

Role of Clinical and Surgical Factors for the Prediction of Immediate, Early and Late Functional Result and Its Relationship with Cardiovascular Outcome after Partial Nephrectomy: Results from the Prospective Multicenter RECORd 1 Project

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Purpose: We sought to determine the predictors of short-term and long-term renal function impairment after partial nephrectomy.

Materials and Methods: Clinical data on 769 consecutive patients who underwent partial nephrectomy were prospectively recorded at a total of 19 urological Italian centers from 2009 to 2012 in the RECORd1 (Italian Registry of Conservative Renal Surgery) Project. We extracted clinical data on 708 of these patients who were alive, free of recurrent disease and with a minimum 2-year functional followup.

Results: Of the patients 47.3% underwent open, 36.6% underwent laparoscopic and 16.1% underwent robot-assisted partial nephrectomy. The median baseline estimated glomerular filtration rate was 84.5 ml/minute/1.73 m² (IQR 69.9–99.1). Immediate (day 3 postoperatively), early (month 1) and late (month 24) renal function impairment greater than 25% from baseline was identified in 25.3%, 21.6% and 14.8% of cases, respectively. Female gender and the baseline estimated glomerular filtration rate were independent predictors of immediate, early and late RF impairment. Age at diagnosis was an independent predictor of immediate and late impairment. Uncontrolled diabetes was an independent predictor of late impairment only. Open and laparoscopic approaches, and pedicle clamping were independent predictors of immediate and early renal function impairment. Overall 58 of 529 patients (11%) experienced postoperative cardiovascular events. Body mass index and late renal function impairment were independent predictors of those events.

Conclusions: Surgically modifiable factors were significantly associated with worse immediate and early functional outcomes after partial nephrectomy while clinically unmodifiable factors affected renal function during the entire followup. Late renal function impairment is an independent predictor of postoperative cardiovascular events.

Key Words: kidney, nephrectomy, robotic surgical procedures, postoperative complications, cardiovascular system

Abbreviations and Acronyms

BMI	=	body mass index
CKD	=	chronic kidney disease
CVe	=	cardiovascular event
DMT2	=	diabetes mellitus type 2
eGFR	=	estimated glomerular filtration rate
OPN	=	open PN
PN	=	partial nephrectomy
RAPN	=	robot-assisted PN
RF	=	renal function
RN	=	radical nephrectomy
WIT	=	warm ischemia time

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To date PN has been the standard treatment of localized renal tumors.¹ When preserving the normal parenchyma is feasible, conservative treatment offers equivalent oncologic results² with better preservation of RF³ compared to RN.

Thus, RF preservation represents a distinct goal of PN. Ischemia time has been historically associated with RF impairment and recommendations support that WIT should be limited to 20 to 25 minutes.^{4,5} Even so, in the last decade several other clinical unmodifiable factors (preoperative renal function, surgical indication, patient age, gender and tumor nephrometry features) and surgical modifiable factors (off clamp or selective clamp procedure, surgical technique and approach) were found to be associated with early and late RF impairment.⁶ These different aspects are often interconnected and the impact on RF is progressively hidden by compensatory hypertrophy from the contralateral and the operated kidney.^{5,7,8} Therefore, many controversies persist and this remains an important area of investigation. In this scenario a better understanding of the role of clinical comorbidities, tumor related features and surgical factors to predict the RF outcome might provide more accurate indications for patient counseling to define a personalized strategy treatment.⁹

In the current study we investigated predictors of short-term and long-term RF evolution, and accounted for possible confounders using a national collaborative project which generated a prospectively compiled, internet based, comprehensive PN data set.

MATERIAL AND METHODS

The RECORd (Italian Registry of Conservative Renal Surgery) Project is a 4-year prospective, observational, multicenter study promoted by LUNA (Leading Urological No profit foundation Advanced research) of SIFU (Società Italiana di Urologia). Overall 769 consecutive patients underwent PN for a renal tumor at a total of 19 Italian urological institutions from January 2009 to December 2012.¹⁰ An online case report form was generated and centrally controlled to limit missing or wrong data inputs and send timely alerts in case of ignored followup visits.

Uncontrolled DMT2 was defined as patients with glycated hemoglobin (HbA1c) values between 7.5% and 11.0%. The surgical indication was defined as elective—localized unilateral RCC with a healthy contralateral kidney, relative—localized unilateral RCC with the coexistence of comorbidities such as diabetes, hypertension or lithiasis that could potentially affect kidney function in the future, and imperative—bilateral or multiple tumors, moderate to severe chronic kidney disease or neoplasm involving an anatomically or functionally solitary kidney.

Tumor anatomy was thoroughly described according to the location on the longitudinal and transverse planes, and the degree of exophyticity. Renal function was measured as serum creatinine and eGFR using the MDRD (Modification of Diet in Renal Disease) formula at baseline, day 3, and months 1, 6, 12 and 24 after surgery. Patients were treated with OPN, laparoscopic PN or RAPN as well as simple enucleation or standard PN according to surgeon and center preferences.

For the current study we extracted data on 708 patients who were alive, free of disease recurrence and with a minimum 2-year functional followup. Overall 42 patients (5.4%) were excluded from analysis because of recurrence at the time of data analysis, and 19 (2.5%) were excluded because they received surgical or medical therapy for progression.

The functional outcome was measured as an imperative or a relative reduction in eGFR and a decrease in eGFR greater than 25% from baseline. We chose the eGFR decrease greater than 25% from the baseline threshold according to the definition of progression to CKD in the NICE (National Institute for Health and Care Excellence) guidelines.¹¹ Based on results at the different time points the imperative and relative eGFR declines at post-operative day 3, and months 1 and 24 were adopted as study end points and defined as immediate, early and late RF impairment, respectively.

CVe was defined as new onset of myocardial infarction up to 3 weeks after surgery managed by medical treatment, coronary artery disease, unstable angina requiring hospitalization and medical treatment, transient ischemic attack and stroke, a heart failure event, coronary syndrome requiring percutaneous transluminal coronary angioplasty or peripheral artery disease requiring intervention.

Statistical Analysis

Parametric and nonparametric continuous variables are reported as appropriate. Logistic univariable and multivariable regression analyses were done identify predictors of functional renal impairment. A multivariable Cox proportional hazards regression model of CVe was fitted. Discrimination was evaluated by the ROC AUC and the Harrell concordance index as appropriate. Statistical significance was considered at $p < 0.05$ and all reported p values are 2-sided. Analyses were done with STATA®, version 14.1.

RESULTS

Table 1 summarizes the baseline features of [T1] the cohort. Median preoperative eGFR was 84.5 ml/minute/1.73 m². Preoperative eGFR was within the range of normality (CKD stage 1) in 39% of patients. A 12.9% rate of baseline CKD stage 3 or greater was observed. A clampless procedure was used in 37.6% of patients. Hilum clamping was done in the remaining 442 patients (62.4%) with a median WIT of 17 minutes (IQR 13–22).

Supplementary table 1 (<http://jurology.com/>) shows postoperative and followup outcomes. Median functional followup was 27 months (IQR 25.5–29.5).

Table 1. Preoperative characteristics of 708 patients treated with partial nephrectomy for renal tumors

No. male (%)	451	(63.7)
No. ECOG score 1 or greater (%)	231	(32.6)
Median age (IQR)	64.5	(53.0–71.5)
Median kg/m ² BMI (IQR)	26.0	(24.2–28.1)
No. indication (%):		
Elective	571	(80.6)
Relative	101	(14.3)
Absolute	36	(5.1)
No. tumor side (%):		
Rt	367	(51.8)
Lt	335	(47.3)
Bilat	6	(0.8)
No. multiple lesions (%)	33	(4.7)
No. tumor site (%):		
Polar superior	189	(26.7)
Mesorenal	302	(42.7)
Polar inferior	217	(30.6)
No. tumor growth pattern (%):		
50% or Greater exophytic	517	(73.0)
Less than 50% exophytic	172	(24.3)
Entirely endophytic	19	(2.7)
No. tumor localization (%):		
Perihilar	37	(5.2)
Anterior face	171	(24.2)
Posterior face	225	(31.8)
Medial margin	59	(8.3)
Lateral margin	216	(30.5)
Mean \pm SD clinical diameter (cm)	3.1 \pm 1.2	
No. clinical T (%):		
T1a	557	(78.7)
T1b	126	(17.8)
T2	25	(3.5)
No. chronic kidney disease stage (%):*		
1	275	(38.8)
2	341	(48.2)
3a	69	(9.7)
3b	22	(3.1)
5	1	(0.1)
Median mg/dl baseline creatinine (IQR)	0.9	(0.8–1.0)
Baseline ml/min/1.73 m ² eGFR (IQR)	84.5	(69.9–99.1)

* No stage 4 CKD.

At followup RF showed a trend toward an immediate reduction and further progressive recovery. Specifically the observed median decrease in eGFR from baseline was 11.4% immediately after surgery, 10.9% after 1 month (vs the eGFR change immediately after surgery $p < 0.001$) and 9.6% after 24 months ($p < 0.001$). Overall 25.3%, 21.6% and 14.8% of patients experienced eGFR impairment greater than 25% on postoperative day 3, and at months 1 and 24. Notably the median eGFR reduction and the eGFR impairment greater than 25% from baseline did not significantly change from determinations at months 1 and 6 ($p = 0.27$) or months 12 and 24 ($p = 0.41$).

Supplementary table 2 (<http://jurology.com/>) lists the results of univariable and multivariable logistic analyses to estimate the predictors of immediate, early and late significant (greater than 25%) loss of eGFR. Female gender and preoperative eGFR were independently associated with all 3 outcomes. Age was associated with immediate and late impairment. Uncontrolled DMT2 was associated only with late impairment. An imperative indication

for PN was an independent predictor of an immediate decrease in RF. Open and laparoscopic surgical approaches, and pedicle clamping were independent predictors of immediate and early RF impairment.

At a median followup of 86 months (IQR 70–102) 58 of 529 patients (11%) experienced postoperative CVes (supplementary table 3, <http://jurology.com/>). Table 2 lists the results of univariable and multivariable logistic analyses to estimate predictors of CVes. BMI and RF impairment greater than 25% at month 24 were independent predictors of postoperative CVes.

DISCUSSION

The results in the current study come from a large, prospectively compiled and contemporary data set of 708 patients, representing a real world scenario. The observed median reduction in eGFR from baseline was 11.4% immediately after surgery, and 10.9% and 9.6% at 1 and 24 months while 25.3%, 21.6% and 14.8% of patients, respectively, experienced eGFR impairment greater than 25%. Notably the median eGFR reduction and eGFR impairment greater than 25% from baseline did not significantly change between determinations at months 12 and 24. This suggests that ipsilateral recovery as well as contralateral compensatory action occur within the first 12 months postoperatively.

It was possible to confirm that the RF decline after PN is related to several factors that have different impacts according to followup time. Indeed, 2 modifiable surgical factors, including the open or laparoscopic surgical approach and pedicle clamping, were related to immediate and early RF impairment but they did not influence late recovery. Similarly an imperative indication for PN was associated only with immediate RF impairment. Conversely several unmodifiable patient features, such as gender, age and baseline eGFR, correlated not only with immediate and early RF decreases but also with further progressive deterioration of RF. Uncontrolled DMT2 predicted only late, greater than 25% RF impairment.

These results in part are consistent with those of previous studies and in part they disagree. Indeed, we confirmed that pedicle clamping is detrimental to early RF, as demonstrated in several comparisons between off and on clamp procedures in solitary kidney settings¹² and in normal contralateral kidney settings.¹³ The significantly early eGFR decrease observed in these cases suggests the onset of immediate acute cellular injury independent of WIT even when WIT is below the 25-minute cutoff. Indeed, in our series median WIT was 17 minutes (IQR 13–22) and only 21.2% of cases had WIT greater than 25 minutes. This might be the reason

Table 2. Univariable and multivariable Cox regression analyses of preoperative, surgical and functional characteristics associated with postoperative cardiovascular events in 529 patients treated with partial nephrectomy for renal tumors (AUC 0.832)

	Univariable		Multivariable	
	OR (CI 95%)	p Value	OR (CI 95%)	p Value
Female gender	1.62 (0.94–2.82)	0.09		
Age (continuous)	1.03 (1.00–1.05)	0.03	1.02 (0.99–1.05)	0.22
BMI (continuous)	1.09 (1.03–1.15)	0.004	1.08 (1.01–1.15)	0.03
ECOG score 1 or greater	2.45 (1.41–4.25)	0.002	1.29 (0.64–2.61)	0.48
Baseline Hb (continuous)	0.75 (0.62–0.91)	0.003	0.84 (0.68–1.06)	0.14
Baseline eGFR (continuous)	1.00 (0.99–1.02)	0.62	—	—
Clinical tumor diameter	1.04 (0.81–1.27)	0.59	—	—
Polar lesion site:			—	—
Superior	1.51 (0.76–3.01)	0.43		
Medial	0			
Inferior	1.39 (0.74–2.64)			
Growth pattern:		0.04		0.16
50% or Greater exophytic	0		0	
Less than 50% exophytic	2.50 (1.15–5.43)		2.19 (0.44–7.01)	0.34
100% Endophytic	3.40 (0.81–14.23)		2.28 (0.98–5.28)	0.06
Surgical indication:		0.32	—	—
Elective	0			
Relative	1.07 (0.76–2.00)			
Absolute	2.04 (0.89–5.27)			
Uncontrolled hypertension	1.34 (0.67–2.64)	0.41	—	—
Uncontrolled diabetes mellitus type 2	4.46 (1.98–10.03)	<0.0001	2.49 (0.93–6.69)	0.07
Surgical approach:		0.96	—	—
OPN	1.07 (0.51–2.27)			
Laparoscopic PN	1.01 (0.46–2.15)			
RAPN	0			
Surgical technique:			—	—
Enucleation	0	0.51		
Standard PN	1.21 (0.69–2.12)			
Pedicle clamping	1.23 (0.66–2.28)	0.52	—	—
Warm ischemia time greater than 25 mins	1.45 (0.63–2.36)	0.24	—	—
Hemostatic application	0.81 (0.18–3.54)	0.77	—	—
Renal bed renorrhaphy	0.98 (0.33–2.89)	0.98	—	—
Greater than 25% eGFR change:				
Postop day 3	1.81 (1.02–3.20)	0.04	0.72 (0.20–2.49)	0.60
Mo 1	5.85 (3.24–10.57)	<0.0001	2.18 (0.84–5.71)	0.11
Mo 24	8.04 (4.44–14.56)	<0.0001	4.63 (1.88–8.39)	0.001

why WIT considered as a continuous or a categorical variable was not found to be a significant predictor of RF impairment.

Surgical approach was also an independent determinant of immediate and early RF deterioration. Indeed, when compared to RAPN, OPN and laparoscopic PN were independent predictors of greater than 25% immediate impaired RF (OR 5.26, $p < 0.001$ and 2.82, $p = 0.004$) and early impaired RF (OR 4.78, $p < 0.0001$ and OR 2.86, $p = 0.01$, respectively). The advantage provided by laparoscopic and robotic minimally invasive PN has been reported due to a preconditioning effect of pneumoperitoneum, rendering the kidney more resistant to ischemic insult.¹⁴ However, the literature is not consistent with this hypothesis and more recent studies have shown that the surgical approach (laparoscopic vs open) was not independently related to nadir and ultimate eGFR.^{15,16}

In our series only the robotic approach was independently protective against immediate and early RF deterioration. Possibly the robotic platform combines the functional benefits of a minimally

invasive procedure with decreased WIT, leading to more precise tumor excision and kidney reconstruction compared to open and laparoscopic PN.^{17,18} At any rate the functional superiority of RAPN over OPN and laparoscopic PN is still debated. Several groups have reported only functional noninferiority of RAPN vs OPN^{19–21} but possible future superiority was suggested by a recent meta-analysis including 21 studies.²²

The effect of resection techniques on renal function has not been sufficiently addressed, although it may be reasonable that wider resection margins could reduce the quantity of preserved parenchyma and consequently renal function.⁶ However, in our study the resection technique (enucleation vs enucleoresection) did not impact the functional outcome.

Furthermore, none of these modifiable surgical factors were shown to be related to long-term RF. This was probably due to ipsilateral renal function recovery and compensatory hypertrophy of the nonaffected kidney.^{5,23}

Unmodifiable patient features such as gender, age and baseline eGFR correlated with immediate

and early RF declines. However, most of these factors as well as uncontrolled DMT2 were found to be independent predictors of late RF deterioration. Those features were already reported previously.^{21,24} There is a solid rationale to explain the impact of these features on renal function except for female gender. To our knowledge the latter feature represents a unique finding of the current study. It might have been caused only partly by an intrinsic limitation of the MDRD formula in older women with eGFR 60 ml/minute/1.73 m² or less.^{25,26} In brief, it can be stated that the worse the conditions at diagnosis, the higher the risk of a negative functional outcome. These considerations should be carefully considered to tailor patient counseling as well as indications for nephron sparing surgery, postoperative management and functional followup.

In our series a subanalysis of 529 patients with updated followup available revealed that CVE developed in 11% after PN, confirming that the risk of CVE after conservative renal surgery is not negligible. After accounting for several baseline characteristics, cardiovascular confounders and functional outcomes on multivariable analysis BMI and late RF impairment were independent predictors of CVE. Of note, immediate and early RF impairments were also significant on univariable analysis but the higher impact of impaired RF at month 24 decreased the significance of the 2 variables in the multivariable model.

In line with our results Capitanio et al reported a CVE rate of 5.5%, 9.9% and 20.2% 1, 5 and 10 years after PN in a wide cohort of Italian patients treated with PN and RN.³ Comorbidity, uncontrolled hypertension and conservative vs radical treatment were independent predictive factors of CVE in the full data set while in patients who underwent PN a higher CVE risk was reported in those in whom any grade of CKD developed. In an analysis of more than 1,000 patients treated with renal surgery (PN and RN) for cT1b renal masses Weight et al reported a 24% incidence of cardiovascular death.²⁷ The higher risk of CVE in North American patients compared to their European counterparts might explain the higher rates compared to our study (the CVE rate was not reported). Those investigators reported that the risk of cardiac death increased as postoperative RF decreased while preoperative eGFR was no longer significant on multivariate analysis.

These results support increasing evidence that it is crucial to prevent RF after renal surgery to avoid the development of CVE despite the clinical characteristics of patients at baseline.

The current study is not devoid of limitations due to the wide set of surgeons and hospitals. However, heterogeneity of surgical volume might increase the

reproducibility of results compared with the single center, single surgeon setting. The threshold of RF impairment was set at a greater than 25% eGFR reduction, although this was identified in other studies as a clinically meaningful threshold in patients with normal baseline RF. Postoperative proteinuria was not available. Nephrometry scores were lacking because they were published after our project began. However, many tumor features such as clinical diameter, growth pattern, polar site and localization, including hilar location and side, were recorded and analyzed.

Also, the volume of preserved parenchyma after PN has not been specifically evaluated by visual or radiological methods.^{6,28} Moreover, although standardized classification systems of resection strategies and resection techniques have been proposed in the recent literature,^{29,30} no objective classification of enucleation and standard partial nephrectomy could have been objectively classified in our study, given its retrospective nature and the lack of a classification system in the past.

In contrast, some distinctive features of our study enhanced the quality of the data collected, such as prospective recruitment, rigorous control of data input, at least 24 months of followup and the short (4-year) enrolment duration for uniform clinical assessments, indications, surgical techniques and laboratory examinations. Finally, the end point of a greater than 25% RF decrease from baseline captures the magnitude of the functional damage more accurately than CKD migration, for which borderline cases experience a stage shift only for a minimal reduction in eGFR.

CONCLUSIONS

In a large contemporary series of PN modifiable factors, including surgical approach and pedicle clamping, were independent predictors of immediate and early RF deterioration after PN. Conversely unmodifiable patient features, including gender, age and baseline eGFR, correlated with immediate and early RF declines as well as late deterioration of RF. Uncontrolled DMT2 independently correlated with late greater than 25% RF impairment only. BMI and late RF impairment were independent predictors of CVE development.

APPENDIX

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