

## Renal Function After Unilateral Nephrectomy

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### ABSTRACT

**BACKGROUND:** It is clear that Chronic Kidney Disease (GFR <60mls/min) is associated with reduced life expectancy, partly due to an increased risk of cardiovascular disease. To consider the implications for the selection of total versus partial unilateral nephrectomy, we compared retrospectively the renal function of patients undergoing either operation in Lothian.

**METHODS:** Details were collated across NHS Lothian for 1165 patients. Blood results pre and post-nephrectomy could be retrieved for 334 patients (Group 1). Blood results were also available from at least 6 months post surgery for 194 patients (Group 2). Renal function was estimated using the Abbreviated Modification of Diet in Renal Disease formula.

**RESULTS:** Overall within group 1, total/partial nephrectomy patients' GFR fell by 14.35ml/min/1.73m<sup>2</sup>, (95%CI 11.98-16.72) with post-nephrectomy GFR <60mls/min in 34.1%. Within group 2, patients' GFR fell by a mean of 14.09ml/min/1.73m<sup>2</sup>, (95%CI 10.93-17.24) with new GFR <60mls/min in 36.1%. Comparing partial versus total nephrectomy, the mean reduction in GFR and occurrence of post-nephrectomy GFR <60mls/min was 8.13ml/min/1.73m<sup>2</sup>, 16.7% and 14.73ml/min/1.73m<sup>2</sup>, 35.4% respectively in group 1. The odds ratio for post-nephrectomy GFR <60mls/min was 2.7 (95%CI 1.4-5.3). Group 2 included too few partial nephrectomy patients for comparison.

**CONCLUSION:** Smaller reductions of GFR after partial versus total unilateral nephrectomy are of magnitudes that are significant for overall life expectancy in large cohorts, and possibly relevant for patients with indications for nephrectomy and longer life expectancy. Patients who undergo nephrectomy should have their renal function assessed at least 6 months post-surgery to detect new GFR <60mls/min and trigger appropriate evaluation.

**Key Words:** chronic kidney disease; nephrectomy; surgical follow-up

## Introduction

### Background

Nephrectomy is by no means a novel surgical intervention having first been introduced for the treatment of localised renal cell carcinoma (RCC) in 1969 (1). Indications for nephrectomy include renal cell or urothelial cancer and benign conditions that lead to a poorly functioning or non-functioning kidney (2). Nephrectomy is most often performed for RCC. Since Robson et al. first described radical nephrectomy (RN), and from the evolution of laparoscopic techniques in 1990, laparoscopic radical nephrectomy (LRN) has been considered the gold standard curative treatment for stage T2 RCCs (3). With ever-evolving technology and surgical techniques, there has been a debate over the last decade about the

use of partial or total nephrectomy for small renal masses (T1). Issues include whether nephron-sparing surgery (NSS) gives better oncologic and renal function outcomes than patients having a total nephrectomy.

A collaborative review published in the European Association of Urology found no significant difference in overall survival and cancer-specific survival between the two techniques. This is further supported by a 2010 review concluding that partial nephrectomy should be the treatment of choice for renal cortical tumours  $\leq 4$ cm. Nephron-sparing surgery has been found to be protective against chronic kidney disease whereas radical nephrectomy predisposes to it (4). This is because PN preserves more nephron units (5).

To date, there has been only one randomised control trial comparing the oncologic outcome of nephron-sparing surgery to radical nephrectomy for small renal tumours. Results from this study somewhat contradict previous literature. They show that both surgical options provide excellent oncologic results. The conclusions (concerning overall survival) find that in the intention to treat population NSS appears to be less effective than RN. However, in the targeted population of RCC patients, outcomes no longer favour RN (6). It is important to note that quality of life and renal functional outcomes of the patients were not addressed in this trial. Although the oncologic outcomes appear to be much the same, Zini et al. demonstrated an overall rise in mortality and non-cancer related death in patients undergoing RN with RCC T1aN0M0 (7).

In 2006 a paper funded by the U.S. National Institutes of Health sought to challenge radical nephrectomy as the treatment of choice for small renal cortical tumours. The authors concluded that radical nephrectomy is a significant risk factor for the development of chronic kidney disease (11). They go on to suggest that RN might no longer be regarded as the gold standard treatment for the resection of RCC  $\leq 4$ cm. Arguments for RN come from long-established renal function outcome data from donor transplant patients that indicate no long-term decline in estimated GFR. Those against RN highlight that donor patients are a highly selected group, with excellent baseline renal function, whereas those with existing RCCs have lower baseline renal function, which determines their poor prognosis (12). However, in-depth analysis has shown that RCC does not predispose to CKD (13) whereas many of those facing nephrectomy surgery suffer clinically important adverse renal outcomes (4). Furthermore, renal function (measured as the absence of new-onset glomerular filtration rates [GFRs]  $< 60$ ml/ml per  $1.73\text{m}^2$ ) was found to be significantly higher in those undergoing partial nephrectomy (14).

### ***Rationale for Study***

Chronic kidney disease is raising public health concern worldwide and is now thought to be an independent risk factor in much pathology, including cardiovascular disease (8). A 2004 community-based study linked declining estimated GFR with risk of death, cardiovascular events and hospitalisation (9). Most literature describes renal insufficiency as an estimated GFR  $< 60$ ml/min/ $1.73\text{m}^2$  (stage 3A chronic kidney disease as currently classified by NICE). Go et al. not only show that there is an increased risk of cardiovascular events at an estimated GFR  $< 60$ ml/min/ $1.73\text{m}^2$  but further suggest that cardiovascular events sharply increase again with an estimated GFR  $< 45$ ml/min/ $1.73\text{m}^2$  (stage 3B chronic kidney disease). The Framingham Risk Score, which usually predicts cardiovascular risk accurately, often underpredicts cardiovascular disease in CKD patients. However, efforts to alter the equation, by incorporating eGFR, have made negligible improvement (10). For the purpose of this study we are particularly interested in renal function post nephrectomy and the relationship between it and other co-morbidities – specifically cardiovascular health.

## Objectives

Projected renal function after nephrectomy is an area of interest that sparks much debate. To date there is little literature accurately documenting the long-term renal function outcomes post-nephrectomy. Current literature focuses on oncologic outcomes comparing radical nephrectomy to nephron-sparing surgery. Although there is an established link between chronic kidney disease and cardiovascular decline, we sought to identify the rate of CVD in patients undergoing a nephrectomy.

The aim of this study was to determine the effect of removing a kidney on the renal function and cardiovascular system. Further, if we take both radical and nephron-sparing techniques to be equal in terms of surgical outcome, the aim was to quantify patients' renal function after either total or partial nephrectomy.

## Methods

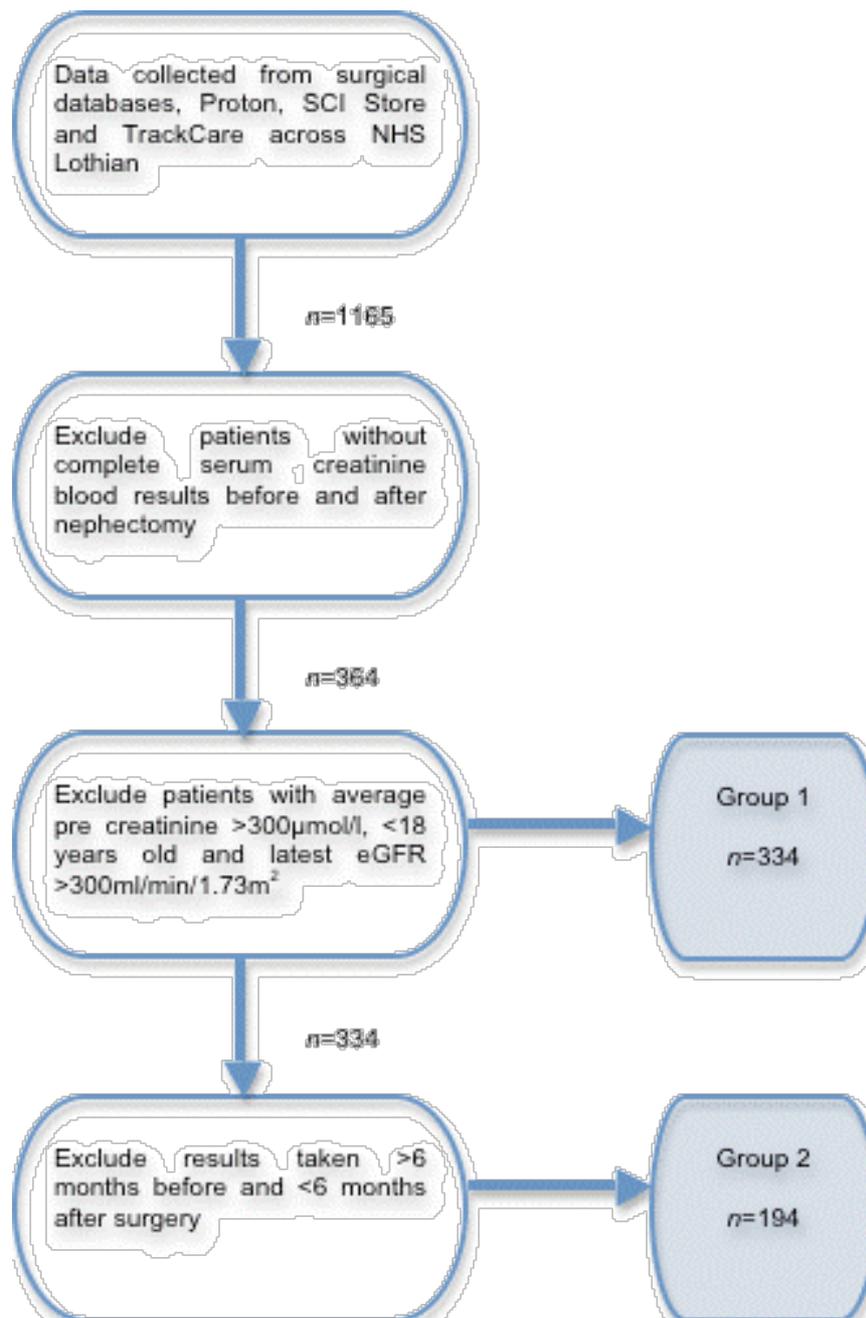
Patient information was collected from three surgical databases across NHS Lothian, TrakCare and Proton. Pre-op, post-op and follow-up blood results were captured from SCI store. Advice was sought from South East Scotland Research Ethics Service and further NHS ethical review was not needed. Caldicott Guardian approval was received for the use of person-identifiable information. Patients' corresponding estimated glomerular filtration rates (eGFR) were calculated through the abbreviated Modification of Diet in Renal Disease (MDRD-eGFR) equation (15). From this, each patient was categorised into their relevant Chronic Kidney Disease (CKD) stage as currently dictated by the National Institute of Clinical Excellence (8). Patients who subsequently started dialysis treatment following surgery were categorised as CKD stage 5. Two groups of patients were identified - all patients who had complete blood results (group 1) and those patients who had pre-operative and post-operative follow-up blood results collected within six months prior to surgery and at least six months following surgery respectively (group 2). Groups were divided into those that had total or partial nephrectomy. Patients excluded from analysis included patients with a baseline serum creatinine  $>300\mu\text{mol/l}$  before nephrectomy, patients under eighteen years old as the MDRD-eGFR equation is not valid for this age group, and patients who had a follow-up eGFR  $>300\text{ml/min}/1.73\text{m}^2$ , which lay outside the boundaries of normality.

At each interval, change in eGFR between groups was compared using *t*-test. For frequency distributions that did not meet the assumptions of normality, Wilcoxon ranked-sign test was used. Incidence of CKD was compared in all groups using contingency tables and  $\chi^2$  tests. The difference in baseline serum creatinine for those that started dialysis treatment was compared using *t*-test. *P* values of  $<0.05$  were considered statistically significant. Pearson's correlation coefficient (*r*) was calculated for each comparison as a measure of effect size to quantify the strength of experimental effect. This is to be used in future work building a multinomial logistic regression model. All analysis was carried out in MS Office Excel 2003 and IBM SPSS Statistics 19.

## Results

### Description of Groups and Patients

Of the 1165 patients identified from the surgical databases, SCI store, Proton and TrakCare, 334 patients were included in Group 1 and 194 in Group 2 (Figure 1). There were very few partial nephrectomy patients with complete serum creatinine results ( $n=24$ ).



**Figure 1. Flowchart showing selection process for patient groups.**

The characteristics of the cohort are summarised in Table 1. There are slightly more men in the groups and a similar median age for all. The vast majority of cases are laparoscopic total nephrectomy; 71.4% of the whole cohort were still alive at time of analysis. 5.1% of patients had a history of cardiovascular disease, although past medical history was missing for 73.1% of the whole cohort.

Characteristics	Whole cohort	Group 1	Group 2	p value*
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Sex (%)	M	624 (53.6)	183 (54.8)	105 (54.1)	0.89
	F	541 (46.4)	151 (45.2)	89 (45.9)	0.89
Alive/Dead (%)	A	832 (71.4)	284 (85)	163 (84)	0.79
	D	296 (25.4)	49 (14.7)	30 (15.5)	0.79
	U	37 (3.2)	1 (0.3)	1 (0.5)	
Age, median		63	66	66	0.64
Total/Parital Nephrectomy (%)	T	1008 (86.5)	302 (90.4)	179 (92.3)	0.81
	P	61 (5.2)	24 (7.2)	13 (6.7)	
	U	96 (8.2)	8 (2.4)	2 (1)	
Open/Laparoscopic (%)	O	216 (18.5)	56 (16.8)	32 (16.5)	0.89
	L	880 (75.5)	275 (82.3)	162 (83.5)	0.89
	U	69 (5.9)	3 (0.9)		
Count of results before operation, mean (SD)			3.43 (4.21)	3.91 (4.64)	
Count of results after operation, mean (SD)			10.66 (12.92)	13.42 (14.78)	
No. days first creatinine pre-operation, median			39	26	
No. days latest creatinine post-operation, median			435	791.5	

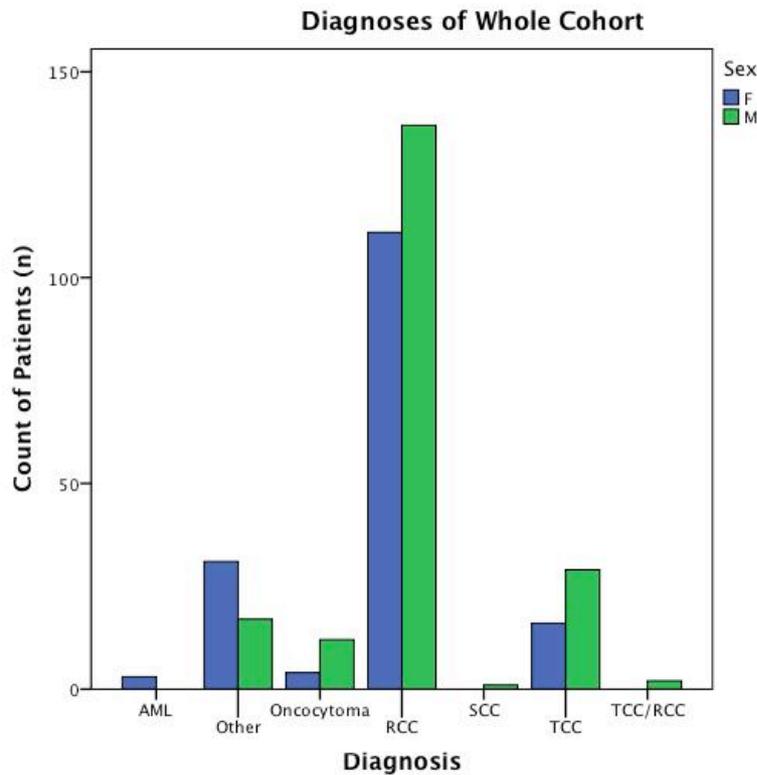
**U = unknown.** SD = standard deviation.

Corresponding eGFRs for each interval were not distributed normally (Kolmogorov-Smirnov,  $p < 0.05$ ). However the distributions of difference of means were (K-S,  $p > 0.05$ ), therefore t-test was appropriate for comparing these results.

\*Comparison of Group 1 and Group 2.

**Table 1. General characteristics of patients and groups including creatinine follow up time.**

The majority (56.5%) of patients were diagnosed with renal cell carcinoma as shown in Figure 2. RCC accounted for 44.3% of deaths while cardiovascular cause only accounted for 5.4% of total deaths. 22.7% of patients were diagnosed with other non-functional kidney disease. Diagnosis was missing for 5.2% of the whole cohort while cause of death was missing for 19.9%.



**Figure 2. Column chart showing diagnoses of patients.**

Unknown diagnoses are not included. AML=angiomyolipoma RCC=renal cell carcinoma SCC=squamous cell carcinoma TCC=transitional cell carcinoma

### **Reduction in eGFR Following Nephrectomy**

We compared the mean differences in eGFR pre-operation, immediately post-operation and at last follow-up for total versus partial nephrectomy patients within the two groups. On average, patients in Group 1 had a higher eGFR before nephrectomy (Mean=82.90, SE=1.50) compared to their latest follow-up result (Mean=68.55, SE=1.60). There was a mean drop in eGFR of 14.35ml/min/1.73m<sup>2</sup> (95%CI 11.98-16.72),  $p < 0.001$ ,  $r = 0.54$ . Therefore baseline eGFR has a large effect on post-nephrectomy renal function. Patients' eGFR dropped dramatically post-surgery ( $p < 0.001$ ) and then rose slightly during the follow up period ( $p < 0.001$ ).

Of particularly interest was the comparison of the mean difference in eGFR at last follow-up for total and partial nephrectomy patients in Group 1. On average, partial nephrectomy patients had a higher eGFR post-operatively (Mean=85.22, SE=7.96) compared with total nephrectomy patients (Mean=67.08, SE=1.63). Having had similar baseline eGFRs, partial nephrectomy patients' latest result is a mean of 18.14ml/min/1.73m<sup>2</sup> (95%CI 1.34-34.95) higher than total nephrectomy patients,  $p < 0.05$ ,  $r = 0.42$ .

Group 2 displayed a similar pattern of results. However, there were few partial nephrectomy patients with kidney function tests available who had been followed up for six months. Again, patients' eGFR in Group 2 was higher before nephrectomy (Mean=81.11, SE=1.96) compared to their latest follow-up (Mean=67.02, SE=2.11). There was a mean drop in eGFR of 14.09ml/min/1.73m<sup>2</sup> (95%CI 10.93-17.24),  $p<0.001$ ,  $r=0.28$ . Baseline eGFR, therefore, has a small effect on post-nephrectomy renal function. Patients' eGFR dropped dramatically again post-surgery ( $p<0.001$ ) and then rose marginally during the follow-up period ( $p<0.01$ ).

Splitting Group 2 into total and partial nephrectomy patients (and then assessing the last follow-up eGFR result) partial nephrectomy patients had a higher eGFR (M=73.42, SE=11.66) compared with total nephrectomy patients (Mean=66.43, SE=2.14). Given similar baseline eGFRs for both, partial nephrectomy patients' eGFR was a mean of 7ml/min/1.73m<sup>2</sup> (95%CI -18.9-32.87) higher on follow-up compared with their total nephrectomy counterparts,  $p>0.05$ ,  $r=0.17$ .

### **Change in Chronic Kidney Disease Stage**

Total and partial nephrectomy was compared in Group 1, which can be seen in Table 2. There was an association between type of nephrectomy and change in CKD stage, as categorised by new onset eGFR <60ml/min/1.73m<sup>2</sup>  $\chi^2(1)=2.62$ ,  $p=0.05$ . Odds ratio of eGFR <60ml/min/1.73m<sup>2</sup> was 2.73 (95%CI 1.4-5.3) for patients undergoing total nephrectomy.

**Table 2. Contingency table showing new onset eGFR <60ml/min/1.73m<sup>2</sup> for total and partial nephrectomy.**

		New onset eGFR <60		Total	
		N	Y		
Total/Partial	T	Count	157	86	243
		% within Total/Partial	64.6%	35.4%	100.0%
	P	Count	15	3	18
		% within Total/Partial	83.3%	16.7%	100.0%
Total		Count	172	89	261
		% within Total/Partial	65.9%	34.1%	100.0%

Group 2 could not be compared using chi-square based upon patient numbers of partial and total nephrectomy.

### Dialysis Patients

Eleven patients started dialysis treatment following surgery, two (18.2%) of whom have since died. Figure 3 shows a boxplot of baseline serum creatinine before surgery. Average baseline serum creatinine was higher for those who ended on dialysis treatment (Median=199) compared to those who did not (Median=88).

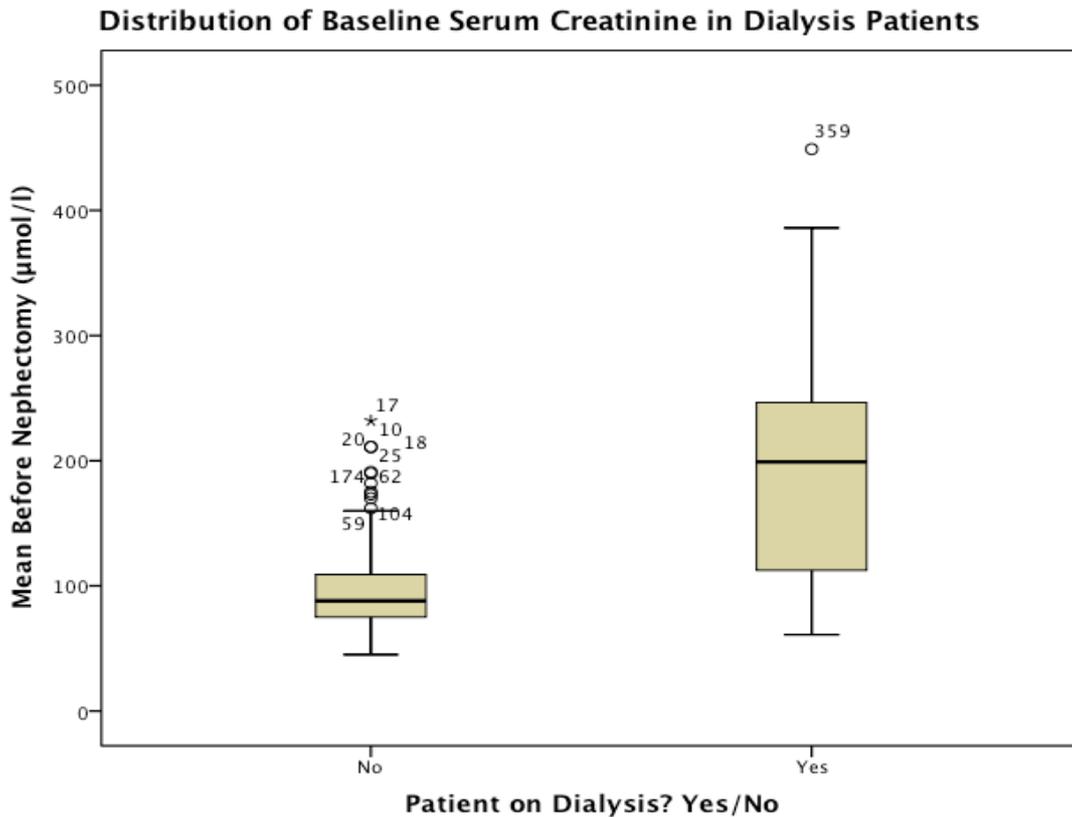


Figure 3. Boxplot showing distribution of mean baseline serum creatinine comparing dialysis patients ( $n=11$ ) with those that did not require treatment ( $n=352$ ).

Baseline serum creatinine was higher for those who eventually started dialysis treatment (Mean=205.73, SE=37.83) compared to those who did not (Mean=93.85, SE=1.47). There was a mean difference of 111.88µmol/l (SE=37.86µmol/l),  $p<0.01$ ,  $r=0.68$ .

### Discussion

The findings of this study show that removing a kidney, whether it is total or partial nephrectomy, results in reduced renal function as measured by estimated GFR. There was a decline in renal function of 14.35ml/min/1.73m<sup>2</sup> ( $p<0.001$ ) and 14.09ml/min/1.73m<sup>2</sup> ( $p<0.001$ ) for Group 1 and 2 respectively. When comparing total and partial nephrectomy, renal function was significantly protected in those who underwent partial nephrectomy. Their eGFR was 18.14ml/min/1.73m<sup>2</sup> ( $p<0.05$ ) higher on follow-up (Group 1). We showed that this correlated with an increased risk in developing chronic kidney disease. In Group 1, 35.4% of total nephrectomy patients developed new onset eGFR <60ml/min/1.73m<sup>2</sup> compared with 16.7% of partial nephrectomy patients,  $p=0.05$ . The odds ratio showed that partial nephrectomy patients were 2.73 times less likely to develop new onset eGFR

$<60\text{ml}/\text{min}/1.73\text{m}^2$ . Therefore, although  $p$  is not significant, we have shown that partial nephrectomy can protect against chronic kidney disease.

Further efforts were made to establish why some patients developed renal failure requiring dialysis. Of the 11 patients that subsequently started dialysis their baseline serum creatinine was elevated (Mean= $112\mu\text{mol}/\text{L}$ ). This suggests that, as one would expect, a risk factor for developing end stage renal failure following nephrectomy is raised baseline serum creatinine. Using Pearson's correlation coefficients we have shown that baseline eGFR is a strong predictor of post-nephrectomy renal function ( $r=0.54$ , Group 1). Reinforcing that excellent baseline renal function is paramount for a good outcome.

There are several weaknesses in this study that limit our ability to comment. Diagnosis was predominately renal cell carcinoma so these patients could have faced adverse renal outcomes regardless of surgical technique. There was inadequate documentation regarding the past medical history, including CVD and associated risk factors, of patients. Therefore, we are unable to comment on the rate of cardiovascular disease in those undergoing nephrectomy.

Few complete blood results were collected ( $n=364$ ) for patients. This limited the sample sizes. Smaller than predicted sample sizes, compounded with few patients undergoing partial nephrectomy, resulted in analyses of Group 2 yielding insignificant results with unacceptable error. Effort could have been made to use Fischer's exact test to overcome this. The ethnicity of patients was missing which introduced a  $<1\%$  error into our MDRD-eGFR calculations.

There are several important comparisons to be made with current literature. The findings of this study support the current hypothesis that radical nephrectomy predisposes to poor renal outcome and the rate of CKD is higher in this population (11, 14). Further, our results are mirrored in previous studies that show partial nephrectomy to be protective against this (4, 5). Although we have inadequate documentation to comment on the cardiovascular health of our patients, literature suggests that nephrectomy predisposes to CVD (9). We have shown an increased risk of developing a new independent risk factor for CVD following nephrectomy as represented by new onset eGFR  $<60\text{ml}/\text{min}/1.73\text{m}^2$ . We are, however, unable to comment on the overall mortality and morbidity of these patients. Ideally, we would have calculated the associated increase in CVD risk percentages. However, others' attempts at incorporating eGFR into the Framingham Risk Score have so far been unsuccessful (10).

We found that raised baseline serum creatinine and poor renal function were strong predictors of adverse outcomes post-nephrectomy. This is reflected in donor kidney patient research that suggests excellent renal function before surgery protects against adverse outcomes while poorly functioning kidneys pre-operatively predispose to them (12).

Results from this study add to mounting evidence that radical nephrectomy predisposes to chronic kidney disease through a reduction in renal function by removal of an inappropriate number of nephron units. Partial nephrectomy is shown to be protective. Therefore, in surgically appropriate cases, nephron-sparing surgery could be optimal in order to preserve renal function and prevent an associated increased risk in cardiovascular disease.

This study does not go as far as quantifying the risk of developing new onset eGFR  $<60\text{ml}/\text{min}/1.73\text{m}^2$  or the chances of starting dialysis treatment. Further work will aim to

build a multinomial logistic regression model to predict these outcomes. Baseline eGFR has a strong influence on post-nephrectomy renal function and our proposed model aims to quantify the strengths and significance of other variables in renal function outcome post-nephrectomy.

## Conclusion

Concerns over detrimental reduction in renal function following radical nephrectomy raised in the literature (4, 7, 11, 12) are reinforced through this study. We have found a significant reduction in renal function with an associated increased risk of chronic kidney disease (and therefore cardiovascular disease) using this technique. Further studies are required to fully qualify these risks.

Current findings suggest that, in appropriate cases, partial nephrectomy is optimal in order to protect long-term renal function. All patients that undergo nephrectomy should have their renal function assessed preoperatively and at least 6 months post-surgery to detect new GFR <60ml/min/1.73m<sup>2</sup> and trigger appropriate evaluation.

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