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ORIGINAL ARTICLE

Should partial nephrectomy be considered "elective" in patients with stage 2 chronic kidney disease? A comparative analysis of functional and survival outcomes after radical and partial nephrectomy

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Abstract

Purpose To compare renal function and survival outcomes in patients with baseline chronic kidney disease (CKD) stage 2 undergoing partial (PN) or radical nephrectomy (RN), as nephron-sparing surgery is considered to be elective in this group.

Methods Retrospective analysis of patients with CKD stage 2 and T1/T2 renal mass undergoing PN or RN from 2001 to 2015. Patients were stratified into substage CKD 2a or CKD 2b and analyzed between types of surgery. Primary outcome was overall survival (OS), eGFR < 45 at last follow-up was the secondary outcome. Multivariable analysis (MVA) was conducted for predictors of eGFR < 45 and OS. Kaplan–Meier analyses were conducted for freedom from eGFR < 45 and OS.

Results 1213 patients analyzed (CKD 2a 609/CKD 2b 604) on MVA, RN (OR 3.68, $p = 0.001$) and CKD 2b (OR 3.3, $p = 0.002$) were independently associated with development of eGFR < 45 at last follow-up and RN (OR 3.76, $p = 0.005$) and eGFR < 45 (OR 2.51, $p = 0.029$) were associated with decreased OS. Kaplan–Meier analyses revealed that patients with CKD 2a/PN had the highest 5-year freedom from eGFR < 45 (94.3%) compared to CKD 2a/RN patients (91.5%), CKD2b/PN patients (87.6%) and CKD 2b/RN patients 82.0% ($p < 0.001$). Kaplan–Meier analyses for OS demonstrated that patients with CKD 2a/PN had significantly greater 5-year OS (97.6%) compared to CKD 2a/RN patients (95.2%), CKD 2b/PN patients (93.2%), and CKD 2b/RN patients (92.4%, $p = 0.043$).

Conclusions Patients with baseline CKD stage 2, particularly CKD 2b and undergoing RN, are at increased risk of GFR < 45, which was associated with decreased OS. In patients with CKD 2b, a nephron-sparing strategy is indicated and should be prioritized when feasible.

Keywords Carcinoma · Renal cell · Chronic kidney disease · Glomerular filtration rate · Nephrectomy · Partial nephrectomy · Overall survival

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Introduction

Renal cell carcinoma (RCC) is increasingly diagnosed with an estimated 403,262 new cases and 175,098 deaths worldwide in 2018 [1]. Historically, radical nephrectomy (RN) has been considered to be the standard of care for localized renal malignancy. However, increasing incidence of incidentally discovered small renal masses and awareness of the deleterious consequences of chronic kidney disease (CKD) [2–5], combined with data demonstrating oncological equivalence with partial nephrectomy (PN) [6–8], has led to a paradigm shift where PN has emerged as the reference standard for management of T1a renal mass [9–11]. Increasing and selective utilization for larger masses (T1b and T2 disease) has demonstrated similar oncologic outcomes to RN [12–16]. Nonetheless, PN carries significantly greater risk of complications compared to RN [9, 16], and data from the only randomized trial comparing RN and PN failed to demonstrate a survival advantage for PN in RCC despite oncological equivalence and renal functional benefit [17, 18].

Presence of moderate/severe renal insufficiency (CKD stage 3 or higher, eGFR < 60 ml/min/1.73 m^2) has been considered a threshold for strong or imperative indication for PN, while patients with higher eGFR and normal contralateral kidney have been thought of as having elective indication [9–11]. Nonetheless, patients with CKD stage 2 (eGFR 60–90 ml/min/1.73 m^2) and mild renal functional impairment may carry greater risk of renal functional degeneration to thresholds of increased risk and their sequelae with surgical nephron loss. We sought to examine renal functional outcomes and overall survival (OS) in patients with baseline CKD stage 2 undergoing surgery for renal cortical neoplasm.

Patients and methods

Study population

Retrospective institutional review board approved international multicenter (UC San Diego, San Raffaele, Spectrum Health) analysis of all patients undergoing RN or PN with localized cortical renal masses (cT1/T2) between 2001 and 2015 who had baseline CKD stage 2 (eGFR 60–90 ml/min/1.73 m^2), as estimated by CKD-EPI equation [19]. Our evaluation and operative protocols have been previously described [15, 20, 21]. Patients referred with renal mass suspicious for malignancy underwent preoperative evaluation which included detailed history and physical examination, laboratory workup, cross-sectional imaging of the abdomen (computerized tomography or magnetic resonance imaging) and chest imaging (computerized tomography or plain radiography). All procedures were performed by urologic oncologic surgeons, and determination of type of operation and operative approach were carried out by individual attending surgeons based on patient comorbidities, mass characteristics, and technical feasibility. For PN, cold ischemia was generally employed when the resection time was estimated to be > 25 min. Long-term follow-up was dictated by pathological findings. Patients with advanced or metastatic disease (stage 3/4 RCC, $n = 374$) [22], urothelial malignancy ($n = 259$), and those without preoperative CKD stage 2 ($n = 1819$) were excluded from the analysis.

Data collection and analysis

Data were collected by database managers from institutional databases. Preoperative characteristics including age, sex, ethnicity, hypertension (HTN), diabetes (DM), cardiovascular disease (CVD), clinical tumor size/stage [22], and baseline eGFR were recorded. Postoperative details including surgical approach, complications (Clavien–Dindo) [23], tumor pathology, pathologic tumor size/stage, survival, and follow-up eGFR were detailed. Follow-up eGFR was determined based on the eGFR recorded at last clinical follow-up. Patients were stratified into baseline CKD 2 substages: CKD 2a (eGFR 75–89) and CKD 2b (eGFR 60–74.9) groups and analyzed between stage CKD 2a and 2b groups as well as type of surgery (RN vs. PN) within CKD stage subgroup [3].

Primary outcome was overall survival (OS). Secondary outcomes included development of CKD stage 3 (eGFR < 60), CKD stage 3b (eGFR < 45), change between preoperative eGFR and eGFR at last follow-up (ΔeGFR), cancer-specific survival (CSS), and non-cancer-specific survival (NCSS). Multivariable logistic regression was utilized to elucidate independent risk factors for the development of eGFR < 60, eGFR < 45, and OS, and Kaplan–Meier analysis was performed for OS, CSS, NCSS and freedom from eGFR < 45. Analysis was performed with SPSS, version 23 (SPSS Inc., Chicago, IL, USA), with $p < 0.05$ denoting statistical significance.

Results

A total of 1213 patients were included for analysis (mean age 61.7 years, median follow-up 49 months, mean clinical tumor size of 4.1 cm, preoperative eGFR of 75.1); 50.2% ($n = 609$) had CKD 2a while 49.8% ($n = 604$) had CKD 2b; 55.8% ($n = 677$) underwent PN while 44.2% ($n = 536$) underwent RN.

Table 1 shows demographic and clinical characteristics for the entire cohort and stratified by preoperative CKD 2 substage. There was no significant difference between CKD 2a and 2b groups for mean age (61.3 vs. 62.1 years, $p = 0.121$), incidence of diabetes mellitus (10.6% vs. 12.4%, $p = 0.364$), tumor size (4.1 cm vs. 4.1 cm, $p = 0.743$), and use of PN (54.5% vs. 57.1%, $p = 0.658$).

Table 2 compares operative, oncologic, and renal functional outcomes for the full cohort and stratified by CKD 2 substage. No differences were noted between CKD 2a and 2b groups for blood loss ($p = 0.102$), length of hospital stay ($p = 0.781$), 30-day overall complication rate ($p = 0.804$), and positive margin rate ($p = 0.539$). No significant

Table 1 Demographics and clinical characteristics of the overall cohort and stratified by CKD 2 substage

Variable	Entire cohort ($n = 1213$)	CKD 2a ($n = 609$)	CKD 2b ($n = 604$)	p value
Mean age (years, ± SD)	61.7 ± 11.3	61.3 ± 11.0	62.1 ± 11.0	0.121
Median follow-up (IQR, months)	51.5 (38–62.5)	57.1 (45–69)	46.0 (30–56)	< 0.001
Gender				0.208
Female	425 (35.0%)	224 (36.8%)	201 (33.3%)	
Male	788 (65.0%)	385 (63.2%)	403 (66.7%)	
Mean BMI (kg/m^2, ± SD)	26.8 ± 10.5	26.5 ± 4.5	27.1 ± 5.2	0.091
HTN	570 (47.0%)	272 (44.7%)	298 (49.3%)	0.107
DM	137 (11.3%)	64 (10.6) %	73 (12.4%)	0.364
CVD	103 (8.3%)	44 (7.2%)	68 (9.7%)	0.123
Mean clinical tumor size (cm ± SD)	4.1 ± 2.5	4.1 ± 2.5	4.1 ± 2.6	0.743
Procedure				0.658
Partial nephrectomy	677 (55.8%)	332 (54.5%)	345 (57.1%)	
Radical nephrectomy	536 (44.2%)	277 (45.2%)	259 (42.5%)	

Table 2 Operative and renal functional outcomes of the entire cohort stratified by CKD 2 substage

Variable	Entire cohort ($n = 1213$)	CKD 2a ($n = 609$)	CKD 2b ($n = 604$)	p value
Mean EBL (ml, + SD)	430 ± 663	395 ± 453	466 ± 838	0.102
Days in hospital	7.0 ± 4.2	7.1 ± 4.4	7.0 ± 3.9	0.781
30-Day complications	185 (15.3%)	92 (15.1%)	93 (15.4%)	0.804
Mean pathologic tumor size (cm ± SD)	4.0 ± 2.6	3.9 ± 2.4	4.0 ± 2.8	0.370
Malignant pathology	1010 (83.3%)	503 (82.6%)	507 (83.9%)	0.539
Positive margin	36 (3.0%)	27 (4.5%)	9 (1.6%)	0.015
Mean preoperative GFR (ml/min/1.73 m^2 ± SD)	75.1 ± 8.6	82.5 ± 4.5	67.7 ± 4.4	< 0.001
For radical nephrectomy	75.7 ± 8.5	83.1 ± 4.5	68.3 ± 4.4	< 0.001
For partial nephrectomy	74.7 ± 8.8	82.2 ± 4.5	67.4 ± 4.3	< 0.001
Mean eGFR at last follow-up (ml/min/1.73 m^2 ± SD)	62.5 ± 19.3	69.5 ± 19.2	55.6 ± 18.7	< 0.001
For radical nephrectomy	55.9 ± 16.6	61.8 ± 3.2	50.2 ± 3.1	< 0.001
For partial nephrectomy	67.8 ± 19.7	75.1 ± 3.2	60.9 ± 3.1	< 0.001
Mean ΔeGFR ± SD	12.6 ± 19.4	13.0 ± 19.4	12.1 ± 18.6	0.293
For radical nephrectomy	19.8 ± 16.8	21.3 ± 17.1	18.1 ± 15.4	0.115
For partial nephrectomy	6.8 ± 19.5	7.1 ± 19.2	6.5 ± 19.2	0.417
GFR < 60 at last follow-up	577 (47.6%)	233 (38.2%)	344 (57.0%)	< 0.001
For radical nephrectomy	347 (28.6%)	154 (25.3%)	193 (32.0%)	0.011
For partial nephrectomy	230 (19.0%)	79 (13.0%)	151 (25.0%)	< 0.001
GFR < 45 at last follow-up	184 (15.2%)	62 (10.2%)	122 (20.2%)	< 0.001
For radical nephrectomy	125 (10.3%)	45 (7.4%)	80 (13.2%)	0.001
For partial nephrectomy	59 (4.9%)	17 (2.8%)	42 (7.0%)	0.001
GFR < 30 at last follow-up	41 (3.4%)	16 (2.6%)	25 (4.2%)	0.156
For radical nephrectomy	23 (1.9%)	11 (1.8%)	12 (2.0%)	0.837
For partial nephrectomy	18 (1.5%)	5 (0.8%)	13 (2.2%)	0.067

differences were noted for ΔeGFR between CKD 2a and CKD 2b patients overall (13 vs. 12.1, $p = 0.293$), in the setting of RN (21.3 vs. 18.1, $p = 0.115$) or PN (7.1 vs. 6.5, $p = 0.417$). Nonetheless, prevalence of eGFR < 60 and < 45 at last follow-up was greater for CKD 2b as opposed to CKD 2a (57.0% vs. 39.2%, $p < 0.001$ and 20.2% vs. 10.2%, $p < 0.001$, respectively).

Table 3 demonstrates comparative analysis between radical and partial nephrectomy, with substratification of outcomes in RN and PN groups based on pre-existing CKD

Table 3 Comparative analysis of demographics and functional outcomes in PN and RN patients with CKD stage 2

Variable	PN ($n=677$)	RN ($n=536$)	p value
Mean age (years, ± SD)	62.5 ± 11.2	60.7 ± 11.3	0.006
Gender			0.773
Female	344 (34.6%)	191 (35.5%)	
Male	433 (65.4%)	345 (64.5%)	
Mean BMI (kg/m^2 ± SD)	28.1 ± 5.0	26.8 ± 4.7	0.117
HTN	330 (48.8%)	250 (47.0%)	0.831
DM	109 (16.1%)	63 (11.8%)	0.032
CAD	59 (8.7%)	43 (8.0%)	0.440
Mean clinical tumor size (cm, ± SD)	3.8 ± 1.8	4.0 ± 2.7	0.069
Time of treatment			< 0.001
2001–2008	104 (15.4%)	244 (45.5%)	
2007–2015	573 (84.6%)	292 (54.5%)	
Preoperative CKD stage			0.452
2a	332 (49.0%)	275 (51.3%)	
2b	345 (51.0%)	261 (48.7%)	
Mean EBL (ml, ± SD)	397 ± 639	480 ± 718	0.063
Mean pathologic tumor size (cm, ± SD)	3.7 ± 1.8	4.1 ± 2.9	0.026
Total complications	160 (23.6%)	91 (17.1%)	0.061
Clavien 3–5 complications	55 (8.1%)	17 (3.2%)	< 0.001
Days in hospital	6.9 ± 4.4	7.2 ± 3.9	0.258
Mean preoperative eGFR (ml/min/1.73 m^2, ± SD)	74.7 ± 8.8	75.7 ± 8.5	0.034
Mean last eGFR (ml/min/1.73 m^2, ± SD)	67.8 ± 19.7	55.9 ± 16.6	< 0.001
Mean ΔeGFR	− 6.8 ± 19.5	− 19.8 ± 16.8	< 0.001
CKD 2a	− 10.1 ± 19.2	− 23.7 ± 17.1	< 0.001
CKD 2b	− 3.5 ± 19.2	− 15.7 ± 15.4	< 0.001
GFR < 60 at last follow-up	230 (34.0%)	347 (64.7%)	< 0.001
CKD 2a	79 (23.8%)	154 (56.0%)	< 0.001
CKD 2b	151 (43.8%)	193 (75.1%)	< 0.001
GFR < 45 at last follow-up	59 (8.7%)	125 (23.3%)	< 0.001
CKD 2a	17 (5.1%)	45 (16.4%)	< 0.001
CKD 2b	42 (12.2%)	80 (31.1%)	< 0.001
GFR < 30 at last follow-up	18 (2.7%)	23 (4.3%)	0.149
CKD 2a	5 (1.5%)	11 (4.0%)	0.310
CKD 2b	13 (3.8%)	12 (4.7%)	0.681

2 substage. Patients undergoing PN were older (62.5 vs. 60.7, $p=0.006$) and had higher incidence of DM (16.1% vs. 11.8%, $p=0.032$). There was no significant difference in mean tumor size (3.8 vs. 4.0, $p=0.069$) and utilization of PN increased with time ($p=<0.001$), and while no significant difference in overall 30-day complications was noted between groups ($p=0.06$), PN had significantly greater Clavien 3–5 (major) complications (9.1% vs. 3.2%, $p<0.001$).

There was no difference in the presence of baseline CKD 2a vs. 2b ($p=0.452$) between PN and RN groups. Patients undergoing PN had decreased ΔeGFR (− 6.8 vs. − 19.8, $p<0.001$). Similarly, when patients were substratified by CKD 2 stage, ΔeGFR was less for PN vs. RN for CKD 2a (− 10.1 PN vs. − 23.7 RN, $p<0.001$) and CKD 2b (− 3.5 vs. − 15.7 RN, $p<0.001$).

Overall, patients undergoing PN had decreased development of eGFR < 60 (34.0% vs. 64.7%, $p<0.001$), and decreased development of eGFR < 45 (8.7% vs. 23.3%, $p<0.001$). PN had lower rates of development of eGFR < 60 and eGFR < 45, whether in the setting of CKD 2a (for eGFR < 60, PN 23.8% vs. RN 56.0%, $p<0.001$; for eGFR < 45, PN 5.1% vs. RN 16.4%, $p<0.001$) or CKD 2b (for eGFR < 60, PN 43.8% vs. RN 75.1%, $p<0.001$; for eGFR < 45, PN 12.2% vs. RN 31.1%, $p<0.001$).

Table 4a and 4b demonstrate results of logistic regression multivariable analysis for eGFR < 60 and < 45 at last follow-up. Factors entered into the multivariable models included age (continuous), BMI (continuous), medical comorbidities (HTN, DM, CAD), clinical tumor size (continuous), year of treatment (continuous), type of surgery (radical vs. partial

Table 4 Multivariable logistic regression analyses for risk factors associated with (a) development of eGFR < 60 ml/min/1.73 m^2 at last follow-up, (b) development of eGFR < 45 ml/min/1.73 m^2 at last follow-up, and (c) all-cause mortality

Variable	OR	95% CI low	95% CI high	*p* value
(a) Logistic regression, eGFR < 60				
Age	1.00	0.98	1.02	0.964
BMI	1.05	1.01	1.09	0.016
HTN	1.05	0.74	1.48	0.782
DM	0.91	0.51	1.61	0.739
CAD	0.91	0.47	1.78	0.789
clinical tumor size	0.97	0.91	1.03	0.277
Year of treatment	1.01	0.98	1.05	0.374
Radical nephrectomy	4.38	2.78	6.93	< 0.001
Malignancy	0.86	0.56	1.33	0.503
CKD 2b	2.57	1.68	3.91	< 0.001
(b) Logistic regression, eGFR < 45				
Age	1.01	0.98	1.03	0.666
BMI	1.00	0.94	1.06	0.984
HTN	1.24	0.74	2.08	0.413
DM	0.66	0.25	1.76	0.404
CAD	1.24	0.48	3.20	0.653
clinical tumor size	1.04	0.95	1.13	0.376
Year of treatment	1.00	0.94	1.06	0.991
Radical nephrectomy	3.68	1.72	7.87	0.001
Malignancy	0.99	0.51	1.94	0.973
CKD 2b	3.30	1.26	5.69	0.010
(c) Logistic regression, all-cause mortality				
Age	0.99	0.96	1.02	0.450
BMI	1.00	0.93	1.08	0.999
HTN	0.60	0.29	1.27	0.181
DM	1.72	0.60	4.93	0.311
CAD	0.40	0.05	3.22	0.390
clinical tumor size	0.86	0.73	1.01	0.059
Year of treatment	1.06	0.96	1.18	0.243
Radical nephrectomy	3.76	1.50	9.41	0.005
Malignancy	3.87	0.90	16.61	0.068
eGFR < 45	2.51	1.10	5.72	0.029

nephrectomy), malignant pathology, and the presence of CKD 2b (yes vs. no). We noted that for the development of eGFR < 60 at last follow-up increasing BMI (OR 1.05, $p = 0.016$), RN (OR 4.38, $p < 0.001$) and CKD 2b (OR 2.57, $p < 0.001$) were independently predictive (Table 4a). Similarly, we found that for the development of eGFR < 45 at last follow-up, RN (OR 3.68, $p = 0.001$) and CKD 2b (OR 3.3, $p = 0.010$) were independent risk factors.

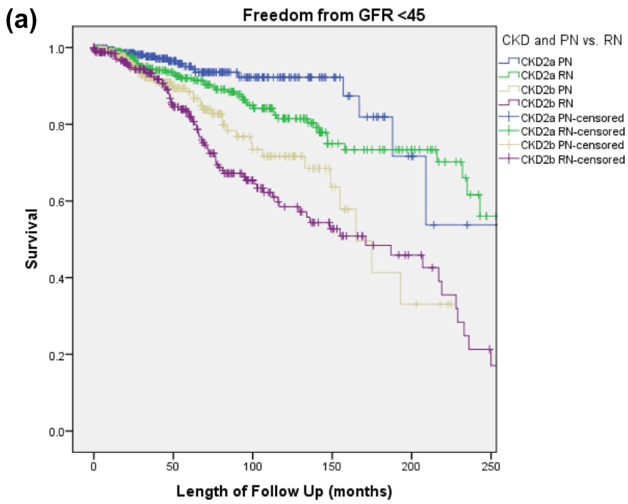
Table 4c represents the results of logistic regression multivariable analysis for factors associated with all-cause mortality. Factors entered in the model included age (continuous), BMI (continuous), medical comorbidities (HTN, DM, CAD), clinical tumor size (continuous), year of treatment (continuous), type of surgery (radical vs. partial nephrectomy), malignancy (yes vs. no) and de novo eGFR < 45 (yes vs. no). Independent risk factors associated with mortality included RN (OR 3.76, $p = 0.005$) and eGFR < 45 (OR 2.51, $p = 0.029$).

Figure 1a–e demonstrate Kaplan–Meier analyses for freedom from eGFR < 45, OS, NCSS and CSS. Figure 1a demonstrates freedom from eGFR < 45 stratified by CKD substage and surgical approach and showed a significant difference with patients with CKD 2a who underwent PN having the highest 5-year freedom from eGFR < 45 (94.3%) compared to CKD 2a RN (91.5%), CKD2b PN (87.6%) and CKD 2b RN 82.0% ($p < 0.001$). Additionally, when stratified by both CKD substage and surgical approach, an overall survival advantage was seen in favor of PN (CKD 2a PN 97.6%, CKD 2b PN 95.2%, CKD 2a RN 93.2%, CKD 2b RN 92.4%, $p = 0.043$, Fig. 1b). Additional Kaplan–Meier analyses were performed on the subset of patients who had details of cancer-specific mortality ($n = 884$). There was no difference in the 5-year estimated cancer-specific survival between CKD 2 stage (CKD 2a 96.4% vs. CKD 2b 96.1%, $p = 0.328$, Fig. 1c), while 5-year NCSS was significantly higher in CKD 2a (98.3%) vs. CKD 2b (93.7%), $p = 0.017$ (Fig. 1d). Clinical stage 1 RCC tumors had improved 5-year CSS compared to stage 2 RCC (97.2% vs. 90.6%, $p = 0.031$, Fig. 1e).

Discussion

To our knowledge, this is the first analysis of renal functional and survival outcomes focusing on patients with baseline CKD stage 2 undergoing renal surgery. We noted that the consequences of surgical nephron loss in the setting of pre-existing CKD 2 are unequal, as patients with CKD 2b substage (eGFR 60–74.9) were more likely to suffer postoperative decline in eGFR to < 60 and < 45, and more likely to have decreased renal function and overall survival in the setting of RN. Our findings suggest that patients with CKD stage 2—previously thought of as being elective for nephron-sparing surgery—may represent a higher risk group for renal functional degeneration, particularly those with CKD 2b substage. In these patients, a nephron-sparing strategy may be protective and should be considered to be a relative indication when oncologically feasible.

Previous work has shown that PN, as compared to RN, results in greater preservation of renal function [4, 5, 24, 25]. In EORTC 30904, 541 patients with small renal mass (≤ 5 cm), a normal contralateral kidney, and 'normal' creatinine were randomized to RN or PN. Although baseline GFR was not calculated, 93.4% of RN and 92.9% of PN patients had a baseline creatinine that was < 1.25 times the upper limit of normal. With median follow-up of 6.7 years, incidence of eGFR < 60 at last follow-up was significantly



Number at Risk

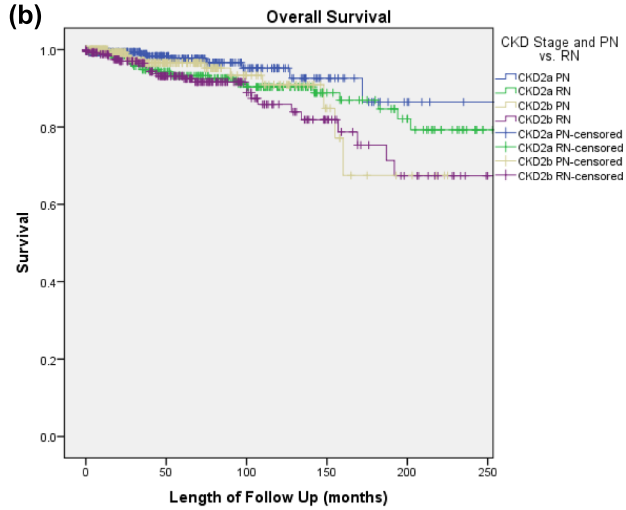
CKD 2a PN	333	148	61	22	5	1
CKD 2a RN	276	183	114	48	30	12
CKD 2b PN	346	114	42	12	4	0
CKD 2b RN	258	147	66	30	15	6

Log Rank p<0.001

Freedom from eGFR<45

5 year Freedom from eGFR<45

Variable	5 Year (SE)	10 Year (SE)
CKD 2a PN	94.3 % (1.7)	87.4% (5.2)
CKD 2a RN	91.5 % (1.9)	81.5% (3.1)
CKD 2b PN	87.6 % (2.5)	68.5% (5.5)
CKD 2b RN	82.0 % (2.8)	58.5% (4.4)



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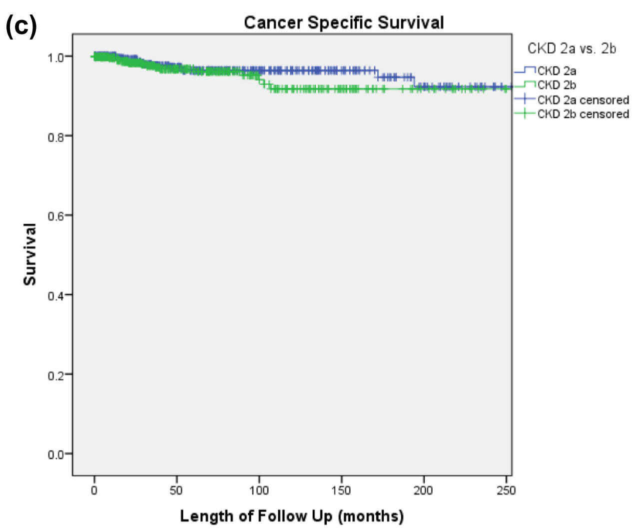
CKD 2b PN	346	114	42	12	4	0
CKD 2b RN	258	147	66	30	15	6

Log-rank p=0.043

Overall Survival

Variable	5 Year (SE)	10 Year (SE)
CKD 2a PN	97.6 % (1.1)	92.6% (3.2)
CKD 2a RN	95.2 % (1.8)	90.3% (2.2)
CKD 2b PN	93.2 % (1.7)	90.9% (3.5)
CKD 2b RN	92.4 % (1.9)	83.9% (3.8)



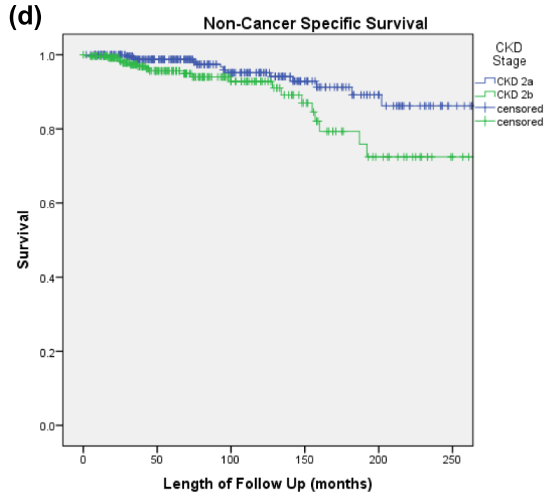
Number at Risk

CKD 2a	448	243	137	70	36	14
CKD 2b	436	187	85	41	19	6

Log rank p=0.328

Cancer Specific Survival

Variable	5 Year (SE)	10 Year (SE)
CKD 2a	96.4% (1.1)	95.0% (2.0)
CKD 2b	96.1% (1.2)	92.7% (2.3)



Number at Risk

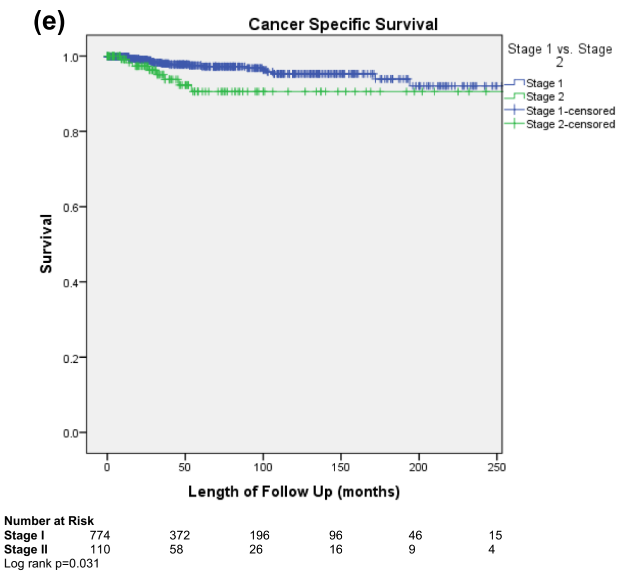
CKD 2a	286	183	122	64	33	7
CKD 2b	262	140	77	38	18	5

Log rank=0.017

Non-Cancer Specific Survival

Variable	5 Year (SE)	10 Year (SE)
CKD 2a	98.3% (1.0)	92.9% (0.8)
CKD 2b	93.7% (1.6)	90.8% (0.5)

Fig. 1 **a** Kaplan–Meier analysis for freedom from eGFR < 45 comparing CKD 2 substage and surgical approach (CKD 2a PN, CKD 2a RN, CKD 2b PN, CKD 2b RN); **b** Kaplan–Meier analysis for OS comparing CKD 2 substage and surgical approach (CKD 2a PN, CKD 2a RN, CKD 2b PN, CKD 2b RN); **c** Kaplan–Meier analysis for CSS comparing CKD 2a and CKD 2b; **d** Kaplan–Meier analysis for NCSS comparing CKD 2a and CKD 2b; **e** Kaplan–Meier analysis for CSS comparing stage 1 and stage 2 RCC



Cancer Specific Survival		
Variable	5 Year (SE)	10 Year (SE)
Stage I	97.2 % (0.7)	95.6% (1.2)
Stage II	90.6 % (3.3)	90.6% (3.3)

Fig. 1 (continued)

lower for PN (38.4% vs. 58.8%, $p < 0.001$) as was incidence of eGFR < 45 (13.3% vs. 24.7%, $p < 0.001$) [18]. While concerns have been raised regarding underpowering of this study as oncological equivalence and renal functional benefit for PN did not translate into overall survival benefit, this study has raised important questions about the impact of surgically induced nephron loss, particularly in the setting of uncompromised prior renal function [17, 18]. Our rates of development of eGFR < 60 and < 45 in PN and RN groups (eGFR < 60 PN 34.0% and RN 64.7%; eGFR < 45 PN 8.7% and RN 23.3%, $p < 0.001$ for both) were similar to those reported by Scosyrev et al.; however, we noted a modest but significant survival benefit to patients who underwent PN (Fig. 1b), which may be reflective of an otherwise larger sample size or more importantly selection bias, despite a multivariable analysis demonstrating that RN and eGFR < 45 were independently associated with decreased OS.

Mason et al. analyzed 1379 patients (665 PN, 714 RN) from the Canadian Kidney Cancer Information System undergoing RN or PN for RCC, of whom 335 patients (24.3%) had baseline CKD stage 2. With a median follow-up of 26 months, the authors noted that patients undergoing RN had lower eGFR at 3, 12, and 24 months postoperatively ($p < 0.001$). Additionally, severe CKD (eGFR < 30) was more common in RN (12.5% vs. 4.1%, $p < 0.001$) [25]. Our findings are similar and serve to clarify the degree of risk in CKD stage 2 patients, a population which has not been traditionally examined in depth. In our analysis of CKD 2a and 2b subgroups, we noted that patients with CKD 2b had higher rates of eGFR < 60 (57.0% vs. 38.2%, $p < 0.001$) and eGFR < 45 (20.2% vs. 10.2%, $p < 0.001$), and that receipt of RN amplified the risks posed in CKD stage 2b (for the development of eGFR < 45 and decreased OS). Taken together, our findings suggest that patients with mild CKD, especially those whose preoperative eGFR levels are < 75 ml/min/1.73 m^2 (CKD 2b) may form a unique higher risk subgroup of patients for functional degeneration and potential negative impact on survival and may not be a purely 'elective' indication for nephron-sparing management.

Previous retrospective population-based studies have shown that CKD is associated with worsened overall survival and higher rates of cardiovascular morbidity [3]. A meta-analysis by Kim et al., including 31,729 RN and 9281 PN revealed benefits in favor of PN. All-cause mortality was reduced by 19% (HR, 0.81, $p < 0.001$), cancer-specific mortality by 29% (HR 0.71, $p < 0.001$), and severe CKD by 61% (HR 0.39, $p < 0.001$) [26]. Sun et al. utilized the Surveillance Epidemiology and End Results-Medicare-linked database to evaluate survival effects of PN in the setting of T1a RCC. In a propensity-based analysis of 1068 RN and 1068 PN, non-cancer mortality was reduced by 17% (HR 0.83, $p = 0.04$) [27]. Indeed, even while illuminating, findings which suggest benefit for cancer-specific survival in the setting of PN are likely contaminated by selection bias. Conversely, we noted a modest but significant benefit in favor of PN for OS in the CKD stage 2 setting (Fig. 1b), and did not demonstrate any difference in CSS between CKD stage 2 subgroups (Fig. 1c). These findings in addition to our demonstration of improved NCSS in CKD 2b patients (Fig. 1d) and confirmation of CSS survival differences for AJCC stage 1 and stage 2 RCC (Fig. 1e) suggest that differences in OS between RN and PN and CKD stage 2 subgroups are driven by non-oncological factors.

Indeed, impact of surgically induced nephron loss and conversely the potential benefits of nephron preservation on renal functional degeneration and survival have been a topic of considerable discussion and controversy since the publication of the survival and functional outcomes of EORTC 30904 which suggested that the potential benefits of nephron preservation are not as impactful on survival outcomes as what had been suggested in large cohort retrospective studies [17, 18, 28]. Lane et al. developed the concept of CKD-S (surgically induced CKD) as opposed to that medically induced CKD (CKD-M). They analyzed 4299 patients undergoing surgery for RCC with a median follow-up of 9.4 years. Patients were categorized as no CKD (new baseline GFR > 60), CKD-S (new baseline GFR < 60 but preoperative > 60), and CKD-M/S (new baseline and preoperative GFR both < 60). When comparing CKD-M/S to CKD-S and no CKD, the authors noted that CKD-M/S had higher rates of 50% drop in eGFR (21% vs. 11% vs. 10%, $p < 0.001$), all-cause mortality (47% vs.

28% vs. 19%, $p < 0.001$), and non-RCC mortality (32% vs. 15% vs. 10%, $p < 0.001$). Nonetheless, postoperative baseline eGFR < 45 significantly predicted worse survival outcomes even in the CKD-S population [29]. Similarly, Pettus et al. analyzed 1479 patients undergoing RN or PN for localized RCC and noted that postoperative eGFR < 45 was independently associated with decreased OS (HR 2.8; $p = 0.001$) [30]. Taken together, our findings and those of Lane et al. and Pettus et al. suggest that crossing the threshold of eGFR < 45, whether by a postoperative baseline, or at last follow-up, may be associated with worsened overall survival. Furthermore, we noted that in the CKD stage 2 population, patients with preoperative baseline eGFR 74-60 (CKD stage 2b) and those undergoing RN are at heightened risk of developing eGFR < 45, and as such suggest the need to prioritize nephron-sparing strategies when possible in this higher risk subgroup.

Our analysis is limited by its retrospective design and inherent biases therein. Individual selection bias and performance bias based on surgical experience and volume are potential confounders. In a multicenter retrospective analysis, detection bias due to misclassification, variation in follow-up and definitions may introduce further confounding. While we provided detailed information on co-morbid disease states such as obesity, DM, hypertension, and cardiovascular disease, information on co-morbidity profile and surgical risk which may have provided a composite overview of patient functional and life expectancy status was not analyzed. We were neither able to include morphometric measures such as RENAL score which have been shown to correlate with oncological [15] as well as functional outcomes [31] nor were we able to analyze findings of nuclear renal scans [32] or calculated renal volume [33] to provide a more granular assessment of functional outcomes. Similarly, information on surgical approach (open vs. minimally invasive) and resection and renorrhaphy technique which may have influenced functional preservation in PN was not analyzed. Nonetheless, CKD 2a and 2b groups had similar demographic parameters and patients who underwent PN and RN had no significant difference in BMI, incidence of hypertension proportion of CKD2a/2b or clinical tumor size. While our findings should be interpreted with caution, they nonetheless represent the first focused look on patients with mild chronic renal insufficiency and suggest that a subgroup of these patients, whose preoperative baseline eGFR is between 74 and 60, may be at heightened risk of poor functional and survival outcomes, and in this group prioritization of a nephron-sparing strategy when feasible is indicated. Ultimately, longer follow-up is necessary and prospective investigation is ideal to more comprehensively elucidate risks present in patients with pre-existing CKD stage 2 at the time of diagnosis.

Conclusion

Patients with preoperative CKD stage 2b and those undergoing RN are at increased risk of developing eGFR < 45, which was associated with decreased overall survival. Nephron-sparing surgery should be considered to be a definitive indication when oncologically safe in this at-risk population.

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Compliance with ethical standards

Conflict of interest None of the authors have any conflict of interest to declare.

Ethical standards Ethical standards have been met; study is IRB approved at both institutions.

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