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Predicting Renal Function Outcomes After Partial and Radical Nephrectomy

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Abstract

Background: Partial nephrectomy (PN) is generally favored for cT1 tumors over radical nephrectomy (RN) when technically feasible. However, it can be unclear whether the additional risks of PN are worth the magnitude of renal function benefit.
Objective: To develop preoperative tools to predict long-term estimated glomerular filtration rate (eGFR) beyond 30 d following PN and RN, separately.
Design, setting, and participants: In this retrospective cohort study, patients who underwent RN or PN for a single nonmetastatic renal tumor between 1997 and 2014 at our institution were identified. Exclusion criteria were venous tumor thrombus and preoperative eGFR <15 ml/min/1.73 m^2.
Intervention: RN and PN.
Outcome measurements and statistical analysis: Hierarchical generalized linear mixed-effect models with backward selection of candidate preoperative features were used to predict long-term eGFR following RN and PN, separately. Predictive ability was summarized using marginal R^2_{GLMM}, which ranges from 0 to 1, with higher values indicating increased predictive ability.
Results and limitations: The analysis included 1152 patients (13 206 eGFR observations) who underwent RN and 1920 patients (18 652 eGFR observations) who underwent PN, with mean preoperative eGFRs of 66 ml/min/1.73 m^2 (standard deviation [SD] = 18) and 72 ml/min/1.73 m^2 (SD = 20), respectively. The model to predict eGFR after RN included age, diabetes, preoperative eGFR, preoperative proteinuria, tumor size, time from surgery, and an interaction between time from surgery and age (marginal $R^2_{\text{GLMM}} = 0.41$). The model to predict eGFR after PN included age, presence of a solitary kidney, diabetes, hypertension, preoperative eGFR, preoperative proteinuria, surgical approach, time from surgery, and interaction terms between time from surgery and age, diabetes, preoperative eGFR, and preoperative proteinuria (marginal $^2_{\text{GLMM}}$). Limitations include the lack of data on renal tumor complexity and the single-center design; generalizability needs to be confirmed in external cohorts.
Conclusions: We developed preoperative tools to predict renal function outcomes following RN and PN. Pending validation, these tools should be helpful for patient counseling and clinical decision-making.
Patient summary: We developed models to predict kidney function outcomes after partial and radical nephrectomy based on preoperative features. This should help clinicians during patient counseling and decision-making in the management of kidney tumors.

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1. Introduction

Surgical management of a localized renal mass involves balancing oncologic risk, renal function preservation, and avoidance of perioperative complications and morbidity. Given the lack of cancer-specific survival benefit with radical nephrectomy (RN) over partial nephrectomy (PN) [1], the superior renal function outcomes with PN [2–4], and the potential cardiovascular and overall survival benefits with avoiding chronic kidney disease (CKD) [4–6], guidelines have recommended prioritizing PN when technically feasible, particularly for cT1 tumors [7,8].

However, nephron-sparing approaches carry an increased risk of perioperative complications with increasing tumor complexity [9–14]. Moreover, the mixed literature on the oncologic implications of a positive surgical margin [15–18] may at least urge caution in the overly ambitious use of PN.

Preoperative oncologic risk stratification by estimating the risk of adverse histology [19–21] and metastatic potential [22,23], and preoperative estimation of complication risk have been described well previously [9,10,24]. However, to date, only a few studies have reported on predicting short-term postoperative renal function [25–29], with none predicting long-term differential renal function after PN and RN. Having an estimate of expected long-term renal function outcomes after PN and RN may help clinicians and patients judge whether it is worth accepting the complication risk and potential oncologic risk of a complex PN. As such, our objective was to create a preoperative predictive tool for long-term renal function as well as the risk of early postoperative renal failure, following PN and RN.

2. Patients and methods

2.1. Study design and participants

Following institutional review board approval, we used our prospectively maintained Nephrectomy Registry [11,21,30,31] to identify 1234 patients treated with RN and 2075 patients treated with PN for a single, unilateral renal mass between 1997 and 2014 by 24 surgeons. Patients with distant metastases, lymphadenopathy, or venous tumor thrombus on imaging; patients with a solitary kidney undergoing RN; and patients with a preoperative estimated glomerular filtration rate (eGFR) of <15 ml/min/1.73 m^2 were excluded (Supplementary Fig. 1).

2.2. Follow-up, candidate predictors, and study outcomes

As previously described [11,21,30,31], patients were generally seen in the clinic at 3 mo postoperatively, with renal function assessment and cross-sectional imaging. Patients were then recommended to have similar assessments at 6, 12, 18, 24, and 36 mo, with annual follow-up thereafter.

Features considered a priori as potential predictors of renal function outcomes included age, sex, race, presence of a solitary kidney (for the PN group), smoking status, Eastern Cooperative Oncology Group (ECOG) performance status, diabetes, hypertension, body mass index (BMI), preoperative eGFR, preoperative proteinuria (based on predicted 24-h protein; categorized as none/mild: <150 mg/d, moderate: 150–500 mg/d, and severe: >500 mg/d) [32], tumor size, and open versus minimally invasive surgical approach.

The primary outcome was eGFR as calculated using the Chronic Kidney Disease Epidemiology Collaboration formula, modeled as a function of time beyond 30 d from surgery [33]. During follow-up, eGFR values assessed during dialysis were set to 0 and those following a kidney transplant were not included. The secondary outcome was early postoperative renal failure defined as eGFR <15 ml/min/1.73 m^2 or receipt of dialysis within 30 d of surgery..

2.3. Statistical analysis

Associations with early postoperative renal failure within 30 d of surgery were evaluated using univariable logistic regression models. Given the rarity of this outcome, multivariable analyses were not possible. Predictive ability was summarized with the area under the receiver operating characteristics curve (AUC), with 0.5 representing a coin flip and 1.0 representing perfect predictive ability.

Associations with long-term postoperative eGFR beyond 30 d following surgery were evaluated using hierarchical generalized linear mixed-effect models with random patient-specific intercepts and slopes, and autoregressive covariance structures. This approach takes into account both within- and between-patient variability in measurements. The random intercept and slope model was compared with a reduced model with only random intercepts using a likelihood ratio test; the full model suggested a better fit. Adding the autoregressive covariance structure lowered the Akaike information criterion for both RN and PN models.

Multivariable models were developed using backward selection of the preoperative features under study and their two-way interactions with time, with the significance level for an effect to be retained in the model set to 0.01. Backward selection maintained a hierarchy such that main effects were included whenever the interaction with time was retained in model selection. Plots of residuals were used to evaluate distributional assumptions, and influence diagnostics obtained by iterative methods were used to identify overly influential individual data points or overly influential patients. Predictive ability was summarized with the marginal and conditional R^2_{GLMM} recommended by Nakagawa and Schielzeth [34] and Johnson [35], representing the proportion of variation explained by fixed effects and the proportion of variation explained by both fixed and random effects, with 0.0 representing no predictive ability and 1.0 representing perfect predictive ability. The marginal R^2_{GLMM} is helpful in characterizing the ability of the fixed effects (ie, the preoperative features in the model) to predict eGFR for a future patient, which is more relevant for individual patient counseling. Meanwhile, the conditional R^2_{GLMM} can be viewed as representing the total amount of variability in postoperative eGFR that can be explained by the model when accounting for both the fixed effects and explicit modeling of between- and within-patient variability using random effects. Predicted eGFRs were obtained using the marginal estimates (the average of the patient-specific intercepts and slopes) from the multivariable models. Using a complete case approach, the primary analysis considered patients with complete data for all the preoperative features studied in the selection process for inclusion in multivariable models.

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Long-term eGFR beyond 30 d postoperatively

Of the eligible patients, 1152 (93%) RN patients and 1920 (93%) PN patients had an available eGFR assessment beyond 30 d from surgery and were included in the primary analysis (Table 1 and Supplementary Fig. 1). Mean age, preoperative eGFR, and tumor size were, respectively, 63 yr (standard

Table 1 – Preoperative cohort characteristics[a]

Feature	Mean (SD)	
	RN (*N* = 1152)	PN (*N* = 1920)
Age (yr)	62.9 (12.4)	59.6 (12.0)
BMI (kg/m^2; *N* = 1143:1900)	30.1 (6.4)	30.0 (6.2)
Preoperative eGFR (ml/min/1.73 m^2)	66.3 (18.1)	72.0 (20.3)
Tumor size (cm; *N* = 1151:1898)	7.2 (3.9)	3.5 (2.1)
Feature	***N* (%)**	
	RN (*N* = 1152)	PN (*N* = 1920)
Female sex	433 (38)	723 (38)
Race (*N* = 1066:1820)		
White	1020 (96)	1737 (95)
Black/African American	21 (2)	21 (1)
All others	25 (2)	62 (3)
Solitary kidney	NA	109 (6)
Smoking status (*N* = 1134:1883)		
Never	525 (46)	854 (45)
Current	167 (15)	277 (15)
Former	442 (39)	752 (40)
ECOG performance status (*N* = 1143:1909)		
0	987 (86)	1785 (94)
≥1	156 (14)	124 (6)
Diabetes (*N* = 1143:1909)	162 (14)	259 (14)
Hypertension	698 (61)	1111 (58)
Preoperative proteinuria (*N* = 734:1367)		
None/mild	442 (60)	1038 (76)
Moderate	190 (26)	221 (16)
Severe	102 (14)	108 (8)
Minimally invasive approach (vs open)	327 (28)	411 (21)

BMI = body-mass index; ECOG = Eastern Cooperative Oncology Group; eGFR = estimated glomerular filtration rate; NA = not applicable; PN = partial nephrectomy; RN = radical nephrectomy; SD = standard deviation.

[a] Cohort characteristics of the analytic cohort were used for the primary outcome of postoperative estimated glomerular filtration rate beyond 30 d after surgery.

deviation [SD] = 12), 66 ml/min/1.73 m^2 (SD = 18), and 7.2 cm (SD = 3.9) for patients treated with RN and 60 yr (SD = 12), 72 ml/min/1.73 m^2 (SD = 20), and 3.5 cm (SD = 2.1) for patients treated with PN. PN was performed on a solitary kidney in 109 (6%) patients. The mean number of postoperative eGFR assessments was 11.5 (SD = 11.3; range 1–108) after a mean of 61 mo (SD = 51; range 1–237) following RN and 9.7 (SD = 8.9; range 1–67) after a mean of 57 mo (SD = 46; range 1–237) following PN, resulting in 13 206 and 18 652 observations for analysis after RN and PN, respectively. The eGFR values over time for a random subset of patients who underwent RN or PN are illustrated in Fig. 1.

The strongest individual predictor of long-term renal function at any point in time 30 d beyond surgery was preoperative eGFR, with marginal R^2_{GLMM} values of 0.304 and 0.550 for the RN and PN groups, respectively.

In the multivariable model predicting long-term eGFR at any point in time 30 d beyond RN (Table 2), older age, diabetes, lower preoperative eGFR, worse preoperative proteinuria, and smaller tumor size were associated with worse long-term eGFR. Moreover, there was a significant interaction between age and time from surgery, such that there was a greater decline in eGFR over time in older patients. This model had marginal and conditional values of 0.41 and 0.83, respectively.

Meanwhile, in the multivariable model predicting long-term eGFR at any point in time 30 d beyond PN (Table 2), older age, presence of a solitary kidney, hypertension, lower preoperative eGFR, worse preoperative proteinuria, and open surgical approach were associated with worse long-term eGFR. Moreover, there was a significant interaction between time from surgery and age, diabetes, preoperative eGFR, and preoperative proteinuria. Specifically, there was a greater decline in eGFR over time in older patients, diabetic patients, and those with a higher preoperative eGFR and greater degree of preoperative proteinuria. This model had marginal and conditional R^2_{GLMM} values of 0.62 and 0.85, respectively.

3.2. *Risk of early postoperative renal failure (eGFR <15 ml/min/1.73 m^{2}or requiring dialysis) within 30 d of surgery*

Of the eligible patients, 1185 (96%) RN patients and 1919 (92%) PN patients had an available eGFR assessment within 30 d of surgery and were included in this analysis (Supplementary Fig. 1). Characteristics of the analytic cohort for this secondary outcome were similar to those

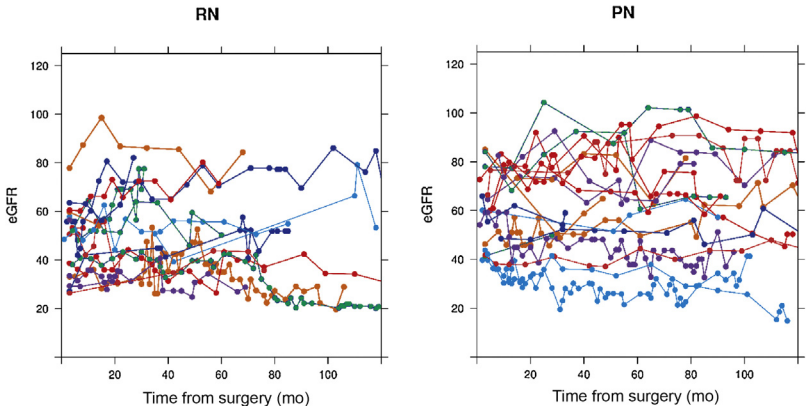

Fig. 1 – Spaghetti plots of eGFR over time for a random subset of patients who underwent RN and PN. In these figures, each line represents a single patient, and each data point represents an eGFR measurement for that patient. eGFR = estimated glomerular filtration rate; PN = partial nephrectomy; RN = radical nephrectomy.

Table 2 – Multivariable models to predict long-term eGFR

Feature	Estimate	SE	*p* value
RN			
Intercept	29.8	2.90	<0.001
Age (yr)	−0.235	0.0309	<0.001
Diabetes	−3.30	0.950	<0.001
Preoperative eGFR (ml/min/1.73m^2)	0.457	0.0202	<0.001
Preoperative proteinuria			
None/mild	Reference		
Moderate	−1.39	0.808	0.08
Severe	−4.26	1.02	<0.001
Tumor size (cm)	0.401	0.0909	<0.001
Time from surgery (mo)	0.148	0.0322	<0.001
Age × time from surgery	−0.0020	0.0005	<0.001
PN			
Intercept	31.8	2.69	<0.001
Age (yr)	−0.221	0.0302	<0.001
Solitary kidney	−6.87	1.16	<0.001
Diabetes	0.685	0.880	0.4
Hypertension	−1.79	0.613	0.004
Preoperative eGFR (ml/min/1.73 m^2)	0.741	0.0176	<0.001
Proteinuria			
None/mild	Reference		
Moderate	−1.84	0.792	0.02
Severe	−5.92	1.14	<0.001
Minimally invasive approach (vs open)	3.05	0.664	<0.001
Time from surgery (mo)	0.164	0.0455	<0.001
Age × time from surgery	−0.0017	0.0005	0.001
Diabetes × time from surgery	−0.0781	0.0150	<0.001
Preoperative eGFR × time from surgery	−0.0012	0.0003	<0.001
Proteinuria × time from surgery			
None/mild	Reference		
Moderate	−0.0315	0.0131	0.02
Severe	−0.110	0.0196	<0.001

eGFR = estimated glomerular filtration rate; PN = partial nephrectomy; RN = radical nephrectomy; SE = standard error.

used for the primary outcome (Supplementary Table 1). Sixteen (1%) and 30 (2%) patients had early postoperative renal failure within 30 d of RN and PN, respectively.

On univariable analyses, ECOG performance status ≥1, diabetes, hypertension, and severe preoperative proteinuria were associated with a greater risk of early postoperative renal failure after RN, while a higher preoperative eGFR and male sex were associated with a lower risk of early postoperative renal failure (Table 3).

Meanwhile, older age, black/African-American race, ECOG performance status ≥1, diabetes, hypertension, larger tumor size, and severe preoperative proteinuria were associated with a greater risk of early postoperative renal failure after PN, while a higher preoperative eGFR and a minimally invasive approach were associated with a lower risk of early postoperative renal failure after PN (Table 3).

Preoperative eGFR was most strongly predictive of early postoperative renal failure after RN (AUC = 0.93) and PN (AUC = 0.89; Table 3). For example, a patient with a preoperative eGFR of 30 would have predicted risks of 16% and 14% after RN and PN, respectively, while a patient with a preoperative eGFR of 60 would have predicted risks of <1% and 1% after RN and PN, respectively.

4. Discussion

We developed tools to predict long-term renal function and risk of early postoperative renal failure following RN and PN. There are several strengths to this study. First, we used a

Table 3 – Univariable predictors of early postoperative renal failure within 30 d of surgery

Feature	RN			PN		
	Odds ratio (95% CI)	*p* value	AUC	Odds ratio (95% CI)	*p* value	AUC
Age (yr)[a]	0.87 (0.59–1.27)	0.5	0.52	1.71 (1.21–2.41)	0.003	0.65
Sex (male vs female)	0.35 (0.13–0.97)	0.04	0.63	1.42 (0.65–3.13)	0.4	0.54
Race			0.52			0.53
White	1.0 (reference)			1.0 (reference)		
Black/African American	1.69 (0.09–31.1)	0.7		6.79 (1.51–30.6)	0.01	
All others	5.05 (0.86–29.7)	0.07		1.13 (0.15–8.49)	0.9	
Solitary kidney	NA	NA	NA	15.3 (7.28–32.3)	<0.001	0.71
Smoking status			0.64			0.61
Never	1.0 (reference)			1.0 (reference)		
Current	0.70 (0.15–3.25)	0.6		0.25 (0.03–1.93)	0.2	
Former	0.26 (0.06–1.20)	0.08		1.58 (0.75–3.33)	0.2	
ECOG performance status ≥1 (vs 0)	4.90 (1.80–13.3)	0.002	0.65	7.33 (3.35–16.0)	<0.001	0.64
Diabetes	3.57 (1.28–9.95)	0.02	0.62	3.69 (1.73–7.83)	<0.001	0.62
Hypertension	4.59 (1.04–20.3)	0.045	0.64	3.79 (1.45–9.95)	0.007	0.63
BMI (kg/m^2) [b]	0.90 (0.59–1.37)	0.6	0.59	1.20 (0.92–1.57)	0.2	0.53
Preoperative eGFR (ml/min/1.73 m^2) [a]	0.18 (0.10–0.31)	<0.001	0.93	0.38 (0.30–0.48)	<0.001	0.89
Tumor size (cm) [c]	1.03 (0.92–1.15)	0.6	0.57	1.24 (1.13–1.36)	<0.001	0.76
Preoperative proteinuria			0.74			0.79
None/mild	1.0 (reference)			1.0 (reference)		
Moderate	1.12 (0.20–6.17)	0.9		2.33 (0.58–9.39)	0.2	
Severe	10.4 (3.15–34.6)	<0.001		24.32 (9.04–65.5)	<0.001	
Minimally invasive approach (vs open)	1.17 (0.40–3.38)	0.8	0.52	0.13 (0.02–0.93)	0.04	0.59

AUC = area under the receiver operating characteristics curve; CI = confidence interval; BMI = body-mass index; ECOG = Eastern Cooperative Oncology Group; eGFR = estimated glomerular filtration rate; PN = partial nephrectomy; RN = radical nephrectomy.

[a] Odds ratio and 95% CI represent a 10-unit increase in the feature listed.

[b] Odds ratio and 95% CI represent a five-unit increase in the feature listed.

[c] Odds ratio and 95% CI represent a one-unit increase in the feature listed.

large cohort with >30 000 eGFR assessments in 3000 patients. Second, our analysis took into account the entire set of eGFR measurements over time for each patient, and not only those within a limited timeframe. Third, we developed separate models for RN and PN, which allowed us to identify and characterize how the studied preoperative features have different effects in each of these settings. Finally, we focused on the most clinically relevant outcomes, namely, early postoperative renal failure (eGFR <15 ml/min/1.73 m^2 or dialysis within 30 d of surgery) and long-term eGFR at any point in time beyond 30 d from surgery.

For example, a 55-yr-old binephric woman with a BMI of 25 kg/m^2, a preoperative eGFR of 70 ml/min/1.73 m^2, and a history of hypertension, diabetes, and moderate proteinuria with a 5 cm renal mass amenable to minimally invasive PN or RN would have a predicted risk of early postoperative renal failure of <1% after either RN or PN, and predicted eGFRs at 5 yr postoperatively of 48 and 64 ml/min/1.73 m^2 after RN and PN, respectively (Supplementary Fig. 2). The magnitude of long-term renal function benefit may sway patients and clinicians toward PN in this instance. In contrast, a 70-yr-old binephric woman with a BMI of 30 kg/m^2, a preoperative eGFR of 50 ml/min/1.73 m^2, and a history of diabetes and severe proteinuria with a 7 cm renal mass that may warrant an open PN or a minimally invasive RN would have predicted risks of early postoperative renal failure of <1% and 2% after RN and PN, respectively, and predicted eGFRs at 5 yr postoperatively of 32 and 36 ml/min/1.73 m^2 after RN and PN, respectively (Supplementary Fig. 2). In this instance, the limited projected long-term renal function benefit may sway patients and clinicians away from a complex PN with a higher risk of complications in favor of a minimally invasive RN. Given the duration of follow-up in this analysis, we would not recommend calculating estimates beyond 10 yr from treatment. This prediction tool can likely provide more accurate estimates of renal function outcomes than clinical gestalt alone, which is the current standard practice. While this tool may be helpful to clinicians pending further validation, it should not be used alone in making management decisions. Several other facets must be taken into account, including oncologic feasibility, anatomic tumor complexity, and related perioperative complication risk.

The reported models illustrate the complexity of the impacts of each individual preoperative feature. For example, in the RN model, there was no interaction between diabetes and time, meaning that the impact of this feature applies equally to an observation at 31 d as it does to an observation at 5 yr. This may be because the removal of healthy nephrons provides the predominant effect on eGFR in these patients with diminished renal function reserve, which is already noted early in the postoperative follow-up and persists thereafter [36,37]. Meanwhile, after nephron-sparing PN, eGFR was not meaningfully impacted by diabetes during the early follow-up, likely due to the fewer upfront loss of nephrons. However, there was a progressive eGFR decline over time (represented by the diabetes-time interaction term), perhaps representing diabetic nephropathy. These data are in line with practice patterns favoring PN over RN when feasible in diabetic patients in order to delay renal function decline [7,8]. However, nephron sparing alone is not sufficient, and postoperative optimization of diabetes control and medical renoprotection is also essential.

The effect of tumor size was different for RN and PN as well. After PN, a larger tumor size was associated with a worse eGFR, possibly due to the greater loss of nephrons at the margins of larger tumors and possibly due to ischemia time [38]. Conversely, after RN, a larger tumor size was associated with a better postoperative eGFR, likely attributable to the removal of fewer healthy nephrons compared with smaller tumors.

The findings from studies predicting renal function outcomes are generally compatible with the present study [25–29,39]. However, to date, most studies have evaluated only early postoperative renal function [25–29]. Moreover, measurements at a single time point were used [25–29], which does not take into account measurements that occurred before or after the selected time window, or within-patient variability of renal function measurements. Other studies evaluate the risk of attaining a certain renal function threshold postoperatively, such as a serum creatinine level of ≥2.0 mg/dl [39] or stage-5 CKD [27]. The main limitation of such models is that they apply binary cut-points to renal function, which pools small and large renal function changes together and considers them the same.

The differences in conditional and marginal R^2 values suggest that random subject-specific effects account for a significant amount of variability in eGFR over time [34,35]. This implies that there is some inherent variability in postoperative renal function outcomes that cannot be accounted for by the included fixed effects, more so for the RN models than the PN models.

There are several limitations worth acknowledging. First, this analysis is based on patients treated at a single quaternary referral center, and external validation will be needed before applying this tool to patient care decisions. Second, we did not have data on tumor complexity. It is suspected that complex tumors were more likely to be managed using an open approach. As such, it is unknown whether a surgical approach may in part be an indirect reflection of tumor complexity. Third, we did not consider renal volumetric measurements as a preoperative predictor as we prioritized the ease of use for clinicians. Fourth, preoperative proteinuria data were not available for approximately 30% of the cohort, although results were generally similar in the subset of patients with proteinuria data versus the whole cohort (data not shown). Fifth, while intraoperative variables such as warm or cold ischemia time were not considered, given that the objective was to develop models for preoperative counseling and decision-making, these variables are likely important influencers of postoperative renal function and may allow for more accurate prediction models. Finally, we were unable to control for fasting and hydration status at the time of eGFR measurements.

5. Conclusions

We herein present prediction tools for the risk of early postoperative renal failure and long-term renal function, with separate models for patients undergoing RN and PN. Pending external validation, these models should be helpful for patient counseling and decision-making when trying to decide whether it is worth pursuing a complex nephron-sparing surgery.

Author contributions: Bimal Bhindi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Bhindi, Thompson.
Acquisition of data: Bhindi, Lohse, Boorjian, Leibovich, Thompson.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: Bhindi, Lohse, Schulte, Thompson.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.eururo.2018.11.021.

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