Partial vs. radical nephrectomy and the risk of all-cause mortality, cardiovascular, and nephrological outcomes

Rodney H. Breau, MD[1]; Anil Kapoor, MD[2*]; Danielle M. Nash, PhD[3]; Neal Rowe, MD[1]; Octav Cristea, MD[1]; Garson Chan, MD[4]; Stephanie N. Dixon, PhD[3]; Eric McArthur, MSc[3]; Camilla Tajzler[2]; Ravi Kumar, MD[1]; Christopher Vinden, MD[4]; Jonathan Izawa, MD[4]; Amit X. Garg, MD[3,5]; Patrick P. Luke, MD[4]*

[1]The Ottawa Hospital Research Institute, Division of Urology, University of Ottawa, Ottawa, ON, Canada; [2]McMaster University, Hamilton, ON, Canada; [3]ICES; [4]Divisions of Urology and General Surgery, Department of Surgery Western University, London, ON, Canada; [5]Division of Nephrology, Department of Medicine, Western University, London, ON, Canada

*Co-first authors

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Abstract

Introduction: The study's objective was to examine the effects of renal-preservation surgery on long-term mortality, cardiovascular outcomes, and renal-related outcomes.

Methods: We performed a retrospective cohort study of all partial (n=575) and radical nephrectomies (n=882) for tumors ≤7 cm in diameter between 2002 and 2010 across three academic centers in Ontario, Canada. We linked records from provincial databases to assess patient characteristics and outcomes (median seven years' followup using retrospective data). A weighted propensity score was used to reduce confounding. The primary outcome was all-cause mortality. Secondary outcomes included hospitalization with major cardiovascular events, non-cancer related mortality, kidney cancer-related mortality, and dialysis.

Results: Mean one-year postoperative estimated glomerular filtration rate (eGFR) was 71 mL/min/1.73 m^2 in the partial group and 52 mL/min/1.73 m^2 in the radical group. Partial nephrectomy was associated with a lower risk of all-cause mortality in the first five years after surgery (hazard ratio [HR] 0.42, 95% confidence interval [CI] 0.27–0.66), which did not extend beyond five years (HR 1.01, 95% CI 0.68–1.49). Kidney cancer-related mortality was lower in the partial compared to the radical group for the first four years after surgery (HR 0.16, 95% CI 0.04–0.72). There were no significant differences between the groups for cardiovascular outcomes or non-cancer related deaths.

Conclusions: Overall survival and cancer-specific survival was reduced in radical nephrectomy patients. However, despite reduced renal function in the radical nephrectomy group, non-cancer-related death, cardiovascular events, and dialysis were not significantly different between groups. Long-term benefits of partial nephrectomy may be less than previously believed.

Introduction

Partial nephrectomy is the preferred treatment for localized renal masses because of equivalent cancer control and improved postoperative renal function compared with radical nephrectomy.[1-3] In non-surgical patients, lower renal function is associated with higher cardiovascular events and shorter survival, hence, partial nephrectomy has been considered to be potentially protective against renal failure and future cardiovascular morbidity.[4-7] This is supported by cohort studies and a recent systematic review demonstrating lower cardiovascular-related events for partial nephrectomy.[8-11] Surprisingly, the only randomized trial of partial vs. radical nephrectomy showed that partial nephrectomy resulted in greater mortality.[12] It is possible that the prognostic significance of surgically induced renal function loss differs from a medical renal loss from conditions such as diabetic nephropathy and its association with a higher risk of cardiovascular disease.[5] Using a large cohort of patients undergoing surgery for renal cell carcinoma (RCC), we examined the association between surgery and mortality, long-term cardiovascular events, and renal-related events. We hypothesized that partial nephrectomy vs. radical nephrectomy would be associated with reduced mortality owing to fewer cardiovascular complications and reduced need for renal replacement therapy.

Methods

Study design and setting

Residents of Ontario, Canada have universal access to hospital care and physician services covered under the Ontario

Health Insurance Plan program. These healthcare encounters are recorded in large, population-based databases, which are linked using unique, encoded identifiers and held at the ICES (formerly known as the Institute for Clinical Evaluative Sciences). This study was completed through the ICES Kidney, Dialysis, and Transplantation research program and all analyses were performed at the ICES Western site in London, Ontario. This study was approved by Western University (#102933), the Hamilton Integrated (#14-283-D), and the Ottawa Health Science Network (#20140446-01H) Research Ethics Boards. We followed the reporting guidelines for observational studies (Supplementary Table 1; available at *cuaj.ca*).[13]

Data sources

Institutional medical record departments identified all partial and radical nephrectomy procedures performed between April 1, 2002 and March 31, 2010 (to ensure a minimum of five years followup) from three large academic hospitals in Ontario (London Health Sciences Centre, St. Joseph's Healthcare in Hamilton, and the Ottawa Hospital). These data were then linked to seven other datasets held at ICES to ascertain information on hospitalizations (Canadian Institute for Health Information's Discharge Abstract Database and Same Day Surgery Database); physician billings for healthcare procedures (Ontario Health Insurance Plan claims database); operating physicians (the ICES Physician database); prescription drug information available only for individuals 66 years and older (Ontario Drug Benefit database); information on patients with end-stage kidney disease or previous kidney transplants (the Ontario portion of the Canadian Organ Replacement Register); vital status information, such as birth and death data (Registered Persons Database), and cause of death data from death certificates (Office of the Registrar General).

Patients and exposure status

Only patients from surgical RCC databases were included in the study

The date of the partial or radical nephrectomy procedure was the index date. Patients were excluded from the study if they had a tumor size >7 cm (partial nephrectomy is rarely performed for higher than stage 2 RCC), if the surgery date was not between a hospital admission and discharge date (to ascertain hospitalization characteristics and eliminate any recording errors), if patients had evidence of receiving dialysis in the previous year, if they had a kidney transplant, if there was tumor thrombus, or metastatic disease. If patients had more than one nephrectomy during the study period, the first surgery was considered the index procedure.

Outcomes

Patient outcomes were assessed from index date until end of followup, with the latest possible followup date of March 31, 2015. Emigration from Ontario is very low (0.1%/year) and was the only reason for lost study followup.[14] The primary outcome was all-cause mortality. The secondary outcomes were hospitalization with a major cardiovascular event (myocardial infarction, stroke, coronary artery bypass surgery, coronary angioplasty), a composite of death or hospitalization with major cardiovascular event, non-cancer-related mortality, kidney cancer-related death, any dialysis, and nephrologist visits. Tertiary outcomes were non-cancer-related deaths stratified by preoperative estimated glomerular filtration rate (eGFR). All analyses were censored for death where relevant.

Prespecified subgroup analyses for the primary outcome of all-cause mortality were completed for preoperative eGFR (<45 vs. ≥45 mL/min/1.73 m^2) and tumor size (≤4 cm vs. >4 cm) in order to assess whether pre-existing medical renal disease and tumor stage affected the impact of partial vs. radical nephrectomy on survival. Post-hoc subgroup analyses were also completed for non-cancer-related death stratified by preoperative eGFR and for all-cause mortality stratified by sex.[4,15-17]

Postoperative outcomes (in the 30 days following nephrectomy) were serum creatinine and eGFR, length of hospital stay, nephrologist consults, postoperative intensive care unit (ICU) stay, receipt of dialysis, hospitalizations for major cardiovascular events, and all-cause mortality (Supplementary Table 2; available at *cuaj.ca*).

Baseline characteristics

Baseline characteristics describing the index surgery were abstracted from the medical record, including date of surgery, surgery site, tumor size based on radiographic measurements, and preoperative serum creatinine and eGFR, as tumor size and some kidney function measures were not available in ICES data. Information on laparoscopic vs. open surgery were obtained from the ICES datasets. Other baseline characteristics obtained from ICES datasets included demographics (patient age, sex, neighborhood income level based on the census, and rural or urban residence), Johns Hopkins' Adjusted Clinical Group (ACG) scoring system[18] to assess comorbidities based on resource use in the past year, previous visits to a nephrologist, comorbidities or cardiovascular procedures in the five years prior, and prior prescription medications among patients 66 years or older.

Analysis

All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, U.S.). Baseline characteristics were

compared between partial and radical nephrectomy groups, where a two-sided p-value less than 5% was considered statistically significant, with no adjustment for multiple testing. A multivariable logistic regression model including 11 baseline characteristics was used to calculate propensity scores for the probability of receiving a radical vs. a partial nephrectomy. These 11 variables were age, sex, tumor size, hospital center, surgery type, surgery year, preoperative eGFR, ADG score, previous carotid ultrasound, previous prescription for nitrates, and previous prescription for statins. These characteristics were included either because they were significantly different between the two groups or there was previous evidence of an association with the exposure it was forced into the model. Using this propensity score, we created inverse probability of treatment weights (IPTW) in order for the radical group to better resemble the partial group across the measured baseline characteristics. This 'weighted sample' is essentially a pseudo-sample of people in the radical group who have a similar distribution of baseline characteristics as the partial group. This eliminates some of the potential for confounding based on differences in the characteristics between the two groups, so the associations between groups and the outcomes are less biased, while not excluding any individuals from the analysis.[19] IPTW weights were trimmed at the 1st and 99th percentiles to limit the influence of instable weights.[20]

Hazard ratios (HR) were estimated using Cox proportional hazards regression models, accounting for weighting. To test for proportionality, we created a time-dependent covariate by modelling an interaction of procedure type and log-transformed followup time. If this time-dependent covariate was significant, then the proportionality assumption was considered violated.[21] For outcomes where the proportionality assumption did not hold, the Cox models were time-stratified using Heaviside functions such that the proportionality assumption was met within each time period. Kaplan-Meier curves were generated to visualize differences in survival time between partial and radical nephrectomy groups. As a sensitivity analysis, we repeated analyses using Fine and Gray's model with death as a competing event.

Results

Baseline characteristics

There were 2108 nephrectomy procedures abstracted from three academic hospitals, and 1457 patients in the cohort after the exclusion criteria were applied (Supplementary Fig. 1; available at *cuaj.ca*). The baseline characteristics between the two groups prior to and after propensity score weighting are presented in Table 1. Prior to weighting, the partial nephrectomy group was younger, more likely to have an open procedure, more likely to have smaller tumors, and had higher preoperative eGFR. After propensity score weighting, the groups were well-balanced across the measured health characteristics, with the exception of a slightly higher eGFR (81 [20.7] vs. 78 [16.9] mL/min/1.73 m^2) for the partial compared to the radical group, respectively.

Postoperative outcomes

Perioperative and postoperative outcomes at 30 days and one year are presented in Table 2. The mean (standard deviation [SD]) one-year postoperative eGFR values for the weighted cohort were 71 (22.3) and 52 (13.4) mL/min/1.73 m^2 for the partial and radical groups, respectively (p<0.0001). The proportion of patients who received a nephrology consultation within the year after nephrectomy was 9.4% for the partial group vs. 18.8% for the radical group (p<0.0001), but the need for chronic dialysis was similar and very low in both groups (Table 3).

Mortality and cardiovascular outcomes

Patients were followed for a median (25th, 75th percentile) of 6.9 (5.2, 8.5) years overall, with a maximum followup of 13.8 years (Supplementary Table 3; available at *cuaj.ca*). Patients were followed until mortality or March 31, 2015, whatever date came first. The incidence of all-cause mortality was significantly lower in the partial nephrectomy group compared to the radical nephrectomy group during the first five years of followup: 20.4 vs. 31.5 deaths per 1000 person-years after weighting (HR 0.42, 95% confidence interval [CI] 0.27–0.66, p=0.0001). However, the association was not evident beyond five years (HR 1.01, 95% CI 0.68–1.49, p=0.98). The Kaplan-Meier curve showing all-cause survival probabilities following partial and radical nephrectomy procedures is presented in Fig. 1. Cumulative incidence of all-cause mortality at one, five, and nine years is shown in Supplementary Table 4 (available at *cuaj.ca*). There was a significant interaction effect by sex after five years or more followup, where for females, partial vs. radical nephrectomy had a protective effect, which was reversed in males (interaction p=0.0006 for 5+ years) (Supplementary Fig. 2; available at *cuaj.ca*).

Partial (vs. radical) nephrectomy did not associate with a different risk of hospitalization with a major cardiovascular event: 10.2 vs. 8.4 events per 1000 person-years in the weighted analysis (HR 1.22, 95% CI 0.75–1.96, p=0.43). The incidence of all-cause mortality or major cardiovascular events for the weighted analysis was 29.0 events per 1000 person-years for the partial group and 38.8 events per 1000 person-years for the radical group. This difference was statistically significant in the first four years of followup (HR 0.68, 95% CI 0.48–0.96, p=0.029) but not after four

Table 1. Baseline characteristics pre- and post-propensity score weighting

Characteristic	Pre-weighting			Post-weighting		
	Partial n=575	Radical n=882	p[1]	Partial n=575	Radical n=490[2]	p[1]
Demographics	Ipsum					
Age, years (mean, SD)	59 (12.45)	62 (12.41)	<0.001	59 (12.45)	59 (9.82)	0.84
Range	21–85	19–92		21–85	19–92	
Women	37.9%	41.7%	0.15	37.9%	39.5%	0.59
Income quintile[3]						
1 (lowest)	17.2%	18.7%	0.28	17.2%	16.2%	0.78
2	18.1%	20.9%		18.1%	20.2%	
3	22.3%	19.0%		22.3%	20.2%	
4	19.8%	20.7%		19.8%	19.6%	
5 (highest)	22.6%	20.6%		22.6%	23.7%	
Rural[4]	18.4%	15.1%	0.09	18.4%	16.4%	0.39
Index surgery characteristics						
Surgery site						
London	28.5%	20.4%	<0.001	28.5%	26.9%	0.63
Ottawa	43.1%	38.8%		43.1%	42.1%	
Hamilton	28.3%	40.8%		28.3%	31.0%	
Surgery type						
Laparoscopic	37.9%	54.6%	<0.001	37.9%	39.7%	0.59
Open	49.0%	34.4%		49.0%	46.0%	
Missing	13.0%	11.0%		13.0%	14.3%	
Tumor size						
≤1 cm	10.1%	1.5%	<0.001	10.1%	9.5%	0.67
2 cm	37.0%	7.7%		37.0%	31.4%	
3 cm	30.4%	21.0%		30.4%	32.8%	
4 cm	14.6%	22.6%		14.6%	17.2%	
5 cm	3.8%	20.7%		3.8%	4.6%	
6 cm	2.4%	15.2%		2.4%	2.6%	
7 cm	1.6%	11.3%		1.6%	2.0%	
Surgery year						
2001–2005	22.80%	39.70%	<0.001	22.80%	26.60%	0.33
2006–2010	77.30%	60.30%		77.30%	73.40%	
Preoperative kidney function						
Serum creatinine (mean, SD)[5]	86 (27)	87 (31)	0.54	86 (27)	91 (32)	0.011
eGFR, mL/min per 1.73 m^2 (mean, SD)[6]	81 (20)	77 (20)	0.003	81 (20)	78 (16)	0.035
≥60	80.2%	76.8%	0.10	80.2%	77.0%	0.71
45–<60	9.9%	13.9%		9.9%	10.9%	
30–<45	5.9%	4.3%		5.9%	6.9%	
<30	1.2%	1.6%		1.2%	2.0%	
Missing	2.8%	3.4%		2.8%	3.2%	
Number of days between preoperative test and index date	12 (35.10)	13 (44.46)	0.58	12 (35.1)	13 (23.26)	0.76

[1]p-values were calculated using Student's t-test for continuous variables and the Chi-squared test for binary and categorical variables. [2]After weighing, the frequency/sample size in the radical group was 490. [3]Missing income inputted into income quintile 3. [4]A rural location is defined as populations <10 000. [5]The mean time between the baseline serum creatinine measurement date and the surgery date was 12 for the group and 13 for the group, which did not change after propensity weighting. [6]eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation; all patients were assumed to be non-black in the CKD-EPI equation, given the lack of data for race (a reasonable assumption since less than 5% of the Ontario population is of black race). [7]All comorbidities were assessed in the past 5 years from the surgery date. [8]Percentages calculated from participants >66 years only, as this is the segment of the population that has universal drug benefits. ACE: angiotensin-converting enzyme; ADG: aggregated diagnostic group; ARB: angiotensin receptor blocker; eGFR: estimated glomerular filtration rate; SD: standard deviation.

years (HR 0.97, 95% 0.67–1.43, p=0.90). In the weighted analysis, the incidence of non-cancer-related deaths was not significantly different between patients in the partial or radical groups (HR 0.88, 95% CI 0.62–1.25, p=0.49) (Fig. 2). The

Table 1 (cont'd). Baseline characteristics pre- and post-propensity score weighting

Characteristic	Pre-weighting			Post-weighting		
	Partial n=575	Radical n=882	p[1]	Partial n=575	Radical n=4902	p[1]
Comorbidities[7]						
Stroke/transient ischemic attack	0.9%	1.1%	0.63	0.9%	0.4%	0.39
Peripheral vascular disease	0.9%	1.6%	0.24	0.9%	1.3%	0.46
Coronary artery disease	24.9%	26.9%	0.40	24.9%	24.4%	0.85
Myocardial infarction	3.0%	2.9%	0.99	3.0%	1.8%	0.21
Diabetes	23.7%	23.1%	0.82	23.7%	20.4%	0.20
Hypertension	60.0%	62.2%	0.39	60.0%	60.8%	0.79
Carotid ultrasound	6.6%	9.9%	0.03	6.6%	8.5%	0.24
Coronary angiogram	7.8%	7.5%	0.81	7.8%	6.8%	0.52
Coronary revascularization	4.5%	3.6%	0.39	4.5%	2.9%	0.18
Echocardiography	30.3%	30.3%	1.00	30.3%	28.6%	0.56
Holter monitor	13.2%	12.1%	0.54	13.2%	10.6%	0.19
Stress test	40.7%	42.5%	0.49	40.7%	44.4%	0.22
Nephrology consult (at least one)	7.8%	6.0%	0.18	7.8%	7.9%	0.98
Johns Hopkins' ADG score in past 1 year (mean, SD)	7 (2.89)	7 (2.78)	0.34	7 (2.89)	7 (2.17)	0.97
0–4	17.9%	16.3%		17.9%	18.7%	
5–9	62.8%	62.7%		62.8%	62.2%	
10-–14	17.2%	20.2%		17.2%	18.1%	
15+	2.1%	0.8%		2.1%	1.0%	
Medications in the past 120 days from index date (for subset >66 years)[8]						
Age ≥66 years	34.4%	41.2%	0.01	34.4%	32.6%	0.53
Diabetes drugs	16.7%	14.6%	0.52	16.7%	16.0%	0.82
ACE inhibitors	40.9%	40.2%	0.87	40.9%	44.4%	0.51
ARBs	16.2%	13.8%	0.44	16.2%	14.4%	0.69
Statins	46.0%	36.9%	0.04	46.0%	41.9%	0.42
Nitrates	4.0%	7.7%	0.09	4.0%	6.3%	0.34
Any anti-hypertensive drug	70.7%	73.6%	0.47	70.7%	74.4%	0.43

[1]p-values were calculated using Student's t-test for continuous variables and the Chi-squared test for binary and categorical variables. [2]After weighing, the frequency/sample size in the radical group was 490. [3]Missing income inputted into income quintile 3. [4]A rural location is defined as populations <10 000. [5]The mean time between the baseline serum creatinine measurement date and the surgery date was 12 for the group and 13 for the group, which did not change after propensity weighting. [6]eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation; all patients were assumed to be non-black in the CKD-EPI equation, given the lack of data for race (a reasonable assumption since less than 5% of the Ontario population is of black race). [7]All comorbidities were assessed in the past 5 years from the surgery date. [8]Percentages calculated from participants >66 years only, as this is the segment of the population that has universal drug benefits. ACE: angiotensin-converting enzyme; ADG: aggregated diagnostic group; ARB: angiotensin receptor blocker; eGFR: estimated glomerular filtration rate; SD: standard deviation.

incidence of kidney cancer-related mortality was 1.5 and 5.1 events per 1000 person-years for the partial and radical groups, respectively (Fig. 3). This difference was statistically significant in the first four years of followup (HR 0.16, 95% CI 0.04–0.72, p=0.017) but not beyond four years (HR 0.83, 95% CI 0.20, 3.42, p=0.80).

Preoperative renal function significantly modified the association of nephrectomy type (partial compared to radical) and all-cause mortality in the first five years of followup, with a significant association observed in those with eGFR ≥45 mL/min/1.73 m^2 (HR 0.36, 95% CI 0.21–0.62, interaction p=0.0025). No significant associations were observed after five years of followup, however, there was a trend towards higher risk of all-cause mortality for eGFR <45 mL/min/1.73 m^2 and lower risk for eGFR ≥45 mL/min/1.73 m^2; a significant interaction by preoperative eGFR status was observed (p<0.0001). Importantly, Fig. 4 demonstrates that partial nephrectomy does not significantly reduce non-cancer-related mortality over radical nephrectomy whether preoperative eGFR is less than or greater than 45 mL/min/1.73 m^2.

Given that partial nephrectomy patients had smaller tumors, on average, we hypothesized that tumor-related confounding may explain the association between partial nephrectomy and overall survival. To explore this hypothesis, patients were stratified into tumors ≤4 cm and >4 cm. However, no significant interactions were observed when stratified by tumor size (interaction p=0.32 for both <5 and 5+ year followup intervals) (Supplementary Fig. 3; available at *cuaj.ca*). The Fine and Gray's model to account for

Table 2. Perioperative and postoperative outcomes in 30 days and one year following nephrectomy, with propensity score weighting

Outcome	Partial n= 575	Radical n=490[1]	p
Perioperative outcomes			
Hospital length of stay, days (mean, SD)	4.66 (2.38)	4.73 (3.01)	0.66
Median, IQR	4 (3–5)	4 (3–5)	
Intensive care unit visit	12 (2.1%)	24.2 (4.9%)	0.0104
Mechanical ventilation in the intensive care unit	<6 (<1.0%)	15.1 (3.1%)	0.0001
Postoperative 30-day outcomes			
Stroke/ transient ischemic attack	0 (0.0%)	<6 (<1.2%)	
Peripheral vascular disease	<6 (<1.0%)	<6 (<1.2%)	
Coronary artery disease	58 (10.1%)	41.3 (8.4%)	0.35
Myocardial infarction	<6 (<1.0%)	<6 (<1.2%)	
Postoperative 1-year outcomes			
eGFR, mL/min per 1.73 m^2			
Mean (SD)	71 (22.35)	52 (13.40)	<0.0001
Median (IQR)	71 (57–88)	51 (41–63)	
Normal/stage 1–2	196 (34.1%)	76.1 (15.5%)	
Stage 3a	36 (6.3%)	70.2 (14.3%)	
Stage 3b	24 (4.2%)	64.8 (13.2%)	
Stage 4–5	14 (2.4%)	24.3 (5.0%)	
Missing	305 (53.0%)	255.1 (52.0%)	
Nephrologist consult (at least one)	54 (9.4%)	92.0 (18.8%)	<0.0001
Stroke/transient ischemic attack	<6 (<1.0%)	<6 (<1.2%)	
Peripheral vascular disease	<6 (<1.0%)	<6 (<1.2%)	
Coronary artery disease	88 (15.3%)	76.65 (15.6%)	0.88
Myocardial infarction	<6 (<1.0%)	<6 (<1.2%)	

Note: Data presented as number (percent) unless otherwise noted; cell sizes <6 have been suppressed in accordance with ICES privacy policies. [1]After weighing, the frequency/ sample size in the radical group was 490. eGFR: estimated glomerular filtration rate; IQR: interquartile range; SD: standard deviation.

a competing risk of death showed similar results for secondary outcomes (Supplementary Table 5; available at *cuaj.ca*).

Discussion

Several studies have demonstrated a significant association of cardiovascular events, hospitalization, and even death with the reduction of eGFR in the analyses of large, high-risk population databases.[5-7] Therefore, despite showing that partial nephrectomy conferred superior renal function compared with radical nephrectomy, we were surprised to show that there was not a difference in the long-term need for dialysis, nor was there a difference in cardiovascular events or non-cancer-related mortality between partial and radical nephrectomy groups. However, the aforementioned studies were performed in community-based populations, with the majority of patients having medical renal disease as the cause of lower eGFR. Indeed, in our current study, patients with preoperative eGFR <45 ml/min/1.73m^2 had inferior all-cause mortality irrespective of operative intervention, illustrating the impact of medical renal disease on overall health. In contrast, healthy patients with significant acute renal loss from nephrectomy (donor nephrectomy) do not have a long-term higher risk of death, cardiovascular events, or hospitalization compared with the general population.[22] Although there may be a higher risk of renal replacement therapy long-term, this risk is relatively low.[23] Therefore, there appears to be a distinct difference in the impact of long-standing medical renal disease vs. surgical renal loss with regards to general cardiovascular and renal health.

Compared with patients undergoing donor nephrectomy, patients with RCC are older and have a more significant history of smoking, hypertension, obesity, and diabetes.[24] As well, a number of patients undergoing extirpative surgery for RCC have impaired renal function, with 19% being classified as stage 3 chronic kidney disease or greater in our population, preoperatively. In fact, we have shown that the presence of diabetes and lower preoperative eGFR are independent predictors of ongoing long-term renal functional loss in patients undergoing radical nephrectomy.[24] These patients may theoretically be at heightened risk for hyperfiltration injury and accelerated renal loss to end-stage kidney disease. Nevertheless, in this population of patients with coexisting medical renal disease, the impact of the degree of surgical renal loss (radical vs. partial nephrectomy) on the acceleration of cardiovascular morbidity and mortality risk was unknown.

For patients with renal tumors, partial nephrectomy has been shown to be associated with better renal function preservation compared to radical nephrectomy, while achieving equivalent oncological outcomes.[1,11] However, the long-term impact of this renal function preservation has not been established, and the only randomized controlled trial (EORTC) revealed worse survival in the partial nephrectomy arm.[12] This study has been criticized for a lengthy and limited patient accrual and it is possible that this study was biased by clinicians accruing patients that were healthier, with superior preoperative renal function than "real-world" patients with RCC. For the first time, we have shown that although there is a higher proportion of patients with stage 3 chronic kidney disease or greater one year following radical nephrectomy, non-cancer-related mortality and cardiovascular events were not different compared to the partial nephrectomy group after a five-year minimum followup. Furthermore, while the proportion of patients requiring nephrology consultation was higher in the radical nephrectomy group, the rate of

Table 3. Incidence rates and hazard ratios for primary and secondary outcomes among the weighted cohort. Patients in both groups were followed for a median (25th, 75th percentile) of 6.9 (5.2, 8.5) years, maximum 13.8 years

Outcome	Exposure	Incidence rate per 1000 person years	Hazard ratio (95% confidence interval)	
All-cause mortality			0–<5 years	5+ years
	Partial	20.4	0.42 (0.27, 0.66)	1.01 (0.68, 1.49)
	Radical	31.5	1.00 (referent)	1.00 (referent)
Hospitalization with major cardiovascular event			Total followup period	
	Partial	10.2	1.22 (0.75, 1.96)	
	Radical	8.4	1.00 (referent)	
All-cause mortality or cardiovascular disease			0–<4 years	4+ years
	Partial	29.0	0.68 (0.48, 0.96)	0.97 (0.67, 1.43)
	Radical	38.8	1.00 (referent)	1.00 (referent)
Non-cancer-related mortality			Total followup period	
	Partial	15.2	0.88 (0.62, 1.25)	
	Radical	18.7	1.00 (referent)	
Kidney cancer-related mortality			0–<4 years	4+ years
	Partial	1.5	0.16 (0.04, 0.72)	0.83 (0.20, 3.42)
	Radical	5.1	1.00 (referent)	1.00 (referent)
Any dialysis (acute or chronic)			Total followup period	
	Partial	3.5	1.27 (0.56, 2.86)	
	Radical	2.8	1.00 (referent)	
Nephrologist visit			Total followup period	
	Partial	28.7	0.40 (0.31, 0.51)	
	Radical	78.2	1.00 (referent)	

For outcomes where the proportionality assumption did not hold, the Cox models were time-stratified such that the proportionality assumption was met within each time period (at 4 or 5 years).

renal replacement therapy was similarly low in both groups. Even in a subset of patients with stage 3 chronic kidney disease preoperatively (eGFR <45), there was no difference in non-cancer-related mortality between groups. Another study using the ICES databases found an association between partial nephrectomy and reduced need for dialysis.[25] While that study evaluated all patients in Ontario, the analysis was limited because of lack of baseline renal function data.

Unlike the previous EORTC randomized trial comparing partial and radical nephrectomy, we found that cancer-related mortality was higher in the radical nephrectomy group within the first four years of followup.[12] This trend persisted

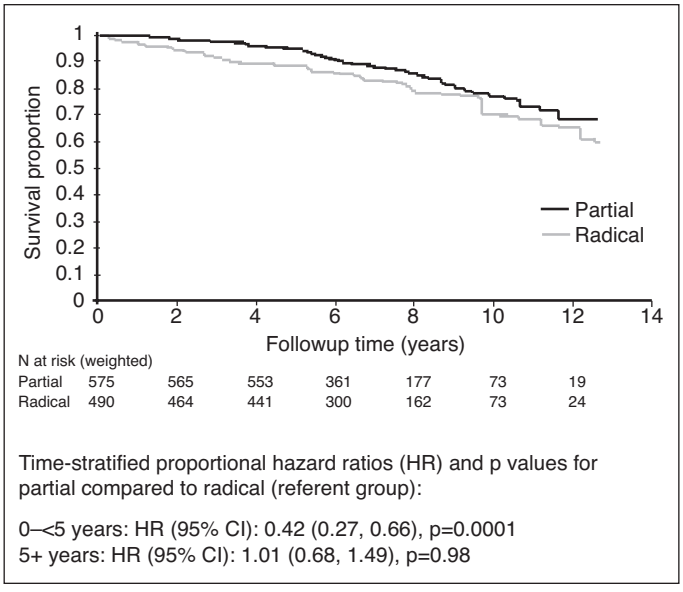

Fig. 1. Kaplan-Meier curve of survival time following partial and radical procedures. CI: confidence interval; HR: hazard ratio.

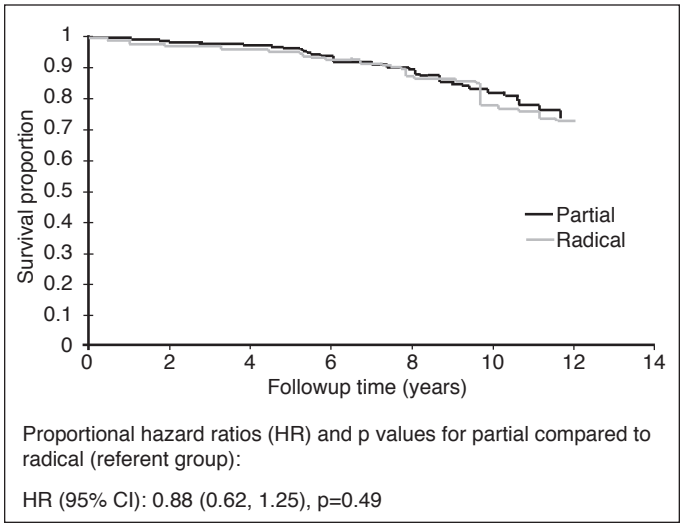

Fig. 2. Kaplan-Meier curve of non-cancer-related survival time following partial and radical procedures. CI: confidence interval; HR: hazard ratio.

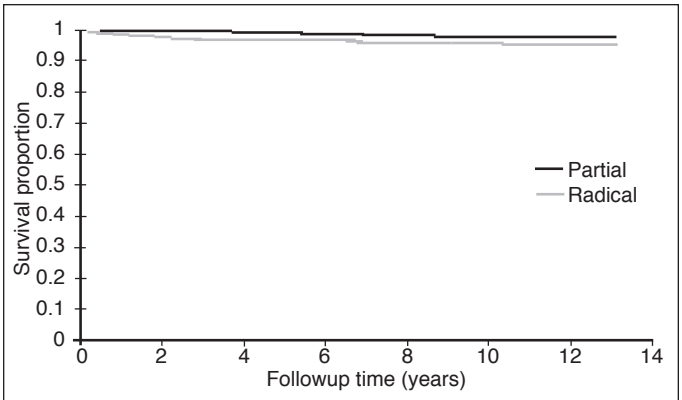

Fig. 3. Kaplan-Meier curve of kidney cancer-related survival time partial and radical procedures. CI: confidence interval; HR: hazard ratio.

even when we analyzed the data in subsets of patients with tumors ≤4 cm and >4 cm. This was not explained by a higher early complication rate or mortality (<30-day). We believe this finding may be the result of residual confounding, despite use of propensity score weighting, with higher-risk patients receiving radical nephrectomy. This hypothesis could not be examined in more detail because we did not capture postoperative tumor type, tumor grade, or tumor stage, all factors associated with cancer prognosis.[26] It is likely that radical nephrectomy was performed in patients with more central tumors or with tumors with a more aggressive radiological appearance. As central tumors are associated with poorer prognosis, this may explain the inferior oncological outcomes in the radical nephrectomy group.[27]

In addition to the lack of detailed baseline tumor information, this study should be interpreted with caution because of the lack of long-term reassessment of renal function through the ICES database. While the length of followup is longer than most studies in this field, the time to cardiovascular events may be longer than what we were able to observe and the protective effect of partial nephrectomy may emerge with longer followup.

Conclusions

Based on this analysis, the type of extirpative procedure was not associated with non-cancer-related mortality, cardiovascular events, or renal outcomes. This indicates that the hyperfiltration effect from greater surgical renal loss (radical nephrectomy) may not have the same implications with the progressive effect associated with medical renal disease.

Competing interests: The authors report no competing personal or financial interests related to this work.

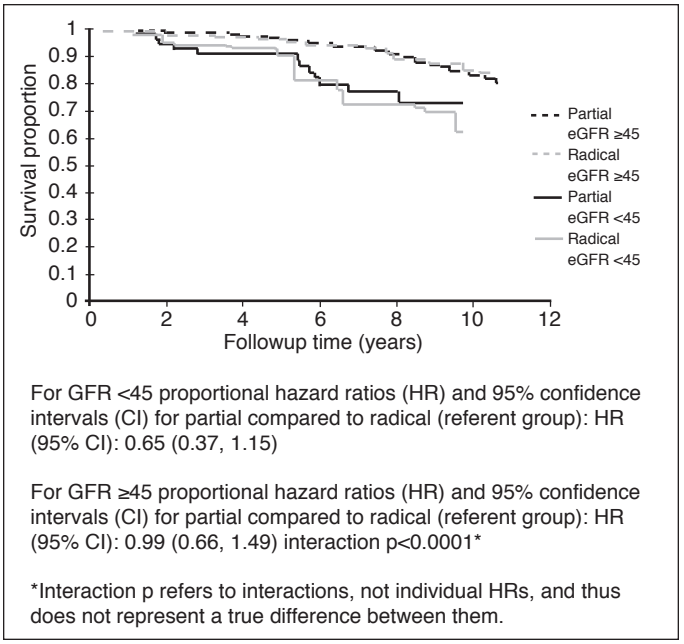

Fig. 4. Kaplan-Meier curve of non-cancer-related survival in patients stratified by preoperative estimated glomerular filtration rate (eGFR). CI: confidence interval; HR: hazard ratio.

Access to data: The data set from this study is held securely in coded form at the Institute for Clinical Evaluative Sciences (ICES). While data-sharing agreements prohibit ICES from making the data set publicly available, access can be granted to those who meet prespecified criteria for confidential access, available at *www.ices.on.ca/DAS*. The use of ICES data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board. The full data set creation plan is available from the authors upon request.

This paper has been peer-reviewed

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Correspondence: Dr. Patrick P. Luke, Divisions of Urology and General Surgery, Department of Surgery Western University, London, ON, Canada; Patrick.Luke@lhsc.on.ca