.7 (14.2)	65.5 (23.8)	0.107
Stage of postop CKD			0.312
3, n (%)	15 (25.8)	30 (34.1)	
4, n (%)	0 (0)	2 (2.3)	
5, n (%)	0 (0)	2 (2.5)	

cr = creatine; eGFR = estimated glomerular filtration rate; CKD = chronic kidney disease

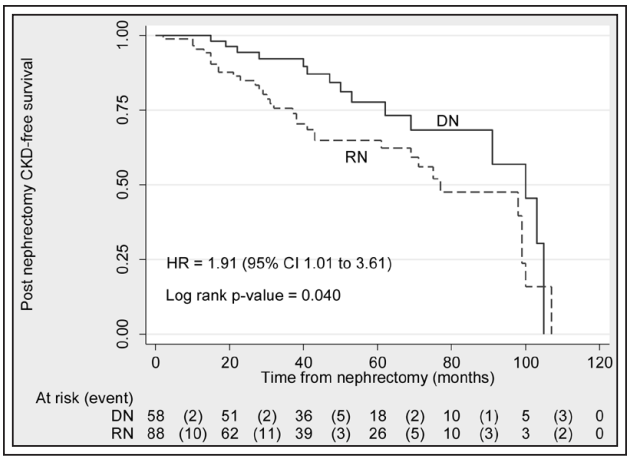

Figure 1. Kaplan-Meier survival curves comparing post nephrectomy chronic kidney disease (CKD)-free survival between patients with donor and radical nephrectomy. Median time to CKD (range): 98 (2 to 107). Median time to CKD for the DN group (range): 100 (11 to 105). Median time to CKD for the radical nephrectomy group (range): 77 (2 to 107).

respectively, p = 0.107). The Kaplan Meier survival curves showed that patients undergoing RN developed CKD significantly earlier than DN patients (HR = 1.91; 95% CI 1.01 to 3.61; p = 0.040), Figure 1. The median time to CKD was 77 months (range 2-107) for the RN group and 100 months (range 11-105) for DN. Figure 2 shows that a cut off value of 83 mL/min/1.73 m^2 for baseline eGFR before operation had the optimal

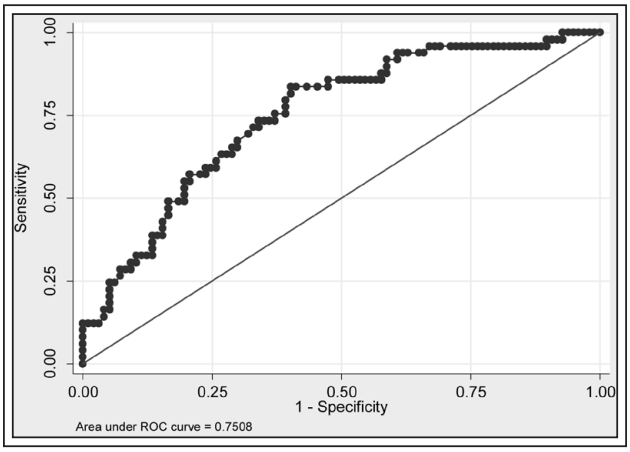

Figure 2. Area under the ROC with preop eGFR as predictor. The area under the ROC is estimated to be 0.75 with 95% CI 0.67 to 0.83. The cut off point for preop eGFR is chosen to be 83 mL/min/1.73 m^2 to achieve optimal sensitivity of 69.4% (95% CI 54.6% to 81.7%) and specificity of 68.0% (95% CI 57.8% to 77.1%).

sensitivity and specificity for predicting CKD after surgery.

Table 2 shows the effect of individual risk factors for developing post nephrectomy CKD. On univariable analysis, age (p < 0.001), male gender (p = 0.003), preoperative baseline eGFR (p < 0.001), type of nephrectomy (DN versus RN) (p = 0.045), comorbidities including diabetes (p = 0.045), hypertension (p = 0.046) and ischemic heart disease (p = 0.033) were all significantly associated with CKD occurrence after nephrectomy. Race was not a significant factor.

However, after adjusting for the effect of RN/DN surgery, age and comorbidities, preoperative eGFR was the only significant predictor of postoperative CKD, Table 3. RN alone is not predictive for CKD (HR 1.70 (0.91 to 3.19), p = 0.096). The hazard of developing postoperative CKD reduced by 5% (95% CI 2 to 7) for every mL/min/1.73 m^2 increase in preoperative eGFR.

Discussion

This study has shown that patients who underwent radical and donor nephrectomy at a single institution were derived from two distinct populations with significantly different demographics and comorbidities, resulting in different baseline renal function and subsequent risk of developing CKD. Over a median follow up period of 3.5 years, RN patients had a hazard risk of 1.9 times that of DN patients in developing CKD after surgery.

The implications of CKD had been well reported by Go et al in a population of more than 1 million individuals; CKD defined as eGFR less than 60 mL/min/1.73 m^2 was associated with increased risk of death, cardiovascular event and hospitalizations.[8] 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.[10] Such 'treatment disconnect'[10] may be due to the potential of surgical treatment by RN increasing postoperative CKD morbidity, which in turn increases associated competing causes of death. There is, therefore, an increasing need to focus on improving the non-oncological outcomes of patients with renal cancer.

In recent years, physicians have recognized that serum creatinine is a poor estimation of glomerular filtration. Of our 117 patients who underwent RN, a quarter of them had baseline CKD. As noted, the prevalence of patients with pre-existing CKD was 24.8% (n = 29) in the RN group with no patients in DN having CKD (p < 0.001) even before surgery. Of

TABLE 2. **Effect of individual risk factors on postop chronic kidney disease**

Risk factor	No. with postop CKD (%)	Crude HR (95% CI)	p value
Age (years)	-	1.05 (1.02 to 1.07)	< 0.001
Gender, n (%)			
Female	13 (18.1)	1.00	-
Male	36 (48.7)	2.68 (1.41 to 5.10)	0.003
Race, n (%)			0.987
Chinese	39 (34.8)	1.00	-
Malay	8 (33.3)	0.88 (0.41 to 1.91)	0.754
Indian	1 (25.1)	0.83 (0.11 to 6.08)	0.855
Others	1 (16.8)	1.10 (0.15 to 8.17)	0.922
Diabetes, n (%)	9 (69.2)	2.14 (1.02 to 4.52)	0.045
Hypertension, n (%)	22 (48.9)	1.79 (1.01 to 3.18)	0.046
Ischemic heart disease, n (%)	9 (75.0)	2.24 (1.07 to 4.70)	0.033
Nephrolithiasis, n (%)	2 (66.7)	0.85 (0.19 to 3.83)	0.831
Radical nephrectomy, n (%)	34 (38.6)	1.87 (1.01 to 3.46)	0.045
Preop Cr (umol/L)	-	1.04 (1.02 to 1.06)	< 0.001
Preop eGFR, n (%)			
≥ 83 mL/min/1.73 m^2	15 (18.5)	1.00	-
< 83 mL/min/1.73 m^2	34 (52.3)	3.37 (1.81 to 6.30)	< 0.001

CKD = chronic kidney disease; HR = hazard ratio; cr = creatine; eGFR = estimated glomerular filtration rate

these RN patients with pre-existing CKD, 7 (24.1%) had normal serum creatinine levels (Cr < 105 umol/L). Similarly, a larger population study showed that 22% of patients with solid renal tumors and normal creatinine levels at baseline had CKD stage 3 or greater.[11] With the development of creatinine-based equations such as MDRD, more accurate identification of baseline renal function should facilitate better delivery of renal function centered care to patients requiring radical nephrectomy.[12] Our finding that preoperative eGFR is a strong predictor of postoperative CKD should also prompt urologists to take this variable into consideration rather than creatinine level when counseling patients for CKD before surgery.

However, estimating GFR using the MDRD equations have its limitations. This is fundamentally a screening tool and not a true reflection of renal function of individual patients and is less reliable in patients with eGFR of > 60 mL/min/1.73 m^2 as the MDRD equation was developed in a population with CKD.[13] We primarily used the MDRD equation as a screening tool for the development of CKD stage III in patients after radical or donor nephrectomy and have avoided making references to absolute changes of eGFR after surgery. This is consistent with previous landmark papers by Huang et al and others[3,14-16] who have used eGFR for detecting CKD after radical and partial nephrectomies. The original eGFR modelling was based on a 2 kidney model – where

TABLE 3. **Association between radical nephrectomy and postop CKD, adjusted for significant risk factors in the multivariable Cox proportional hazard regression model**

Risk factor	Adjusted HR (95% CI)	p value
Preop eGFR		
≥ 83 mL/min/1.73 m^2	1.00	-
< 83 mL/min/1.73 m^2	3.22 (1.72 to 6.02)	< 0.001
Radical nephrectomy	1.70 (0.91 to 3.19)	0.096

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate

parenchymal loss reflected glomerulosclerosis; its value in determining the progressive loss of function related to surgical removal of parenchyma has not been clearly defined. Recently, there are increasing studies which studied the validity of these equations on patients who underwent nephrectomy (either radical nephrectomy[17] or donor nephrectomy[18]) and found that MDRD does correlate well with measured GFR by nuclear isotope scans and creatinine clearance.

Age,[19] gender, comorbidities and baseline kidney function[20] have been reported recently as important factors impacting on post nephrectomy renal function and survival which was similar to our findings. After multivariate analysis in our study, preoperative eGFR was only the significant independent predictor and represents baseline renal reserve before nephrectomy, upon which the other factors like age and comorbidities have an impact and are therefore correlated. Age itself is an important factor affecting calculated eGFR and the decline in eGFR with age has been attributed to a normal biological phenomenon secondary to changes in the vascular tree and changes in renal function.[21] Although our study does not directly show this, comorbidities in addition to age can account for the lower baseline and more rapid decline of eGFR after surgery. From the Kaplan-Meier curve, the decline in eGFR with time in the donors represents impact of increasing age in the group with no comorbidities. Comparatively, the Kaplan-Meier curve of RN patients shows a much more rapid and significant decline with age over time. In addition, there is evidence from published reports with regards to the impact of comorbidities. Pottelbergh[22] et al studied the association between renal function and the incidence of ESRF in patients older than 50 years and found that baseline eGFR and comorbidities are independent risk factors for developing ESRF. Lane[23] et al also showed that preoperative CKD due to medical diseases places patients at increased risk of progressive renal functional decline after surgery for kidney cancer when compared to patients with no CKD. Our study echoes this finding with age and comorbidities impacting the preoperative eGFR of RN patients resulting in greater decline than DN patients with simple reduction of nephron mass.

The decline in GFR in healthy uninephric subjects exhibits a negative correlation with advancing age as in healthy binephric subjects;[24] this renal senescence has been shown to be due to the loss of glomeruli number (glomerulopenia) and glomerulosclerosis with age and explains why with time, a proportion of our kidney donors develop CKD too as in Figure 1. This renal senescence is further accelerated in the typical patient undergoing RN due to their age and associated co-existing morbidities such as hypertension, diabetes and ischemic heart disease. After nephrectomy, there is also a reported vigorous compensatory response of the remaining kidney, which includes a 30%-40% increase in GFR in healthy kidney donors[24] but this is blunted with increasing age and comorbidities.

Conclusion

Patients undergoing RN are distinctly different from kidney donors in terms of age, renal function and comorbidities. RN is not a predictive factor for CKD but the higher prevalence of comorbidities in RN patients results in lower baseline renal function, and significantly accelerate renal senescence towards CKD state in the uninephrectomy state. Patients undergoing DN are at risk of CKD and they should be counseled on this aspect before proceeding with the surgery. □

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