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ORIGINAL RESEARCH

Tumor size and postoperative kidney function following radical nephrectomy

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Background: Chronic kidney disease (CKD) following nephrectomy for kidney tumors is common, and both patient and tumor characteristics may affect postoperative kidney function. Several studies have reported that surgery for large tumors is associated with a lower likelihood of postoperative CKD, but others have reported CKD to be more common before surgery in patients with large tumors.

Objective: The aim of this study was to clarify inconsistencies in the literature regarding the prognostic significance of tumor size for postoperative kidney function.

Study design and setting: We analyzed data from 944 kidney cancer patients managed with radical nephrectomy between January 2012 and December 2013, and 242 living kidney donors who underwent surgery between January 2011 and December 2014 in the Australian states of Queensland and Victoria. Multivariable logistic regression was used to assess the primary outcome of CKD upstaging. Structural equation modeling was used to evaluate causal models, to delineate the influence of patient and tumor characteristics on postoperative kidney function.

Results: We determined that a significant interaction between age and tumor size (P=0.03) led to the observed inverse association between large tumor size and CKD upstaging, and was accentuated by other forms of selection bias. Subgrouping patients by age and tumor size demonstrated that all patients aged ≥65 years were at increased risk of CKD upstaging, regardless of tumor size. Risk of CKD upstaging was comparable between age-matched living donors and kidney cancer patients.

Conclusion: Larger tumors are unlikely to confer a protective effect with respect to postoperative kidney function. The reason for the previously reported inconsistency is likely a combination of the analytical approach and selection bias.

Keywords: renal cell carcinoma, glomerular filtration rate, selection bias, tumor size, kidney cancer, living kidney donors

Introduction

In Australia, despite increased uptake up nephron-sparing approaches, radical nephrectomy remains the most common management approach for kidney masses suspicious of malignancy.[1] Nephron mass reduction is associated with an increased risk of subsequent kidney functional decline and development of chronic kidney disease (CKD). In patients managed with radical nephrectomy, a complex interplay between tumor and patient characteristics determines the pre-to-postoperative change in kidney function. This interplay is not well described.

Patient characteristics associated with postoperative kidney function are those related to the overall health and functional reserve of the kidney, predominantly patient age and comorbidities, which cause damage to the kidneys.[2,3] The associated bilateral

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chronic fibrotic cortical damage, with concomitant nephron dysfunction, reduces the ability of the remaining nephrons to compensate for increased functional demand following resection of the affected kidney.[2,3]

The role of tumor characteristics in determining postoperative kidney function most likely relate to the influence of the tumor on preoperative kidney function, as a consequence of the physical effects of tumor expansion into kidney parenchyma. An expanding tumor is likely to cause dysfunction and eventual loss of adjacent nephrons. Consequently, the glomerular filtration rate (GFR) of the affected kidney is likely to decline. This nephron loss is suggested to generate functional demand, which may be compensated for by increased single-nephron GFR of the remaining nephrons.[4] Tumor size and complexity are likely determinants of this, and some studies have reported that risk of postoperative CKD is greater for patients with small tumors managed with radical nephrectomy, compared with larger tumors.[5,6] Conversely, preoperative kidney function has been reported to be worse in patients with larger tumors.[5,7] This presents a paradox: patients with larger tumors are at increased risk of CKD before nephrectomy, but apparently decreased the risk of CKD after nephrectomy.

The objective of this study was, therefore, to comprehensively investigate the association between tumor size and kidney function following radical nephrectomy, using data from population-based samples of people undergoing nephrectomy for renal cell carcinoma (RCC) or for kidney donation, in order to resolve the apparent paradox stated above. Living kidney donors were included as a comparison group, as their kidney function is not affected by a preexisting tumor and they are generally free from significant underlying health conditions affecting kidney function. We hypothesized that associations would vary according to patient age because of the strong associations between age and CKD,[8] and evidence that compensation for nephron mass reduction is modified by age.[9] We also aimed to thoroughly evaluate potential sources of bias in our results.

Patients and methods

Study population

The present analysis included data from an Australian kidney cancer patterns of care study, which captured relevant information on all patients diagnosed with incident RCC between January 2012 and December 2013 who were residents of the Australian states of Queensland and Victoria.[10] There were 2,323 patients aged ≥18 years who were notified to either Queensland or Victorian Cancer Registries with newly diagnosed RCC. Patients were excluded if they: were not managed surgically (n=229), underwent partial nephrectomy (n=657), had missing values for preoperative (n=270) or postoperative (n=119) estimated GFR (eGFR), or had a preoperative eGFR <45 mL/min per 1.73 m^2 (n=104). After exclusion criteria were applied, data for 944 patients were available for analysis (Figure 1).

We included a sample of living kidney donors as a comparison group. All living donors notified to the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry who donated a kidney in Queensland or Victoria between January 2011 and December 2014 were identified (n=461). Of these, 242 patients had data on 12-month follow-up kidney function available. Missing data were presumed to be missing at random.

Ethical considerations

Approval to access medical records was obtained under the Queensland Public Health Act and the human research ethics committees of Cancer Council Victoria, QIMR Berghofer Medical Research Institute, and Metro South

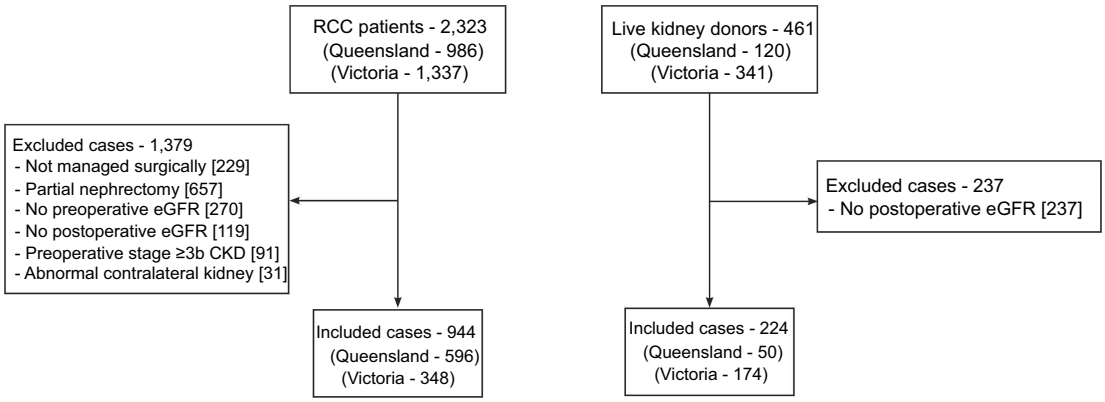

Figure 1 Study participants. Flow diagram demonstrating the application of exclusion criteria in study cohorts.
Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RCC, renal cell carcinoma.

Hospital and Health Service. Accessing ANZDATA records was designated low risk and approved by the University of Queensland.

Exposures

The Queensland and Victorian Cancer Registries provided sufficient identifying information to study staff to access medical records of patients with RCC. Data on age, sex, serum creatinine concentration, comorbidities; and tumor size, location, and histology for patients managed with RCC, were abstracted. Tumor size was recorded as the largest diameter in the pathology report, and grouped as ≤70 mm and >70 mm (the upper bound for classifying T1 tumors).[11] Age was categorized as <65 and ≥65 years, as this threshold has prognostic significance in patients with CKD.[12] We calculated eGFR using the CKD-EPI equation.[13] To evaluate comorbidity burden, a Charlson comorbidity index was calculated for RCC patients, excluding parameters relating to the RCC;[14] this was categorized as low-medium (0–1) and high (≥2). As albuminuria measurements and tumor complexity data were not available for most RCC patients, they were not considered. Demographic data for living donors were supplied by ANZDATA. Living donors were assumed to fall into the low-medium category for comorbidities, due to extensive medical screening and exclusions applied to potential kidney donors in Australia.[15]

Outcomes

Postoperative kidney function was recorded at approximately 12 months after surgery for the majority of patients. We considered postoperative eGFR as a continuous outcome and CKD upstaging as a categorical outcome. CKD upstaging was defined as new-onset postoperative eGFR <60 or <45 mL/min per 1.73 m^2 (if preoperative eGFR was ≥60 or ≥45 mL/min per 1.73 m^2, respectively), corresponding to new-onset stage 3a or 3b (or greater) CKD.[16]

Statistical analysis

Patient and tumor characteristics, and exclusion criteria, were first compared descriptively between groups. To replicate the approach used by previous studies, we then used univariable and multivariable logistic regression to investigate the association between tumor size and CKD upstaging in RCC patients. Multivariable models were adjusted only for potential confounders (not mediators), which we identified using directed acyclic graphs. The association between other patient and tumor characteristics and these outcomes was also evaluated in a similar fashion, in order to contextualize results. As previous studies have demonstrated that CKD upstaging after nephrectomy is relatively common,[10] we also used log-binomial regression to estimate relative risks; however, convergence was not achievable in some multivariable models, so more parsimonious models were used. We were therefore not able to use this as our main analytic strategy.

Previous studies that have evaluated the association between tumor size and postoperative kidney function adjusted for preoperative eGFR,[5,6] which we considered to be a potential mediator of this association. As a sensitivity analysis, we developed an additional model which adjusted for preoperative eGFR.

CKD upstaging may not be the best measure to investigate the relationship between tumor size and postoperative CKD, as many patients with larger tumors have already experienced significant preoperative reduction in kidney function due to tumor expansion, and thus nephrectomy may result in only minimal further decline. To address this, we also compared groups (those with large and small tumors) using linear regression analysis, considering postoperative eGFR as the outcome.

As certain patient characteristics (eg, age, sex, comorbidity burden, and preoperative eGFR) may affect the ability of the kidney to compensate for surgical removal of nephrons, we also assessed whether there was an interaction between these parameters and tumor size, by adding a first-order multiplicative interaction term to logistic regression models. A significant interaction between age and tumor size was noted. To investigate this further, patients were subgrouped by clinically relevant thresholds for both age and tumor size. We used logistic and linear regression models to compare the association between subgroup membership and CKD upstaging, or postoperative eGFR, respectively. We then added living kidney donors grouped by the same age thresholds (designating donors aged <65 years the reference group) in order to see how the results were affected by comparisons with patients who did not have a kidney tumor. There were 129 RCC patients aged >75 years that were not included in this analysis, as there were no comparable living donors of this age. Models were initially adjusted only for confounders, and subsequently also adjusted for preoperative eGFR. Two additional sensitivity analyses were conducted evaluating postoperative eGFR using linear regression analysis, considering broadened inclusion criteria. Patients with a preoperative eGFR >30 mL/

min per 1.73 m^2, and patients with any preoperative eGFR were included in these two subsequent analyses.

As we were particularly interested in the relationship between tumor and patient characteristics, and postoperative eGFR (and whether tumor size directly leads to lower risk of postoperative CKD), we also used structural equation modeling to investigate and visualize this relationship. Because the effect of tumor size on postoperative eGFR at 12 postoperative months would either work indirectly through its influence on preoperative eGFR, or through both direct and indirect pathways, we considered two prespecified models in this analysis. The first assumed there was a direct causal path between tumor size and postoperative eGFR; the second did not consider this pathway, instead assuming that the only causal path between tumor size and postoperative eGFR was indirect, via preoperative eGFR. The relationship between variables was compared across the two models.

All analysis was performed using Stata 13.0 (Stata Corp, College Station, TX, USA).

Results

Clinical characteristics

Characteristics of the study population are presented in Table 1 and Table S1. Exclusion criteria for RCC patients, compared across subgroups, are presented in Table S2. Kidney function was recorded at a median (interquartile range) follow-up time of 12.0 (9.8–13.3) and 12.1 (11.0–13.2) months for patients with RCC and living kidney donors, respectively. Donors were younger on average, with higher preoperative eGFR than RCC patients. The male-to-female ratio of donors was approximately equal, whereas there was a male predominance in patients with RCC. When compared on tumor size, patients with

Table 1 Clinical characteristics of patients grouped by indication/tumor size, and age

	Live kidney donors		**Tumors ≤70 mm**		**Tumors >70 mm**	
Age (years):	<65 (N=189)	≥65 (N=35)	<65 (N=354)	≥65 (N=200)	<65 (N=117)	≥65 (N=52)
Age at time of surgery—years						
Median [IQR]	52 [46–60]	68 [66–70]	56 [49–60]	70 [67–73]	55 [48–60]	70 [67–73]
Sex						
Female	99 (52)	16 (46)	132 (37)	62 (31)	39 (33)	19 (37)
Male	90 (48)	19 (54)	222 (63)	138 (69)	78 (67)	33 (63)
Charlson comorbidity index (score)						
0–1	189 (100)	35 (100)	296 (84)	149 (75)	103 (88)	39 (75)
≥2	-	-	58 (16)	51 (25)	14 (12)	13 (25)
Preoperative eGFR—mL/min per 1.73m^2						
Median [IQR]	98 [88–105]	80 [72–93]	93 [77–105]	76 [65–86]	86 [71–99]	73 [58–89]
<60	3 (2)	3 (9)	20 (6)	34 (17)	14 (12)	14 (27)
Postoperative eGFR—mL/min per 1.73m^2						
Median [IQR]	63 [55–71]	51 [42–58]	60 [49–71]	49 [40–56]	61 [53–72]	52 [43–64]
<60	77 (41)	29 (83)	182 (51)	169 (85)	54 (46)	34 (66)
(45–59)	66 (35)	17 (49)	135 (38)	93 (47)	43 (37)	17 (33)
(<45)	11 (6)	12 (34)	47 (13)	76 (38)	11 (9)	17 (33)
eGFR Decrease—mL/min per 1.73m^2						
Median [IQR]	34 [26–41]	29 [22–36]	30 [23–41]	26 [20–34]	22 [12–35]	18 [8–30]
Follow-up time—months						
Median [IQR]	12.1 [10.0–13.2]	12.1 [11.1–13.0]	12.0 [10.1–13.6]	11.9 [9.9–13.4]	11.9 [9.9–13.1]	11.5 [7.9–13.2]

Notes: Data presented as count (%), unless otherwise indicated. Postoperative kidney function was recorded at approximately 12 months after surgery for the majority of patients.
Abbreviations: eGFR, estimated glomerular filtration rate.

tumors ≥70 mm generally had lower preoperative eGFR and smaller pre-to-postoperative ΔeGFR. When comparing postoperative eGFR between patients subgrouped by age and indication/tumor size, older patients tended to have lower postoperative eGFR values, but there were no major differences in the postoperative eGFR of patients of similar age grouped by tumor size (Figure 2).

Associations with CKD upstaging

Tumor size was the only tumor characteristics associated with CKD upstaging; tumors ≥70 mm were inversely associated (adjusted odds ratio [aOR]: 0.6, 95% CI: 0.4–0.8) when adjustment was made only for potential confounders (Table 2). After adjustment was made for preoperative eGFR (mediator), this inverse association became stronger (aOR: 0.4, 95% CI: 0.3–0.6).

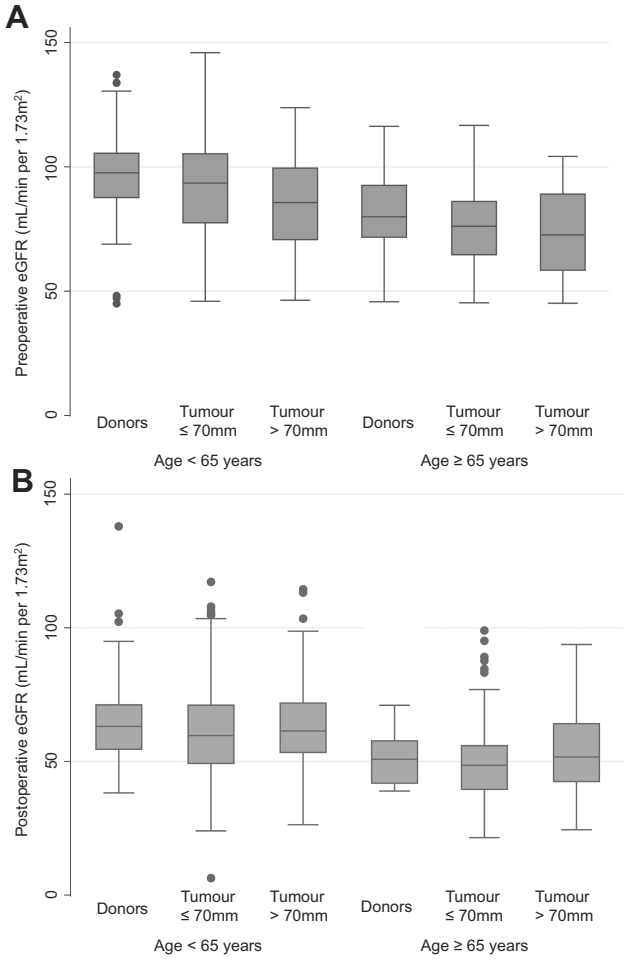

Figure 2 Comparison of (**A**) pre- and (**B**) postoperative estimated glomerular filtration rate (eGFR) by patients grouped by age and tumor size/indication. Box and whisker plot of pre- and postoperative eGFR, with patients subgrouped by age and indication. Postoperative kidney function was recorded at approximately 12 months after surgery for the majority of patients.

The patient characteristics most strongly associated with CKD upstaging were age (aOR per 5-year increase: 1.5, 95% CI: 1.4–1.6), male sex (aOR: 1.4, 95% CI: 1.0–1.9), and preoperative eGFR (aOR per 5-unit decrease: 1.2, 95% CI: 1.2–1.3) (Table 2).

Interaction between patient age and tumor size

There was a significant interaction between age and tumor size (P=0.03). Compared with patients aged <65 years with tumors <70 mm, patients ≥65 years with tumors <70 mm were at increased risk of CKD upstaging (aOR: 5.2, 95% CI: 3.5–7.5), as were patients aged ≥65 years with tumors ≥70 mm (aOR: 1.9, 95% CI: 1.0–3.1). There was no statistically significant difference in the risk of CKD upstaging in patients aged <65 years with tumors ≥70 mm (aOR: 0.8, 95% CI: 0.5–1.1). The association between tumor size and postoperative kidney function stratified by age is presented in Table S3.

Comparisons with living kidney donors

To investigate interactions between age and tumor size further, analyses were performed including living kidney donors, considering donors aged <65 years as the reference group, as by definition postoperative kidney function in these patients was not impacted by tumor factors (Figure 3A; Table 3). Compared with younger donors, patients aged <65 years with tumors of any size had similar risk of CKD upstaging. Donors aged ≥65 years and patients in the same age group with smaller tumors were at similarly increased risk of CKD upstaging compared with donors aged <65 years (aOR: 6.2, 95% CI: 2.5–15.0; and aOR: 6.1, 95% CI: 3.7–10.0, respectively). Patients with larger tumors aged ≥65 years were also at increased risk of CKD upstaging, but to a lesser degree (aOR: 1.9, 95% CI: 1.0–3.5). After adjustment for preoperative eGFR, the association between tumor size and CKD upstaging became inverse for patients with tumors ≥70 mm, while associations for patients with smaller tumors remained similar to age-matched living kidney donors (Figure 3B). Log-binomial regression models estimating relative risk rather than odds ratios showed similar patterns to the logistic regression analysis, but with substantially smaller differences in estimates between the groups of patients aged ≥65 years.

Linear regression analyses evaluating postoperative eGFR demonstrated a similar pattern of results to the

Table 2 Associations between patient and tumor characteristics, and chronic kidney disease (CKD) upstaging in 944 patients who underwent radical nephrectomy for kidney tumors, considering the interaction between tumor size and patient characteristics

	CKD upstaged						
	No N (%)	**Yes N (%)**	**Crude OR (95% CI)**	**Adjusted OR [a] (95% CI)**	**Crude RR (95% CI)**	**Adjusted RR (95% CI)**	**Interaction *P*-value [b]**
Patient characteristics	(N=371)	(N=573)					
Age at diagnosis—years							
<65	282 (76)	248 (43)	1		1		
≥65	89 (24)	325 (57)	4.2 (3.1–5.6)		1.7 (1.5–1.9)		0.03
Per 5 year increase	-	-	1.5 (1.4–1.6)		1.1 (1.0–1.2)		
P-value			<0.001		<0.001		
Age at diagnosis (expanded by tumor size) [c]							
(Tumor <70mm)							
<65	178 (48)	176 (31)	1	1	1	1	
≥65	47 (13)	248 (43)	5.3 (3.7–7.7)	5.2 (3.5–7.5)	1.7 (1.5–1.9)	1.7 (1.5–1.9)	
(Tumor ≥70mm)							
<65	67 (18)	50 (9)	0.8 (0.5–1.2)	0.8 (0.5–1.1)	0.9 (0.7–1.1)	0.9 (0.7–1.1)	
≥65	26 (7)	48 (8)	1.9 (1.1–3.1)	1.9 (1.0–3.1)	1.3 (1.1–1.6)	1.3 (1.1–1.6)	
Sex							
Female	144 (39)	187 (33)	1	1	1	1	
Male	227 (61)	386 (67)	1.3 (1.0–1.7)	1.4 (1.0–1.9)	1.1 (1.0–1.2)	1.1 (0.9–1.2)	0.93
P-value			0.05	0.04	0.05	0.07	
Charlson comorbidity index							
Low-medium (0–1)	312 (84)	437 (76)	1	1	1	1	
High (≥2)	59 (16)	136 (24)	1.6 (1.1–2.3)	1.1 (0.7–1.5)	1.2 (1.1–1.3)	1.0 (0.9–1.2)	0.89
P-value			0.004	0.73	0.002	0.38	
Preoperative eGFR—mL/min per 1.73m^2							
≥80	226 (61)	105 (18)	1	1	1	1	
60–79	100 (27)	368 (64)	7.9 (5.8–11.0)	5.9 (4.2–8.4)	2.5 (2.1–2.9)	2.5 (2.1–2.9)	0.54
45–59	45 (12)	100 (17)	4.8 (3.1–7.3)	2.2 (1.4–3.6)	2.2 (1.8–2.6)	2.2 (1.8–2.6)	0.75
P-value			<0.001	<0.001	<0.001	<0.001	
Tumor characteristics							
Tumor histology							
Clear cell	271 (73)	416 (73)	1	1	1	1	
Other	100 (27)	157 (27)	1.0 (0.8–1.4)	1.0 (0.7–1.4)	1.0 (0.9–1.1)	1.0 (0.9–1.1)	
P-value			0.88	0.83	0.88	0.83	
Tumor crossed polar lines							
No	219 (59)	346 (60)	1	1	1	1	
Yes	119 (32)	186 (32)	0.9 (0.7–1.3)	1.0 (0.7–1.3)	1.0 (0.9–1.1)	1.0 (0.9–1.1)	
P-value			0.94	0.96	0.94	0.99	
Tumor maximum diameter—mm							
≤70	225 (61)	424 (74)	1	1	1	1	
>70	93 (25)	98 (17)	0.6 (0.4–0.8)	0.6 (0.4–0.8)	0.8 (0.7–0.9)	0.8 (0.7–0.9)	

(*Continued*)

Table 2 (Continued).

	CKD upstaged						
	No N (%)	**Yes N (%)**	**Crude OR (95% CI)**	**Adjusted OR [a] (95% CI)**	**Crude RR (95% CI)**	**Adjusted RR (95% CI)**	**Interaction *P*-value [b]**
Missing	53 (14)	51 (9)					
P-value			<0.001	0.004	0.002	0.002	

Notes: Crude and adjustedOR, risk ratio (RR) estimated using logistic regression or log-binomial regression, respectively. [a]Estimates adjusted for confounders only, not potential mediators. Adjustment variables: sex – age; body mass index (BMI) – age, sex, socioeconomic status (SES); Charlson comorbidity index – age, sex, SES; preoperative estimated glomerular filtration rate (eGFR) – age, sex, Charlson comorbidity index, SES; histology – age, sex, BMI, Charlson comorbidity index, smoker status, preoperative eGFR; location relative to polar lines – tumor histology; Tumor maximum diameter – age, Charlson comorbidity index, tumor histology. [b]*P*-value for first-order interaction term between tumor size and each exposure in logistic regression analysis. [c]Adjustment for sex, and Charlson comorbidity index. Percentages do not add up to 100% due to missing data on tumor size for some patients. Postoperative kidney function was recorded at approximately 12 months after surgery for the majority of patients.
Abbreviation: CKD, chronic kidney disease.

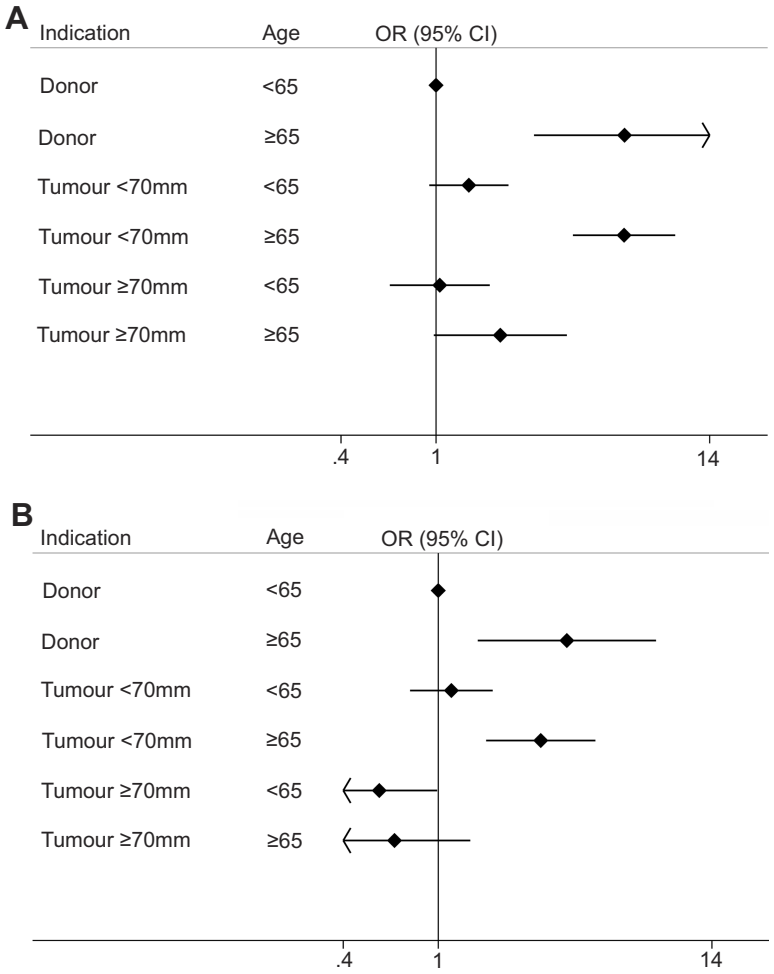

Figure 3 Forest plot showing odds of chronic kidney disease upstaging in patients grouped by tumor size/indication. (**A**) Forest plot showing associations between patients grouped by indication/tumor size and age, with adjustment made only for potential confounders (sex and Charlson comorbidity index). (**B**) The same model as (**A**), with adjustment also made for preoperative estimated glomerular filtration rate (eGFR). The estimates remain relatively similar for all groups, except large tumors, where the effect size reverses following adjustment for eGFR. Postoperative kidney function was recorded at approximately 12 months after surgery for the majority of patients.

logistic regression analysis, where the β coefficient was less negative for patients with larger tumors who were aged ≥65 years, compared with both age-matched patients with smaller tumors and living donors (Table 3). A sensitivity analysis was conducted, broadening inclusion to patients with a preoperative eGFR >30 mL/min per 1.73 m^2, and any preoperative eGFR. This resulted in a smaller difference between the β coefficient for older patients with

Table 3 Comparisons of postoperative kidney function between donor and tumor nephrectomy, grouped by age and tumor size

Linear regression analysis evaluating associations between groups and postoperative eGFR								
Indication	Age	N	Crude β (95% CI)	*P*-value	Adjusted β (95% CI) [a]	*P*-value	Adjusted β (95% CI) [b]	*P*-value
Donor	<65	189	Ref.		Ref.		Ref.	
	≥65	35	−13.0 (−16.0, −9.4)	<0.001	−13.0 (−16.0, −9.3)	<0.001	−5.7 (−8.9, −2.4)	0.001
Tumor <70 mm	<65	354	−2.2 (−4.8, 0.4)	0.09	−0.5 (−3.2, 2.2)	0.72	1.5 (−0.7, 3.8)	0.19
	≥65	200	−15.0 (−17.0, −12.0)	<0.001	−12.0 (−15.0, −9.4)	<0.001	−3.0 (−5.7, −0.3)	0.03
Tumor ≥70 mm	<65	117	0.2 (−3.4, 3.7)	0.92	1.8 (−1.8, 5.4)	0.33	7.0 (3.7, 10.0)	<0.001
	≥65	52	−7.7 (−13.0, −2.5)	0.004	−5.7 (−11.0, −0.3)	0.04	4.5 (−0.2, 9.3)	0.06
Logistic regression analysis evaluating associations between groups and CKD upstaging								
Indication	Age	N	Crude OR (95% CI)	*P*-value	Adjusted OR (95% CI) [a]	*P*-value	Adjusted OR (95% CI) [b]	*P*-value
Donor	<65	189	1		1		1	
	≥65	35	6.2 (2.5–15.0)	<0.001	6.2 (2.5–15.0)	<0.001	3.5 (1.5–8.1)	0.005
Tumor <70 mm	<65	354	1.5 (1.1–2.2)	0.02	1.4 (0.9–2.0)	0.10	1.1 (0.8–1.7)	0.53
	≥65	200	7.1 (4.4–11.0)	<0.001	6.1 (3.7–10.0)	<0.001	2.7 (1.6–4.6)	<0.001
Tumor ≥70mm	<65	117	1.2 (0.7–1.9)	0.53	1.0 (0.6–1.7)	0.88	0.6 (0.3–0.9)	0.05
	≥65	52	2.1 (1.1–3.9)	0.02	1.9 (1.0–3.5)	0.05	0.7 (0.3–1.4)	0.26
Log-binomial regression analysis evaluating associations between groups and CKD upstaging								
Indication	Age	N	Crude RR (95% CI)	*P*-value	Adjusted RR (95% CI) [a]	*P*-value	Adjusted RR (95% CI) [b]	*P*-value
Donor	<65	189	1		1		1	
	≥65	35	2.0 (1.6–2.6)	<0.001	2.0 (1.6–2.6)	<0.001	1.4 (1.1–1.8)	0.006
Tumor <70mm	<65	354	1.3 (1.0–1.6)	0.02	1.2 (0.9–1.5)	0.07	1.2 (0.9–1.4)	0.16
	≥65	200	2.1 (1.7–2.5)	<0.001	2.0 (1.6–2.4)	<0.001	1.5 (1.2–1.8)	<0.001
Tumor ≥70mm	<65	117	1.1 (0.8–1.4)	0.53	1.1 (0.8–1.4)	0.71	0.9 (0.7–1.2)	0.50
	≥65	52	1.4 (1.1–1.9)	0.01	1.4 (1.0–1.9)	0.02	1.1 (0.8–1.5)	0.45

Notes: [a]Adjustment made for sex, and Charlson comorbidity index. [b]Adjustment made for preoperative estimated glomerular filtration rate (eGFR), sex, and Charlson comorbidity index. Postoperative kidney function was recorded at approximately 12 months after surgery for the majority of patients.
Abbreviations: CKD, chronic kidney disease; RR, relative risk.

smaller compared with larger tumors (percentage difference narrowed from 110% to 40%) (Table S4).

Path analysis

To further investigate associations between patient age/tumor size, and postoperative eGFR, we used structural equation modeling to see how this relationship varied when considering indirect causal pathways directed through preoperative eGFR. We considered two models. The first assumed a direct causal pathway between tumor size and postoperative eGFR, as well as an indirect path mediated through preoperative eGFR. When considering direct effects, tumor size was negatively associated with preoperative eGFR and positively associated with postoperative eGFR (Figure S1A). When considering total effects, larger tumors were associated with a higher postoperative eGFR (β: 0.5, 95% CI: 0.1, 0.9; Table S5). The second model assumed no causal pathway between tumor size and postoperative eGFR. The direct effect of tumor size on preoperative eGFR was essential of the same magnitude as in the previous model (Figure S1B) but the total effect was reversed (β: −0.4, 95% CI: −0.6, −0.2), such that larger tumors were associated with lower postoperative eGFR. Age was negatively associated with pre- and postoperative eGFR in both models, and the magnitude of this estimate was essentially unchanged. Sensitivity analyses were conducted to determine if the interaction between age and tumor size affected these models; no major deviations were observed.

Discussion

Our goal was to clarify whether large tumors were associated with lower risk of CKD upstaging and better postoperative kidney function following radical nephrectomy for RCC. This was to address an apparent contradiction in the literature: that patients with large tumors are at higher risk of CKD before

nephrectomy,[7] but apparently decreased the risk of CKD postoperatively.[5] We attempted to resolve this through causal modeling, concluding that large tumors do not confer a protective effect, and that it may not be appropriate to consider a direct causal pathway between tumor size and postoperative eGFR. We have proposed a number of interrelated contributing biases, which may have led to the reported negative association between large tumors and postoperative CKD.

In our cohort, we initially replicated the apparent paradox that patients with larger tumors tended to have lower preoperative eGFR values (Table 1), yet larger tumors were inversely associated with CKD upstaging (Table 2), which is consistent with other reports. In a retrospective cohort study of 271 Japanese patients, those with tumors <70 mm were at increased risk of new-onset CKD compared with patients with tumors ≥70 mm.[6] This was also observed in a retrospective study of 1,371 patients managed at a single Korean center, where, compared with having a tumor >70 mm, having smaller tumors (<40 mm and 40–70 mm) was associated with a greater likelihood of new-onset CKD (aOR: 2.4, 95% CI: 1.6–3.6; and 2.2, 95% CI: 1.5–3.4, respectively).[5,6] These authors also showed that larger tumors were associated with lower preoperative eGFR,[5] a finding supported by results of a study of 1,569 RCC patients from the United States, which showed that 52% of patients with a tumor ≥70 mm had CKD before surgery (eGFR <60 mL/min per 1.73 m^2 and/or urine albumin >30 mg/dL), compared with 40% and 47% of patients with tumors <40 and 40–70 mm, respectively.[7]

We then showed that, when evaluating the association between tumor size and postoperative CKD upstaging/eGFR, this association varied according to the age of the patient. Additional analyses confirmed that there was no statistically significant difference in the risk of CKD upstaging in all patients with RCC younger than 65 years, regardless of tumor size; and that this risk was comparable to living kidney donors in the same age group. This potentially represents a practical example of Simpson's paradox, which occurs when there is an interaction between two exposures in a nonrandomized cohort that can potentially lead to incongruent findings between aggregate and disaggregate results.[17,18] Although a total reversal of effect was not seen in our data (Table S3), when considering the comparisons between living kidney donors and patients with kidney cancer, the difference was great enough to suggest that larger tumors were not associated with a lower risk of CKD upstaging in younger patients (Figure 3A), and that aggregate results were likely influenced by this interaction.

We did identify that the positive association between older age and CKD upstaging was not as pronounced in patients with larger tumors (Figure 3A). This does not seem biologically consistent, as older patients have limited capacity to compensate to nephron reduction, and if tumor size was driving contralateral compensation, it would be expected that this effect would be more pronounced in the younger age group.[9,19,20] Interestingly, we did note this counterintuitive effect was less obvious when comparing relative risk to odds ratio, which could indicate that the odds ratio was exaggerated discrepantly between subgroups when quantifying effect size (Table 3).[21] A substantial part of the reason for this counterintuitive effect is that older patients with larger tumors were more likely to experience declines in kidney function before surgery, and therefore already experienced CKD upstaging before undergoing nephrectomy. This could be a consequence of both the fact that older patients generally tend to have a lower eGFR, and because larger tumors probably caused reductions in kidney function prior to surgery, due to secondary nephron loss. Thus, surgical removal of the affected kidney had very little effect on postoperative kidney function. This hypothesis is supported by the observation that patients in this subgroup had the smallest pre-to-postoperative ΔeGFR compared with any other subgroup (Table 1), and the fact that 27% of older patients with larger tumors had a preoperative eGFR <60 mL/min per 1.73 m^2, compared with 16% of older patients with small tumors. Another potential contributor to this effect is selection bias, introduced because a higher proportion of patients were excluded because they had a preoperative eGFR <45 mL/min per 1.73 m^2 in the subgroup of older patients with larger tumors. This type of selection bias was first reported by Berkson, and occurs when an exposure has an association with both the outcome of interest and the likelihood of a patient being included in a study/subgroup.[22] To partially address this, we evaluated postoperative eGFR using linear regression analysis, expanding inclusion to all patients and those with a preoperative eGFR >30 mL/min per 1.73 m^2. We found the estimates for older patients with small and large tumors were closer in value. This supports the assertion that larger tumors in older patients do not reduce the risk of CKD; notwithstanding, this cannot be stated definitively due to

limitations of this study, and it merits further investigation. It is also possible that this finding is a consequence of survivor-treatment bias, where patients with multiple comorbidities affecting kidney function were more likely to die before developing or being diagnosed with RCC in the older group, in contrast to the younger group, where these patients would more likely have been included.[23] We did not address survivor-treatment bias in this study.

As other studies evaluating the association between tumor size and postoperative CKD adjusted for preoperative eGFR in their analysis, this may have contributed to the strong associations reported in the literature.[5,6] We also noted that adjustment for preoperative eGFR in multivariable models caused a stronger inverse association between tumor size and CKD upstaging/postoperative eGFR, and adjustment reverses the direction of the effect in both subgroups of patients with large tumors in the logistic regression analysis. We suggest that previous findings could have been contributed to by collider-stratification bias, a type of selection bias that occurs when conditioning on an exposure (preoperative eGFR) that can have two or more common causes (eg, tumor size, age, and a variety of unmeasured patient factors).[24] As a possible explanation, consider that preoperative eGFR is influenced by two reasonably independent groups of variables: patient- and tumor-derived characteristics. Patient characteristics (eg, older age) cause reductions in preoperative eGFR due to chronic, bilaterally symmetric pathological changes to the kidney.[3] Conversely, tumor characteristics (eg, tumor size) exert their effect predominantly on preoperative eGFR through ipsilateral nephron reduction, which has a null effect on the function of the contralateral kidney, or (if compensation is present) increases the function of the contralateral kidney before nephrectomy. When conditioning on preoperative eGFR while investigating the effect of tumor size, a spurious backdoor path between tumor size and unmeasured patient characteristics (eg, various unmeasured comorbidities which are associated with CKD) may have been generated, leading to biased estimates (Figure 4).[25] Another potential cause for the effect reversal in the logistic regression models is that the mediating effect of preoperative eGFR was exaggerated due to the commonality of the outcome, which explains why this effect was resolved when a log-binomial model was used.[26]

Aside from analytical issues, it is unclear if a direct path between tumor size and CKD upstaging is biologically plausible. Theoretically, tumor size could affect CKD risk through hemodynamic/structural adaptation in the contralateral kidney following nephron reduction in the kidney affected by the expanding tumor.[27] It is likely that tumor size does not continue to affect eGFR at 12 postoperative months, as the tumor has been removed and the compensatory process is complete. This is supported by data showing that at 12 months following radical

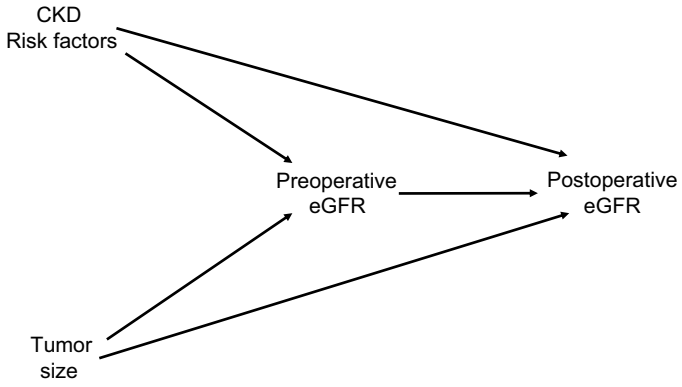

Figure 4 Potential role of collider-stratification bias. This directed acyclic graph (DAG) depicts the hypothesized causal relationship between preoperative estimated glomerular filtration rate (eGFR) and postoperative eGFR, confounded by both tumor size and other risk factors for chronic kidney disease (CKD). In this model, the relationship between tumor size and postoperative eGFR is shown to be mediated by preoperative eGFR, as larger tumors tend to cause preoperative reductions in kidney function. Physiologically, it would be expected that the direct effect of tumor size on postoperative eGFR is quite small in magnitude, because once a tumor has been excised, it should not continue to influence kidney function. Also depicted in this model are other risk factors for CKD, most of which were unmeasured, which would cause reductions in both pre- and postoperative eGFR. Unlike tumor size, other risk factors for CKD will probably lead to ongoing deterioration in kidney function. Therefore, preoperative eGFR becomes a collider in this DAG. When evaluating the association between tumor size and postoperative eGFR, adjusting for this collider may result in a biased estimate, because a spurious causal pathway is opened (Tumor Size → Preoperative eGFR ← CKD Risk Factors → Postoperative eGFR). This becomes a problem because an artificial comparison is generated. The existence of a low preoperative eGFR can be caused by a large tumor, CKD risk factors, or both; however, if a patient has a low preoperative eGFR caused by a growing tumor, it becomes less likely that the preoperative eGFR is caused by CKD risk factors. This is not taken into account by the model, which assumes a low preoperative eGFR has the same likelihood of causing low postoperative eGFR, regardless of the underlying reason (because the CKD risk factors are largely unmeasured, and not accounted for in the model). Consequently, patients with low preoperative eGFR caused by something that is unlikely to be associated with ongoing functional deterioration (a large tumor) are compared with patients who have a low preoperative eGFR caused by something that is likely to be associated with ongoing functional deterioration (CKD risk factors). This results in larger tumors being inappropriately seen as protective.

nephrectomy there were no differences in either eGFR or functional volume of the remaining kidney between patients treated for small compared with large tumors .[28]

Our structural models showed that, when a direct path between tumor size and postoperative eGFR was considered, larger tumors were associated with a higher postoperative eGFR; but, when only a direct path between tumor size and postoperative eGFR was considered, larger tumors were associated with a lower postoperative eGFR (Figure S1B). This complete reversal in the total effects between these two models tends to support the hypothesis that the pathway between tumor size and postoperative eGFR is non-causal.[29] Notwithstanding, this analysis is only exploratory in nature, and limited by the observational design of our study.

The strengths of our study lie in its large size and population-based sampling strategy. It is limited by missing data on tumor complexity and albuminuria, likely underestimation of comorbidities, use of a single follow-up eGFR value, and a reasonably short follow-up duration. There were also some missing data for both pre- and postoperative eGFR, particularly from the state of Victoria, which led to a number of the patients being excluded from this study. These exclusions could potentially have led to further selection bias, if data were not missing at random. The presumed reason for these data being missing was that the clinical record was not accessible to investigators (due to the fact that there is a larger number of private pathology providers in Victoria, compared with Queensland, which investigators were not able to access), and that missingness was not related to patient characteristics or management, which makes it less likely that the conclusions of this manuscript were significantly affected. Notwithstanding, this presumption is difficult to test, and should be considered as a limitation in the interpretation of our results.

Our analyses correct the erroneous assumption that larger-sized kidney tumors reduce the likelihood of having CKD after nephrectomy; previous findings to the contrary appear to have been an artifact of the analytical approach. Patient characteristics, with age being an important indicator, determine the likelihood of postoperative CKD. In practical terms, it is important to consider patient characteristics rather than tumor size when assessing the risk of postoperative CKD for patients managed with radical nephrectomy.

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Author contributions

RJE and SJJ were responsible for the study design and data analysis. VMW, DMB, MDC, IDD, GGG, REN, STW, and SJJ were involved in conception and design, and acquisition of data for Queensland and Victorian kidney cancer patients. RJE, RSF, and GCG were involved in the conception and design, and acquisition of data for living kidney donors. All authors contributed significantly to the interpretation of results, drafting or critically revising the manuscript, gave final approval of the final version, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest related to this work.

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Supplementary materials

Table S1 Clinical characteristics of nephrectomy patients grouped by indication

		Radical nephrectomy	Donor nephrectomy	Excluded [b]	Excluded [c]
		(N=815)	(N=224)	(N=629)	(N=229)
Age at diagnosis—years					
	Median (IQR)	60 (53–68)	55 (48–62)	68 (57–77)	71 (62–78)
	<65	530 (56)	185 (84)	262 (42)	74 (32)
	65–75	285 (30)	35 (16)	153 (24)	74 (32)
	>75	-	-	214 (34)	81 (34)
Sex					
	Female	282 (35)	115 (51)	227 (36)	73 (32)
	Male	533 (65)	109 (49)	402 (64)	156 (68)
Charlson comorbidity index (score)					
	Low (0)	490 (60)	224 (100) [a]	347 (55)	110 (48)
	Medium (1)	179 (22)	-	127 (20)	56 (24)
	High (≥2)	146 (18)	-	155 (25)	63 (28)
Preoperative eGFR—mL/min per 1.73 m^2					
	Median (IQR)	83 (70–98)	96 (83–104)	64 (44–84)	60 (41–86)
	≥80	451 (55)	181 (81)	107 (17)	46 (20)
	60–79	263 (32)	37 (17)	89 (14)	32 (14)
	<59	101 (15)	6 (3)	161 (26)	77 (34)
	Missing	-	-	272 (43)	74 (32)
Tumor diameter—mm					
	Median (IQR)	48 (36–69)	-	47 (35–67)	42 (29–70)
	<40	213 (26)	-	180 (29)	48 (21)
	40–70	341 (42)	-	230 (37)	40 (17)
	>70	169 (20)	-	106 (17)	27 (12)
	Missing	92 (11)	-	113 (18)	114 (50)
TNM staging					
	T1	449 (55)	-	339 (54)	83 (36)
	T2	85 (10)	-	66 (11)	27 (12)
	T3/4	281 (34)	-	222 (35)	72 (31)
	N1	59 (7)	-	39 (6)	65 (28)
	M1	75 (9)	-	48 (8)	140 (61)

Notes: Data presented as count (%) unless otherwise indicated. [a]Donors were assigned a Charlson comorbidity score of zero.[b] Patients who underwent radical nephrectomy but who were excluded from main analysis. [c]Patients who had kidney cancer but did not undergo surgery

Abbreviation: eGFR, estimated glomerular filtration rate.

Table S2 Application of exclusion criteria between patients grouped by age and tumor size in 1,981 patients diagnosed with RCC[a]

	Tumors ≤70 mm		Tumors >70 mm	
Age (years):	**<65**	**≥65**	**<65**	**≥65**
Exclusion criteria	(N=949)	(N=722)	(N=180)	(N=130)
Nonsurgical management	19 (2)	69 (10)	13 (7)	14 (11)
Abnormal contralateral kidney	3 (<1)	2 (<1)	2 (1)	1 (<1)
Missing preoperative eGFR	87 (9)	85 (12)	29 (16)	15 (12)
Missing postoperative eGFR	54 (6)	29 (4)	10 (6)	7 (5)
Partial nephrectomy	414 (44)	210 (29)	6 (3)	3 (2)
Preoperative eGFR <45	18 (2)	32 (4)	3 (<1)	16 (12)
Age >75 years	0 (0)	95 (13)	0 (0)	22 (17)
Excluded	595 (63)	522 (72)	63 (72)	78 (60)
Included	354 (37)	200 (28)	117 (28)	52 (40)

Note: [a]Data presented as count (%), unless otherwise indicated.
Abbreviations: eGFR, estimated glomerular filtration rate (in mL/min per 1.73m^2); RCC, renal cell carcinoma.

Table S3 Association between tumor size and postoperative kidney function, stratified by age

Tumor size	aOR (95% CI)	β (95% CI)	RR (95% CI)
Age <65-years			
<70mm	1	Ref.	1
≥70mm	0.8 (0.5–1.1)	2.3 (−1.1, 5.7)	0.9 (0.7–1.1)
P-value	0.2	0.2	0.2
Age ≥65-years			
<70mm	1	Ref.	1
≥70mm	0.4 (0.2–0.6)	5.2 (1.6–8.9)	0.8 (0.6–0.9)
P-value	<0.001	0.005	0.004

Notes: Postoperative kidney function was recorded at approximately 12 months after surgery for the majority of patients. Adjustment made for age, Charlson comorbidity index, and tumor histology.
Abbreviations: RR, risk ratio; aOR, adjusted odds ratio; β, linear regression coefficient.

Table S4 Comparisons of postoperative kidney function patients grouped by age and tumor size with narrowed exclusion criteria

Linear regression analysis evaluating associations between groups and postoperative eGFR in patients with preoperative eGFR >30 mL/min per 1.73 m^2								
Indication	Age	N	Crude β (95% CI)	*P*-value	Adjusted β (95% CI) [a]	*P*-value	Adjusted β (95% CI) [b]	*P*-value
Tumor <70 mm	<65	360	Ref.		Ref.		Ref.	
	≥65	221	−14.0 (−16.0, −11.0)	<0.001	−13.0 (−15.0, −10.0)	<0.001	−4.1 (−6.4, −1.7)	<0.001
Tumor ≥70 mm	<65	118	2.3 (−1.1, 5.7)	0.18	2.0 (−1.3, 5.5)	0.22	5.3 (2.6, 8.1)	<0.001
	≥65	64	−9.4 (−14.0, −5.0)	<0.001	−8.7 (−13.0, −4.4)	<0.001	2.3 (−1.4, 6.0)	0.21
Linear regression analysis evaluating associations between groups and postoperative eGFR in patients with any preoperative eGFR value								
Tumor <70 mm	<65	372	Ref.		Ref.		Ref.	
	≥65	232	−14.0 (−17.0, −11.0)	<0.001	−12.0 (−15.0, −9.4)	<0.001	−3.2 (−5.5, −0.9)	0.005
Tumor ≥70 mm	<65	120	3.0 (−0.6, 6.8)	0.10	2.3 (−1.0, 6.2)	0.16	5.6 (2.9, 8.3)	<0.001
	≥65	67	−8.5 (−13.0, −3.8)	<0.001	−8.0 (−12.0, −3.1)	<0.001	3.6 (0.06, 7.2)	0.05

Notes: [a]Adjustment made for sex, and Charlson comorbidity index. [b]Adjustment made for preoperative estimated glomerular filtration rate (eGFR), sex, and Charlson comorbidity index. Postoperative kidney function was recorded at approximately 12 months after surgery for the majority of patients.
Abbreviation: β, linear regression coefficient; eGFR, estimated glomerular filtration rate.

Table S5 Direct, indirect and total effects of various exposures on pre- and postoperative eGFR

Analysis performed assuming a direct causal path between tumor size and postoperative eGFR			
	Direct effects β (95% CI)	Indirect effects β (95% CI)	Total effects β (95% CI)
Preoperative eGFR			
Charlson comorbidity index	−0.5 (−2.1, 1.0)	-	−0.5 (−2.1, 1.0)
Age (years)	−0.9 (−1.0, −0.8)	0.0 (−0.1, 0.1) [a]	−0.9 (−1.0, −0.8)
Tumor Ssize (cm)	−1.0 (−1.4, −0.6)	-	−1.0 (−1.4, −0.6)
Postoperative eGFR			
Charlson comorbidity index	−1.7 (−2.9, −0.5)	−0.2 (−1.0, 0.5) [b]	−1.9 (−3.4, −0.5)
Age (years)	−0.2 (−0.3, −0.1)	−0.4 (−0.5, −0.4) [c]	−0.7 (−0.8, −0.6)
Tumor size (cm)	1.0 (0.6, 1.3)	−0.5 (−0.7, −0.3) [d]	0.5 (0.1, 0.9)
Preoperative eGFR	0.5 (0.4, 0.5)	-	0.5 (0.4, 0.5)
Analysis performed assuming no direct causal path between tumor size and postoperative eGFR			
	Direct effects β (95% CI)	Indirect effects β (95% CI)	Total effects β (95% CI)
Preoperative eGFR			
Charlson comorbidity index	−0.4 (−1.8, 1.0)	-	−0.4 (−1.8, 1.0)
Age (years)	−0.9 (−1.0, −0.6)	0.0 (−0.1, 0.1) [a]	−0.9 (−1.3, −0.6)
Tumor size (cm)	−0.9 (−1.3, −0.6)	-	−0.9 (−1.3, −0.6)
Postoperative eGFR			
Charlson comorbidity index	−1.7 (−2.8, −0.6)	−0.2 (−0.8, 0.5) [b]	−1.9 (−3.2, −0.6)
Age (years)	−0.2 (−0.4, −0.2)	−0.4 (−0.5, −0.3) [c]	−0.7 (−0.8, −0.6)
Tumor size (cm)	-	−0.4 (−0.6, −0.2) [d]	−0.4 (−0.6, −0.2)
Preoperative eGFR	0.4 (0.4, 0.5)	-	0.4 (0.4, 0.5)

Notes: [a]Indirect effects of age through Charlson comorbidity index. [b]Indirect effects of Charlson comorbidity index through preoperative eGFR. [c]Indirect effects of age through Charlson comorbidity index and preoperative eGFR. [d] Indirect effects of tumor size through preoperative eGFR. Postoperative kidney function was recorded at approximately 12 months after surgery for the majority of patients.

Abbreviations: β, linear regression coefficient; eGFR, estimated glomerular filtration rate (in units of mL/min per 1.73m^2)

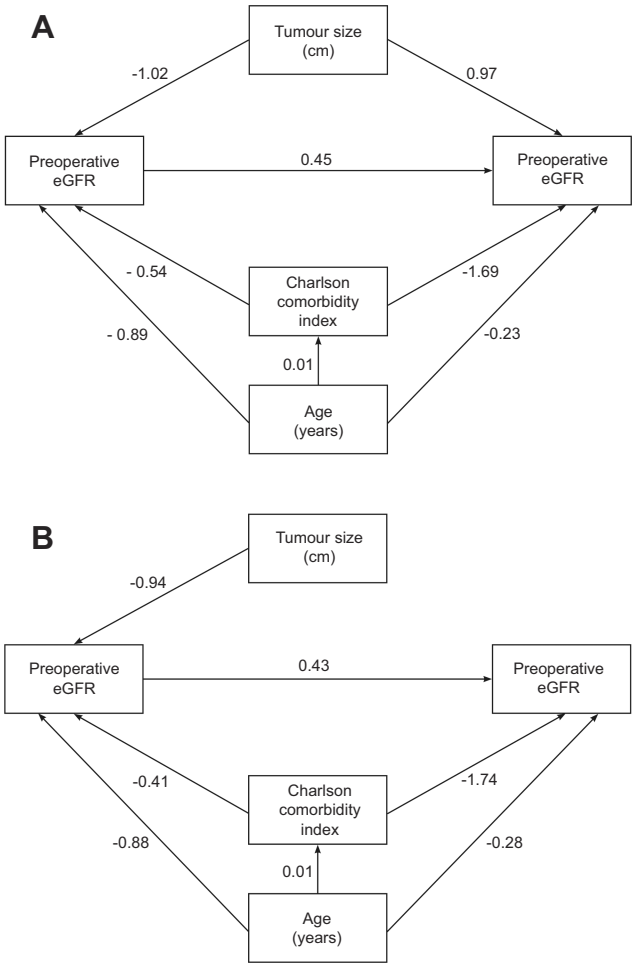

Figure S1 Structural models with and without a direct causal pathway between tumor size and postoperative estimated glomerular filtration rate (eGFR). (**A**) Structural equation model evaluating the relative contributions of the most significant patient and tumor characteristics on postoperative eGFR; this model assumes there is a direct causal effect of tumor size on postoperative eGFR. The net total effect of tumor size on postoperative eGFR is positive (**β**: 0.5, 95% CI: 0.4, 0.5). (**B**) The same model as A, except there is no direct causal association between tumor size and postoperative eGFR. The net total effect of tumor size on postoperative eGFR reverses direction (**β**: −0.4, 95% CI: −0.6, −0.2).