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Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study

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Summary

Background—Chronic kidney disease is a graded and independent risk factor for substantial comorbidity and death. We aimed to examine new onset of chronic kidney disease in patients with small, renal cortical tumours undergoing radical or partial nephrectomy.

Methods—We did a retrospective cohort study of 662 patients with a normal concentration of serum creatinine and two healthy kidneys undergoing elective partial or radical nephrectomy for a solitary, renal cortical tumour (≤4 cm) between 1989 and 2005 at a referral cancer centre. Glomerular filtration rate (GFR) was estimated with the abbreviated Modification in Diet and Renal Disease Study equation. Separate analysis was undertaken, with chronic kidney disease defined as GFR lower than 60 mL/min per 1·73 m^2 and GFR lower than 45 mL/min per 1·73 m^2.

Findings—171 (26%) patients had pre-existing chronic kidney disease before surgery. After surgery, the 3-year probability of freedom from new onset of GFR lower than 60 mL/min per 1·73 m^2 was 80% (95% CI 73–85) after partial nephrectomy and 35% (28–43; p<0·0001) after radical nephrectomy; corresponding values for GFRs lower than 45 mL/min per 1·73 m^2 were 95% (91–98) and 64% (56–70; p<0·0001), respectively. Multivariable analysis showed that radical nephrectomy remained an independent risk factor for patients developing new onset of GFR lower than 60 mL/min per 1·73 m^2 (hazard ratio 3·82 [95% CI 2·75–5·32]) and 45 mL/min per 1·73 m^2 (11·8 [6·24–22·4]; both p<0·0001).

Interpretation—Because the baseline kidney function of patients with renal cortical tumours is lower than previously thought, accurate assessment of kidney function is essential before surgery. Radical nephrectomy is a significant risk factor for the development of chronic kidney disease and might no longer be regarded as the gold standard treatment for small, renal cortical tumours.

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Contributors

W C Huang took part in the study design, data analysis and interpretation, and drafting and revising of the manuscript. A S Levey took part in the data analysis and interpretation, and drafting and revising of the manuscript. A M Serio and A J Vickers took part in the statistical analysis and drafting of the manuscript. M Snyder compiled the data and provided technical support. G V Raj took part in the data acquisition and revising of the manuscript. P T Scardino and P Russo supervised the study, and took part in the study design, study funding, and revising of the manuscript.

Conflicts of interest

We declare no conflicts of interest.

Introduction

Radical nephrectomy has been the gold standard treatment for localised renal cortical tumours for nearly 40 years.[1] However, surgical management of these tumours has evolved greatly in the past decade. Advances in abdominal imaging have led to increased detection of small (≤4 cm), localised, incidental, renal cortical tumours, which account for 60–70% of all diagnosed renal masses.[2] Because of the small size and early stage of these tumours, surgeons are able to do partial nephrectomies without compromising safety and oncological efficacy.[3,4]

In tertiary-care centres in the USA, partial nephrectomy now accounts for 30–65% of all surgical procedures for renal cortical tumours.[5-7] However, this trend does not represent current US surgical practice for renal cortical tumours. Analysis of the Nationwide Inpatient Sample[8] showed that nationally, only 7·5% of all kidney-cancer cases between 1988 and 2002 were treated with partial nephrectomy. Similarly, data from the population-based Surveillance Epidemiology and End Results (SEER) registry[9] showed that from 2001, only 20% of all renal cortical tumours with a size of 2–4 cm were preferentially treated with partial nephrectomy. This practice pattern is seen in other countries with advanced health-care systems. Data from the Hospital Episode Statistics database of the Department of Health in England[10] shows that of the 2671 nephrectomies done in England in 2002, only 108 (4%) were partial nephrectomies.

Such findings are worrying, because the surgical management of small renal cortical tumours could greatly impair the kidney function of patients, including those with two healthy kidneys. Previous studies[11,12] have shown a significantly increased risk of renal insufficiency, defined as concentrations of serum creatinine greater than 177 μmol/L (2 mg/dL), in patients undergoing radical nephrectomy compared with those undergoing partial nephrectomy. However, these studies are restricted by the fact that serum creatinine is an inaccurate measure of overall kidney function, and that a clinically relevant reduction in kidney function occurs in patients with serum creatinine concentrations lower than 177 μmol/L.[13,14]

Current guidelines define chronic kidney disease as an estimated glomerular fitration rate (GFR) lower than 60 mL/min per 1·73 m^2, or by the presence of markers of kidney damage (such as albuminuria or abnormal imaging studies) for 3 months or more.[15] The major outcomes of chronic kidney disease are: loss of kidney function, sometimes leading to kidney failure; complications of reduced kidney function, such as hypertension, anaemia, malnutrition, neuropathy, and reduced quality of life; and increased risk of cardiovascular disease and mortality.[16-18] Because of raised awareness of important health risks associated with chronic kidney disease,[15-19] and worldwide data[8-10] showing the probable overuse of radical nephrectomy, we aimed to review our nephrectomy database and assess kidney function outcomes in patients undergoing surgery for small, solitary, renal cortical tumours.

Methods

Patients

We analysed prospective data from more than 2000 patients who underwent surgery for renal tumours at Memorial Sloan-Kettering Cancer Center (MSKCC) from July, 1989, to September, 2005 (figure 1). After approval from the institutional review board (which included ethics approval), patients who were eligible for both partial and radical nephrectomies were selected for review based on the following criteria: size of solitary renal cortical tumour of 4 cm or less; normal concentrations of serum creatinine before surgery (defined as ≤124 μmol/L); and imaging of a normal contralateral kidney before surgery. We also excluded patients with metastatic disease (n=13), incomplete data (n=10), or insufficient follow-up (n=112).

Preoperative characteristics including age, ethnic origin, sex, serum creatinine concentration, estimated GFR, diabetes mellitus, and hypertension were recorded to ensure that the cohorts undergoing partial or radical nephrectomy were balanced. We also calculated the modified Charlson-Romano index of all patients,[20,21] an objective measure of comparing comorbidity in patients.

Procedures

GFR is regarded as the best overall measure of kidney function.[22] In conjunction with clinical practice guidelines, GFRs were estimated with the abbreviated Modification of Diet in Renal Disease (MDRD) study equation.[13] The equation is: $GFR=32788\times(\text{serum creatinine})^{-1\cdot154}\times(\text{age})^{-0\cdot203}$, from which the result is multiplied by 0·742 for female patients and multiplied by 1·212 for black patients. Postoperative estimates of GFRs were not obtained until 4 or more weeks after nephrectomy.

The study outcome was new onset of estimated GFR lower than 60 mL/min per 1·73 m^2. We also used an estimated GFR threshold lower than 45 mL/min per 1·73 m^2 as an outcome, which defines chronic kidney disease more stringently, and has been shown by many studies[16,19,23] to be associated with a significantly higher risk of complications and comorbidity than the threshold of 60 mL/min per 1·73 m^2.

Since the main outcome measures were the new onset of GFR lower than 60 or 45 mL/min per 1·73 m^2 after surgery, patients with pre-existing GFR values lower than these two thresholds could not be included for outcome analysis.

Statistical analysis

For preoperative characteristics of patients, p values were determined by the Mann-Whitney test for continuous variables and by χ^2 test for categorical variables. Because of the small frequency of certain histological subtypes, Fishers exact test was used for histology. We used multivariable Cox proportional hazards regression to investigate whether operation type (radical or partial nephrectomy) was associated with chronic kidney activity after surgery, by adjusting for age, Charlson-Romano index, hypertension, and preoperative GFR. Diabetes mellitus was not included as an independent variable because it is accounted for in the Charlson-Romano index. In these two time-to-event analyses, the event was defined either as new onset of GFR lower than 60 mL/min per 1·73 m^2 or lower than 45 mL/min per 1·73 m^2 after surgery on the second of two consecutive occasions at least 3 months apart. Since some patients died before reaching the endpoint, we initially proposed analyses accounting for death as a competing risk. Only 6% of patients in our cohort died with no event, suggesting that adjustment for competing risk would have minimum effect. Patients who had no events were therefore censored at the time of their last GFR estimate. A sensitivity analysis was undertaken to ensure that the increased proportion of partial nephrectomies done over time did not affect the results. The proportional hazards assumption was tested graphically and by use of a statistical test based on the distribution of Schoenfeld residuals. We regarded p values less than 0·05 as significant. All statistical analyses were done with Stata 8.2.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Median intervals between postoperative GFR estimations were similar for both groups (radical nephrectomy, 4 months [IQR 1–6] *vs* partial nephrectomy, 6 months [2–7]). Despite having normal preoperative concentrations of serum creatinine, 171 (26%) patients had estimated GFRs lower than 60 mL/min per 1·73 m^2, and 15 (2%) had estimated GFRs lower than 45 mL/min/1·73 m^2 (table 1). Apart from age and tumour size (all tumours were ≤4 cm), we recorded no significant differences in baseline characteristics by type of operation (table 2). Although a significant difference in histological subtypes was found in patients with GFRs lower than 45 mL/min/1·73 m^2, this pathological diagnosis was not known before surgery. Median preoperative estimated GFRs were 73 mL/min per 1·73 m^2 (IQR 67–84) in patients with GFRs greater than 60 mL/min per 1·73 m^2, and 70 mL/min per 1·73 m^2 (60–80) in those with GFRs greater than 45 mL/min per 1·73 m^2.

192 patients developed new onset of GFR lower than 60 mL/min per 1·73 m^2 after surgery (50 of 287 who underwent partial nephrectomy and 142 of 204 who underwent radical nephrectomy). Median follow-up for patients without new onset of GFR lower than this threshold was 19 months (IQR 7–47). Patients with only one postoperative GFR estimation (49 partial nephrectomy, 27 radical nephrectomy) were censored at the time of that GFR estimation. 3-year and 5-year probabilities of freedom from new onset of GFR lower than 60 mL/min per 1·73 m^2 were 80% (95% CI 73–85) and 67% (57–75), respectively, for patients who underwent partial nephrectomy, compared with corresponding values of 35% (28–43) and 23% (16–30) for those who underwent radical nephrectomy ($p<0·0001$; figure 2). Median time to development of GFR lower than 60 mL/min per 1·73 m^2 was 18 months (IQR 10–55) for the radical nephrectomy group and was not reached for the partial nephrectomy group. In the multi variable analysis, patients who underwent radical nephrectomy had a higher risk of new onset of GFR lower than 60 mL/min per 1·73 m^2 than those who underwent partial nephrectomy (hazard ratio 3·82, table 3).

11 of 385 patients who had partial nephrectomy and 94 of 262 who had radical nephrectomy developed new onset of GFR lower than 45 mL/min per 1·73 m^2 after surgery. Median follow-up for patients without new onset of GFR at this threshold was 25 months (IQR 10–53). 64 patients with partial nephrectomy and 37 with radical nephrectomy had only one postoperative estimation of GFR, and were censored at the time of that GFR estimation. 3-year and 5-year probabilities of freedom from new onset of GFR lower than 45 mL/min per 1·73 m^2 were 95% (95% CI 91–98) and 93% (87–96), respectively, for patients who underwent partial nephrectomy, compared with corresponding values of 64% (56–70) and 57% (50–64), for those who underwent radical nephrectomy ($p<0·0001$; figure 3). Median time to development of GFR lower than 45 mL/min per 1·73 m^2 in the radical nephrectomy group was 113 months (IQR 16–not reached), and was not reached in the partial nephrectomy group. Patients who underwent radical nephrectomy had a higher risk of new onset of GFR lower than 45 mL/min per 1·73 m^2 than those who underwent partial nephrectomy (hazard ratio 11·8, table 3).

Although 105 patients developed new onset of GFR lower than 45 mL/min per 1·73 m^2 after surgery, none of these patients or any other patients in the cohort has developed kidney failure needing dialysis.

Discussion

Our findings show that 26% of patients with a solitary, small, renal cortical tumour (<4 cm) and two normally functioning kidneys have pre-existing chronic kidney disease (GFR <60 mL/min per 1·73 m^2). This study also shows that the risk of new onset of chronic kidney disease

is significantly greater in patients undergoing radical nephrectomy than in those undergoing partial nephrectomy for treatment of small, renal cortical tumours.

In 2006, more than 35 000 patients will develop renal cortical tumours in the USA, with a rising incidence of about 3% per year.[24,25] Since more than 60% of newly diagnosed tumours are 4 cm or less in size, more than 20 000 patients every year will have tumours amenable to partial nephrectomy based on size criteria alone.[4] Since data indicate no significant difference in cancer-specific survival between patients undergoing partial nephrectomy for tumours sized 7 cm or less and those undergoing surgery for tumours less than 4 cm, the actual number of patients eligible for the procedure could be more than expected.[26,27]

Our findings are important because an overwhelmingly disproportionate number of patients with small, renal cortical tumours are treated with radical nephrectomy instead of partial nephrectomy.[8-10] Although experienced surgeons report similar complication rates and outcomes for both the procedures,[28,29] the partial approach can be technically challenging and might be associated with a greater risk of complications, especially if done laparoscopically.[29] In our series of open partial and radical nephrectomies,[28] the frequency of complications did not differ between operation type when accounting for multiple variables. We did not record any perioperative mortalities due to technical complications from partial nephrectomy, and the most common complication after the procedure were urinary fistulas (6%), none of which needed re-operation.[28] Nevertheless, the potential complexity of partial nephrectomy—along with increasing use of laparoscopic radical nephrectomy,[7,30] which is much less difficult than partial nephrectomy—could contribute to the high number of radical nephrectomies being done for small renal cortical tumours.

However, the overuse of radical nephrectomy for small, renal cortical tumours is probably due to the widespread misconception that chronic kidney disease after radical nephrectomy is not a major concern in patients with two functioning kidneys and a normal preoperative concentration of serum creatinine. Outcome data from transplantation studies[31-33] have long supported this notion, since donors undergoing nephrectomy do not have higher rates of decreased kidney function, kidney failure needing dialysis, or death.

However, our data show that unlike kidney donors, patients with small, renal cortical tumours are at a significantly higher risk of developing chronic kidney disease after radical nephrectomy than after partial nephrectomy. Even with other important variables accounted for, such as age at time of surgery, preoperative estimated GFR, Charlson-Romano index, and presence of hypertension, patients undergoing radical nephrectomy are at a significantly increased risk of chronic kidney disease. Despite differences in follow-up between surgery groups because of the increased proportion of partial nephrectomies over time, proportional hazards assumptions were met ($p=0{\cdot}5$ and $p=0{\cdot}6$ for events of GFR <60 and GFR <45 mL/min per 1·73 m^2, respectively).

Two factors might explain the increased risk of chronic kidney disease after radical nephrectomy in our patients compared with kidney donors: the GFRs recorded in our study might have been underestimated because of uncalibrated serum creatinine assays; and the baseline estimated GFRs are significantly lower in patients with renal cortical tumours than in those undergoing donor nephrectomy. Some studies[34,35] have suggested underestimation of GFR in patients without kidney disease, by estimating equations derived from studies of patients with chronic kidney disease. This underestimation seems to be greater in studies that did not calibrate the serum creatinine assay to the laboratory from which the estimating equation was derived.[19] Although our study might have overestimated the true number of patients with chronic kidney disease using an estimated GFR cutoff of lower than 60 mL/min per 1·73 m^2,

the use of estimated GFR lower than 45 mL/min per 1·73 m^2 as an additional outcome is most likely to identify patients with chronic kidney disease.

The baseline estimated GFR of our entire cohort of patients (69 mL/min per 1·73 m^2) is substantially lower than in patients from published donor nephrectomy series (92–103 mL/min per 1·73 m^2).[36-38] A comparison with age-matched patients from the third National Health and Nutrition Examination Survey (NHANES III)[39] also reported a median baseline GFR that was 30% greater than that in our patients. This disparity in the baseline GFRs can be attributed to differences in patient age at the time of nephrectomy as well as frequency of pre-existing comorbidities that affect kidney function. In studies of the outcomes of kidney donors, the reported mean ages at time of kidney donation were often younger than 50 years.[36,38,40] In our series, the median age at radical nephrectomy was 58 years (IQR 50–67). With a conservative estimation of GFR reduction over time (1 mL/min per 1·73 m^2per year),[39] this finding alone accounts for a 10% reduction in the baseline GFR of patients with renal cortical tumours. The increased frequency of risk factors for chronic kidney disease, such as hypertension, diabetes mellitus, and smoking, probably explains why about 25% of patients with small, renal cortical tumours also have pre-existing chronic kidney disease and why a significant portion of the remaining 75% are at risk after radical nephrectomy. Until now, most urological studies have used serum creatinine instead of estimated GFR to measure kidney function,[11,12] which could explain why the lower renal function at baseline of patients with renal cortical tumours has largely gone unnoticed.

Our results raise serious concerns regarding the lasting effects of radical nephrectomy on the length and quality of life of patients. Since the cancer-specific survival for patients with small, renal cortical tumours is greater than 90% across all histological subtypes,[4,41] these patients are susceptible to developing long-term sequelae from their treatment. Several studies[16-18] have shown an independent and graded association between decreased estimated GFR and substantial comorbidity, increased admissions, and increased cardiac-related and non-cardiac-related deaths. Patients undergoing radical nephrectomy have a greater than 35% chance of developing a GFR lower than 45 mL/min per 1·73 m^2 within 3 years of surgery, theoretically placing them at risk for these complications. Since patients with renal cortical tumours are at higher lifetime risk for contralateral recurrences and since 20% of small, renal cortical tumours are indolent,[42] the routine use of radical nephrectomy for these tumours is both unnecessary and unjustified.

Our study had some limitations. As a retrospective study, patients were not randomly assigned to a surgical procedure, which meant that the choice of surgery might have been biased by the surgeons' preference based on the preoperative condition of the patient. However, we showed that the cohorts were well balanced before surgery. Furthermore, randomisation in a prospective study would be difficult to implement at our institution, with the knowledge that patients would have no oncological benefit and a potentially significant risk of chronic kidney disease. Another limitation was GFR estimation. As previously mentioned, formulas based on serum creatinine concentrations vary in accuracy in different patient groups. We chose to use the abbreviated MDRD study equation, widely used in other studies to show associations between estimated GFR, comorbidity, and death.[16,18,19] Although this formula is generally accepted as a more accurate method to estimate GFR, the reduction in baseline and follow-up estimated GFRs seen in our cohort could be partly due to formulaic inadequacies of the estimation of GFR as well as the use of uncalibrated serum creatinine values.

Since the mechanism by which decreased GFR increases the risk of cardiovascular disease and death has yet to be established, the ramifications of chronic kidney disease in these patients remain unknown. Longitudinal analysis of nationwide databases similar to the SEER registry is needed to establish whether the iatrogenic and abrupt onset of chronic kidney disease after

surgery places patients at risk for associated complications, such as cardiovascular disease and death.

Our data indicate that many patients are at risk for chronic kidney disease, after unnecessary use of radical nephrectomy for the treatment of small, renal cortical tumours. Therefore, these findings have important and immediate implications on the contemporary management of these tumours. We believe that standardised preoperative GFR estimates should be an integral part of the decision algorithm during planning of the surgical strategy for patients with renal cortical tumours, irrespective of tumour size. Treatment options that provide equivalent oncological results and preserve kidney function outcomes might also replace radical nephrectomy as the gold standard treatment for small, renal cortical tumours. Based on the increasing number of studies showing long-term deleterious effects of chronic kidney disease, doctors should be aware that the preferred treatment for small, renal cortical tumours could have a substantial effect on the quality and length of survivorship of these patients.

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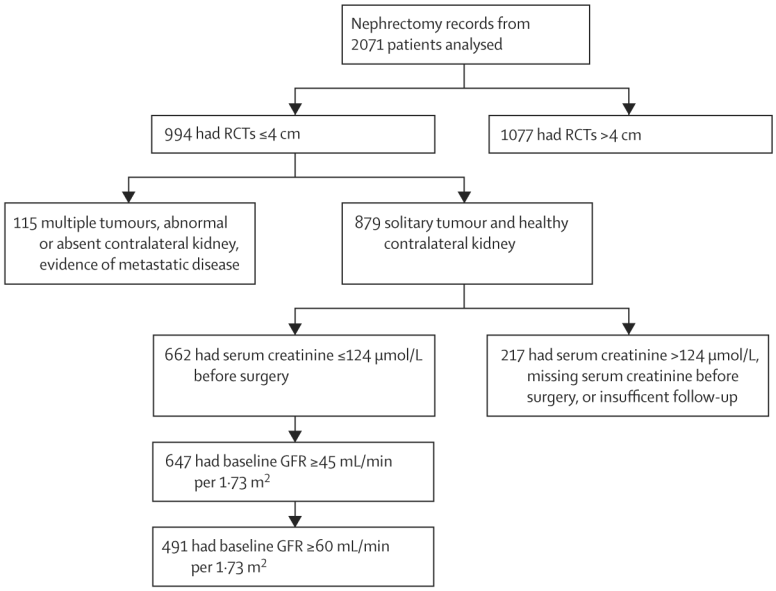
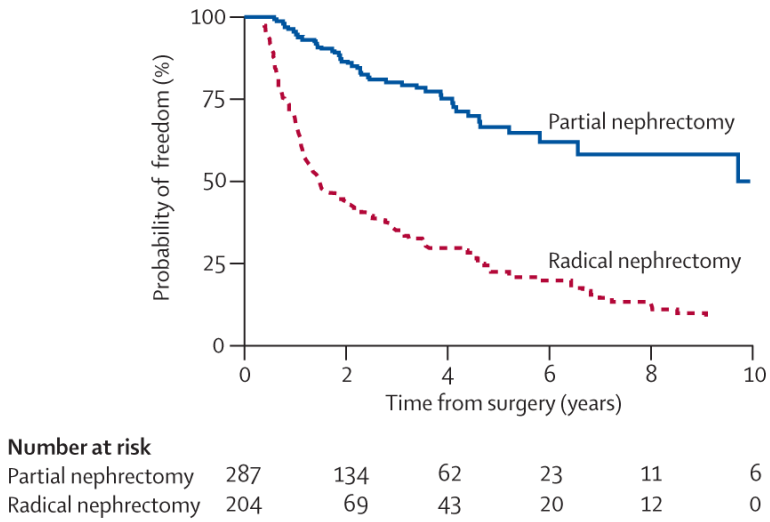


Figure 1. Selection of patients during study
RCT=renal cortical tumours.



Number at risk						
Partial nephrectomy	287	134	62	23	11	6
Radical nephrectomy	204	69	43	20	12	0

Figure 2.
Probability of freedom from new onset of GFR lower than 60 mL/min per 1·72 m^2, by operation type

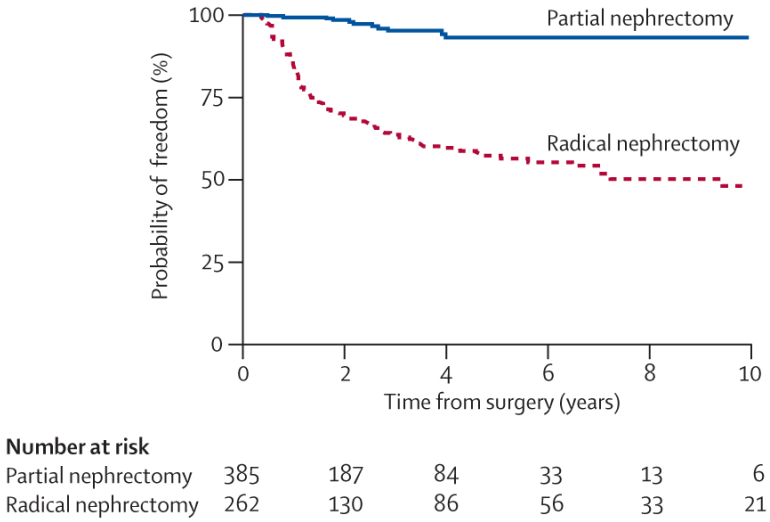


Figure 3.
Probability of freedom from new onset of GFR lower than 45 mL/min per 1·72 m^2, by operation type

Table 1

Distribution of preoperative estimated GFRs (mL/min per 1·73 m^2) of original cohort

	Total (n=662)	Preoperative serum creatinine concentration (μmol/L)		
		<80 (n=228)	80–105 (n=239)	106–124 (n=195)
<30	0	0	0	0
30–44	15 (2%)	0	0	15 (100%)
45–59	156 (24%)	0	69 (44%)	87 (56%)
60–89	406 (61%)	146 (36%)	167 (41%)	93 (23%)
≥90	85 (13%)	82 (96%)	3 (4%)	0

Data are number of patients (% of those with preoperative GFRs).

Table 2

Preoperative and pathological characteristics of patients

	GFR >60 mL/min per 1·73 m^2			GFR >45 mL/min per 1·73 m^2		
	Partial (n=287)	**Radical (n=204)**	**p**	**Partial (n=385)**	**Radical (n=262)**	**p**
Age at surgery (years)	57 (47–65)	63 (55–70)	<0·0001	59 (50–67)	65 (56–71)	<0·0001
Preoperative creatinine (μmol/L)	88 (71–97)	88 (79–97)	0·9	88 (79–106)	88 (79–106)	0·4
Preoperative GFR (mL/min per 1·73 m^2)	74·0 (66·8–86·0)	73·3 (67·1–80·9)	0·2	70·4 (59·8–80·9)	69·2 (61·6–78·7)	0·9
Charlson-Romano index			0·2			0·6
<2	188 (66%)	123 (60%)		234 (61%)	155 (59%)	
≥2	96 (33%)	81 (40%)		148 (38%)	106 (40%)	
Not available	3 (1%)	0		3 (1%)	1 (<1%)	
Ethnic origin			0·7			0·8
White or other	271 (94%)	194 (95%)		367 (95%)	251 (96%)	
Black	16 (6%)	10 (5%)		18 (5%)	11 (4%)	
Sex			0·9			0·9
Male	167 (58%)	119 (58%)		209 (54%)	144 (55%)	
Female	120 (42%)	85 (42%)		176 (46%)	118 (45%)	
Hypertension			0·2			0·4
No	185 (64%)	120 (59%)		229 (59%)	147 (56%)	
Yes	102 (36%)	84 (41%)		156 (41%)	115 (44%)	
Diabetes			0·9			0·8
No	262 (91%)	186 (91%)		349 (91%)	239 (91%)	
Yes	25 (9%)	18 (9%)		36 (9%)	23 (9%)	
Tumour size (cm)	2·4 (1·8–3·0)	3·0 (2·5–3·5)	<0·0001	2·5 (1·8–3·0)	3·0 (2·5–3·5)	<0·0001
Histology (postsurgery)			0·07			0·03
Conventional clear cell	160 (56%)	127 (62%)		206 (54%)	161 (61%)	
Chromophobe	32 (11%)	16 (8%)		44 (11%)	19 (7%)	
Benign	85 (30%)	60 (29%)		122 (32%)	80 (31%)	
Other	10 (3%)	1 (<1%)		13 (3%)	2 (1%)	

Data are median (IQR) or number (%). Partial and radical refers to type of nephrectomy.

Table 3

Factors associated with new onset of GFR after surgery

	GFR <60 mL/min per 1·73 m^2 (n=488)*		GFR <45 mL/min per 1·73 m^2 (n=643)†	
	Hazard ratio (95% CI)	**p**	**Hazard ratio (95% CI)**	**p**
Operation type				
Radical *vs* partial	3·82 (2·75–5·32)	<0·0001	11·8 (6·24–22·4)	<0·0001
Charlson-Romano index				
≥2 *vs* <2	1·16 (0·86–1·56)	0·3	1·24 (0·84–1·83)	0·3
Hypertension				
Yes *vs* no	0·98 (0·73–1·31)	0·9	1·74 (1·16–2·59)	0·007
Age (per 10 years)	1·20 (1·05–1·38)	0·009	1·60 (1·28–2·01)	<0·0001
Preoperative GFR	0·97 (0·95–0·98)	<0·0001	0·94 (0·92–0·96)	<0·0001

*Three patients excluded from analysis because Charlson-Romano index score was not available.

†Four patients excluded from analysis because Charlson-Romano index score was not available.