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Predictive factors for the development of renal insufficiency following partial nephrectomy and subsequent renal function recovery

A multicenter retrospective study

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Abstract

Patients who undergo partial nephrectomy (PN) may exhibit renal function insufficiency, and a subset of these patients achieves renal function recovery. We evaluated the predictors of renal insufficiency and subsequent renal function recovery following PN. Data on 393 patients who underwent PN for solid renal tumors between March 2001 and November 2013, obtained from 6 institutions, were retrospectively reviewed. Renal insufficiency was defined as new onset of chronic kidney disease stage ≥3 postoperatively on the second of 2 consecutive tests. Renal function recovery was defined as an estimated glomerular filtration rate ≥60 ml/minute/1.73 m^2 following renal insufficiency. Tumor complexity was stratified according to the RENAL classification system. The median (interquartile range) age, tumor size, and follow-up period were 53 (45–63) years, 2.6 (1.9–3.8) cm, and 36 (12–48) months, respectively. Tumors were of low complexity in 258/393 (65.6%) of cases. Renal insufficiency developed in 54/393 (13.5%) patients, in which age ≥60 years and preoperative creatinine ≥1.1 mg/ml were independent predictors. Tumor complexity, clamp type, and operative method were not significant prognostic factors. Among patients with newly developed renal insufficiency, 18/54 (33.3%) patients exhibited renal function recovery within a median period of 18 months, of which preoperative creatinine <1.1 mg/ml was an independent predictor. Age ≥60 years and preoperative creatinine ≥1.1 mg/ml were risk factors for renal insufficiency following PN. Patients with renal insufficiency whose preoperative creatinine was <1.1 mg/ml were likely to have renal function recovery.

Abbreviations: CT = computed tomography, EBL = estimated blood loss, eGFR = estimated glomerular filtration rate, HR = hazard ratio, MRI = magnetic resonance imaging, PN = partial nephrectomy, PSM = positive surgical margin, RCC = renal cell carcinoma, WIT = warm ischemia time.

Keywords: carcinoma, complications, partial nephrectomy, renal cell, warm ischemia time

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All procedures involving human participants were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and subsequent amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

All the authors declare that there is no conflict of interest.

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1. Introduction

The National Comprehensive Cancer Network guidelines recommend partial nephrectomy (PN) as the treatment of choice for cT1 tumors.[1] PN was originally indicated if radical nephrectomy would render the patient functionally anephric, necessitating dialysis, such as for renal cell carcinoma (RCC) in a solitary kidney, RCC in 1 kidney with inadequate contralateral renal function, or bilateral synchronous RCC. There is accumulating evidence that the oncologic outcomes of PN are comparable to those of radical nephrectomy.[2,3] Moreover, PN allows preservation of renal function, decrease in overall mortality, and reduced risk of cardiovascular events.[4,5] Hence, over the past decade, PN has become the standard of care for most technically resectable renal tumors.[6] In Korea, the proportion of PN performed has rapidly increased from 2008 to 2014.[7]

As a surrogate for the success of the PN, the trifecta outcome was investigated, which represents no complications, negative surgical margins, and warm ischemia time (WIT) <25 minutes.[8] In addition to the trifecta outcome, long-term renal function was another parameter used to prove the success of PN as one of the pentafecta outcomes.[9] Several factors, including WIT, loss of parenchymal volume, and ischemic damage in preserved tissue during the operation, are known renal function risk factors after PN. These factors are closely related to various surgical factors such as clamping methods, surgical methods, and renorrhaphy. However, published data from a multicenter database of patients with an initial diagnosis of RCC after PN is scarce. Moreover, to the best of our knowledge, no study has reported predictors of renal function recovery following renal insufficiency in patients who underwent PN. The aims of this multicenter analysis were to predict renal insufficiency and to identify the prognostic factors of subsequent renal function recovery following PN.

2. Materials and methods

2.1. Study population and data collection

A total of 393 consecutive Korean patients with RCC treated with PN were selected from the multi-center, Severance Urological Oncology Group PN registry. Data on patients who underwent PN for RCC between March 2001 and November 2013, obtained from 6 institutions, were retrospectively reviewed. The present study's retrospective protocol was reviewed and approved by the Yonsei University Health System Ethics Committee, which waived the requirement for informed consent (2019-005-001). The patient records were anonymized and de-identified prior to analysis. Patient demographics, including age, sex, body mass index, and a history of hypertension or diabetes mellitus, were collected. Perioperative and postoperative outcomes were assessed, including American Society of Anesthesiologists score, tumor size, RENAL nephrometry score, intraoperative surgical complications, operative time, clamp type, ischemic time, estimated blood loss (EBL), and serum chemistry.

Preoperative radiological examination data (computed tomography [CT] or magnetic resonance imaging [MRI]) of the enrolled patients were interpreted by radiologists in the urology department at each participating hospital. The final pathology was determined using surgical specimens and reported by the uropathologists at each institution. Pathological data included pathological tumor size, TNM stage, Fuhrman grade, positive surgical margin (PSM), and histological subtype.

Tumor complexity was stratified according to the RENAL classification system[10]: low (RENAL nephrometry score $\leq$7) or high (RENAL nephrometry score $\geq$8). Postoperative complications ($\leq$30 days after surgery) were graded according to the modified Clavien-Dindo classification.[11] Trifecta achievement was defined as a WIT of <25 minutes, negative surgical margins, and no complications intraoperatively or postoperatively (Clavien-Dindo complication grade $\geq$3) as a surrogate of surgical quality. The estimated glomerular filtration rate (eGFR) was determined using the Modification of Diet in Renal Disease formula.[12] Renal insufficiency was defined as a new onset eGFR <60 ml/minute/1.73 m^2 (chronic kidney disease stage $\geq$3) postoperatively on the second of 2 consecutive tests at least 3 months apart. Renal function recovery was defined as eGFR $\geq$60 ml/minute/1.73 m^2 following renal insufficiency.

Patients without notable complications were followed up with serum chemistries every 3 months for 2 years. Thereafter, the decision of follow up protocols after surgical treatment was based on the surgeons' discretion. All patients received standard care according to contemporary guidelines for the duration of follow-up.

2.2. Study endpoints

The endpoint was the predictors associated with renal insufficiency and subsequent renal function recovery.

2.3. Statistical analysis

Categorical variables were evaluated by the Fisher exact test. Differences in variables with a continuous distribution across categories were assessed using the Mann–Whitney *U* test. Multivariate Cox regression analyses were performed on predictors of renal insufficiency and subsequent renal function recovery that had a *P* value <.05 in the univariate analyses. The signed-rank test for each group was used to compare median serum creatinine and eGFR at different time points. All reported *P* values are two-sided, and statistical significance was set at *P* < .05. Statistical analyses were performed using the Statistical Package for Social Sciences, version 23.0, for Windows (IBM Corp., Armonk, NY, USA).

3. Results

The baseline clinical and demographic characteristics of the patients are shown in Table 1. The median (interquartile range) age, tumor size, and follow-up period were 53 (45–63) years, 2.6 (1.9–3.8) cm, and 36 (12–48) months, respectively. Tumors of low complexity were found in 258/393 (65.6%) cases. Clavien-Dindo complication grade $\geq$3 occurred in 5.1% (20/393) of patients. The main reasons for Clavien-Dindo complication grade $\geq$3 were hemorrhage (8/20, 40%) followed by pseudoaneurysm (5/20, 25%). Radical nephrectomy conversion occurred in 2/20 (0.5%) cases. The median ischemic time was 25.0 (18.0–31.0) minutes, and there were no differences according to tumor complexity. The achievement rates of trifecta and pentafecta were 43.8% and 37.9%, respectively.

Patients with high complexity had a larger tumor size (*P* = .002) and higher Fuhrman grade ($\geq$3) (*P* = .011) than those with low complexity. Tumor complexity was significantly associated with complications (*P* = .005), ischemic time (*P* = .005), and PSM (*P* = .014), but not with postoperative renal insufficiency (*P* = .943). The achievement rate of trifecta for high and low complexities was 31.1% and 50.4%, respectively (*P* < .001), and the achievement rate of pentafecta was 28.1%, 43.0%, respectively (*P* = .004). There were no differences in operative time, type of pedicle clamp, EBL, proportion of renal insufficiency, or follow-up period between the groups according to renal complexity.

Table 2 shows the change in median eGFR over time according to clamping type, RENAL nephrometry score, and WIT. Decreased eGFR at 3 months postoperatively finally recovered to near preoperative levels at 2 years (*P* = .865). Although the eGFR level at 2 years recovered to the preoperative level regardless of clamping method, the patterns of the change in eGFR varied. The patients with WIT $\geq$25 minutes had no recovery of renal function at 2 years compared to preoperative levels.

Renal insufficiency developed in 54/393 (13.7%) patients, in which age $\geq$60 years (hazard ratio [HR], 3.04; confidence interval [CI], 1.681–5.512; *P* < .001) and preoperative creatinine $\geq$1.1 mg/ml (HR, 3.57; 95% CI, 2.050–6.202; *P* < .001) were independent predictors (Table 3).

Table 1

Baseline clinical and demographic characteristics.

Variables	Total	RENAL score ≤ 7	RENAL score ≥ 8	*P* value
	393	258 (65.6)	135 (34.4)	
Age (y)	53.0 (45.0-63.0)	53.5 (45.0–64.0)	53.0 (45.0–61.0)	.346
Sex				
Male	261 (66.4)	91 (35.3)	41 (30.4)	.330
Female	132 (33.6)	167 (64.7)	94 (69.6)	
BMI (kg/m^2)	24.3 (22.2–26.5)	24.5 (22.1–26.6)	24.0 (22.4–26.1)	.865
Comorbidity				
ASA ≥ 2	150 (38.2)	99 (38.4)	51 (37.8)	.916
Method				
Open	118 (30.0)	100 (38.8)	18 (13.3)	<.001
Laparoscopy	53 (13.5)	44 (17.1)	9 (6.7)	
Robot	222 (56.5)	114 (44.2)	108 (80.0)	
Tumor size (cm)	2.6 (1.9–3.8)	2.3 (1.6–3.0)	3.8 (2.7–5.0)	.002
Fuhrman grade				
≥ 3	95 (24.2)	52 (20.2)	95 (70.4)	.011
Preoperative Cr (mg/ml)	0.9 (0.73–1.02)	0.88 (0.70–1.00)	0.91 (0.74–1.04)	.239
Preoperative eGFR (ml/minute/1.73 m^2)	82.2 (68.0–104.7)	82.8 (67.7–104.1)	81.0 (68.1–105.7)	.596
Operative time (minute)	172 (130–219)	176 (135–220)	169 (126–212)	.398
Pedicle clamp				
Total	294 (74.8)	193 (74.8)	101 (74.8)	.373
Selective	63 (16.0)	36 (14.0)	27 (20.0)	
No	36 (9.2)	29 (11.2)	7 (5.2)	
Estimated blood loss (ml)	400 (200–600)	400 (200–600)	400 (200–625)	.226
Complications (Clavien-Dindo classification)				
G1	25 (6.4)	12 (4.7)	13 (9.6)	.005
G2	14 (3.6)	5 (1.9)	9 (6.7)	
G3	20 (5.1)	10 (3.9)	10 (7.4)	
Ischemic time (minute)	25.0 (18.0–31.0)	23.0 (17.0–30.0)	27.5 (22.8–32.3)	.005
Positive surgical margin	27 (6.9)	11 (4.3)	16 (11.9)	.014
Renal insufficiency	54 (13.7)	35 (13.6)	19 (14.1)	.943
Renal function recovery	18 (4.6)	11 (4.3)	7 (5.2)	.694
Trifecta achievement	172 (43.8)	130 (50.4)	42 (31.1)	<.001
Pentafecta achievement	149 (37.9)	111 (43.0)	38 (28.1)	.004
Follow-up period (months)	24.0 (6.0–36.0)	24.0 (6.0–36.0)	24.0 (6.0–48.0)	.916

Data are n (%) or median (interquartile range).

ASA = American Society of Anesthesiologists, BMI = body mass index, Cr = creatinine, eGFR = estimated glomerular filtration rate.

Among these patients, 18/54 (33.3%) patients exhibited renal function recovery within a median (interquartile range) period of 18 (12–36) months, of which preoperative creatinine <1.1 mg/ml was an independent predictor (HR, 4.38; 95% CI, 1.203–15.911; *P* = .025) (Table 4).

4. Discussion

The increasing use of abdominal imaging including ultrasonography, CT, and MRI is the main cause for the increasing detection rate of renal masses.[13] With the dramatically changing epidemiology of renal masses, PN has been considered the

Table 2

Change in median eGFR over time according to clamping type, RENAL nephrometry score, and WIT.

	Median (IQR) eGFR, ml/minute/1.73 m^2			*P* value for Wilcoxon signed-rank test		
	Preoperative	3 months	2 years	2 years vs preop	3 months vs preop	2 years vs 3 months
Overall	82.2 (68.0–104.7)	75.9 (64.4–91.6)	79.4 (66.3–94.4)	.865	.005	.026
Clamping type						
Total	81.6 (67.6–104.5)	75.2 (63.9–89.3)	78.8 (65.8–93.8)	.652	.003	.026
Selective	83.7 (68.0–100.1)	85.4 (70.2–109.4)	77.3 (61.6–85.9)	.394	.480	.754
No	87.5 (74.6–121.4)	77.3 (61.6–85.9)	76.8 (63.3–87.4)	.695	.073	.110
RENAL nephrometry score						
<7	82.8 (67.7–104.1)	77.9 (615.2–95.0)	80.8 (66.9–95.7)	.606	.046	.104
≥ 8	81.0 (68.1–105.7)	72.7 (64.1–86.8)	78.2 (64.6–89.0)	.390	.046	.122
WIT						
< 25 minutes	83.2 (68.9–105.4)	77.9 (66.2–93.2)	80.9 (70.0–97.1)	.050	.324	.020
≥ 25 minutes	81.6 (67.6–104.5)	74.4 (64.0–89.2)	76.5 (63.8–90.6)	.043	.005	.366

eGFR = estimated glomerular filtration rate, IQR = interquartile range, WIT = warm ischemic time.

Table 3

Multivariate analysis for predicting renal insufficiency after partial nephrectomy.

	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age ≥ 60 y	3.90	2.214–6.881	<.001	3.04	1.681–5.512	<.001
Male	1.60	0.859–2.990	.139			
BMI	1.02	0.952–1.095	.564			
Diabetes mellitus	1.54	0.479–4.934	.470			
ASA ≥ 2	1.89	1.093–3.253	.023	1.49	0.851–2.621	.162
Operative methods			.189			
Open	Reference					
Laparoscopy	0.56	0.058–5.341	.611			
Robot	2.33	0.671–8.119	.183			
Tumor size	0.93	0.776–1.111	.417			
Pedicle clamp	1.62	0.875–2.995	.125			
WIT > 25 minutes	1.25	0.731–2.137	.416			
Preoperative creatinine ≥ 1.1 mg/ml	3.88	2.264–6.635	<.001	3.57	2.050–6.202	<.001
RENAL nephrometry score (≥8)	1.08	0.618–1.889	.786			

ASA=American Society of Anesthesiologists, BMI=body mass index, CI=confidence interval, HR=hazard ratio, WIT=warm ischemic time.

paramount treatment option for patients with small renal masses. A satisfactory oncologic outcome is the cardinal goal of all surgical methods. Trifecta and pentafecta have been proposed as measurement tools for the outcomes of PN. Recently published data reported that trifecta outcomes ranged from 31% to 78%.[8,9,14,15] Because of the lack of a definition of trifecta for PN cases and variations in surgical approach and technique, PN studies using trifecta showed heterogeneous outcomes. We used complications (Clavien-Dindo complication grade ≥3), PSMs, and WIT ≥25 minsute to evaluate the trifecta achievement rate. Our achievement rate of trifecta was 43.8%, and this rate is at least partially similar to the results of previous studies.

Moreover, concerns regarding preservation of renal function emerged with the increasing demand for PN. Postoperative renal function after PN is affected by various factors, including decreasing WIT to reduce the ischemic injury, loss of normal parenchymal volume to prevent positive surgical margins, and ischemic damage in preserved tissue during the operation.[16,17]

Table 4

Predictors of renal function recovery in patients with renal insufficiency after partial nephrectomy.

	Univariate		
	HR	95% CI	*P*value
Age ≥ 60 y	0.48	0.147–1.567	.224
Male	0.74	0.203–2.717	.653
BMI	0.95	0.792–1.132	.552
Diabetes mellitus	0.94	0.079–11.143	.962
ASA ≥ 2	0.57	0.177–1.809	.337
Operative methods			
Open	Reference		
Laparoscopy	0.50	0.044–5.700	.577
Robot	3.50	0.817–14.986	.091
Tumor size	1.12	0.732–1.726	.593
Pedicle clamp	0.87	0.255–2.994	.830
WIT > 25 minutes	1.41	0.444–4.448	.562
Preoperative creatinine < 1.1 mg/ml	4.375	1.203–15.911	.025
RENAL nephrometry score (≥8)	1.27	0.393–4.117	.687

ASA=American Society of Anesthesiologists, BMI=body mass index, CI=confidence interval, HR=hazard ratio, WIT=warm ischemic time.

The optimal threshold of WIT to prevent renal function deterioration remains controversial. In the trifecta standard, WIT <25 minutes was used, but recent papers proposed the optimal threshold of WIT to be within 20 minutes.[18,19] Moreover, Thompson et al found that in patients with a solitary kidney, every minute of clamping has short- and long-term renal consequences.[20] In this study, when analyzing WIT at each minute from 20 to 30 minutes, no significant cutoff point was found. However, WIT ≥25 minutes was a factor associated with prolonged recovery or no recovery of the preoperative eGFR.

Postoperative renal function was related to loss of normal parenchymal volume and ischemic damage in preserved tissue.[21,22] Mir MC et al reported that renal function ultimately was primarily associated with parenchymal volume preservation, whereas ischemia played a role in the level of renal function present 4 to 12 months after PN.[22] However, our multicenter analysis based on long-term follow-up demonstrated that the type of ischemia was not related to renal function. The results of this study are expected to be interpreted as a result of compensatory growth in the contralateral kidney and a more refined assessment of the effect of ischemia.

The role of various factors influencing the recovery of renal function after PN have been investigated, including diabetes, hypertension, hypercholesterolemia, male sex, old age, smoking, BMI ≥30 kg/m^2, vascular disease, use of anti-thrombolytic medication, remnant renal volume, and surgical methods and type.[23] However, in our study, only the factor associated with preoperative renal function, creatinine <1.1 mg/ml, was found to affect renal function recovery.

The RENAL nephrometry score reflects the anatomic and surgical complexity. Several studies investigated the RENAL nephrometry score as a tool to predict factors associated with increased operative time, EBL, total renal volume loss, WIT, and complications.[24,25] In the present study, as expected, WIT, complication rate, and positive surgical margins statistically increased with increasing RENAL nephrometry score. However, no study has predicted long term-renal function using the RENAL nephrometry score. Recently, Husain et al reported that healthy renal volume loss or non-neoplastic parenchymal volume was associated with RENAL nephrometry score.[26] Simmons

MN reported that the RENAL nephrometry score was associated with changes in the percent of functional volume preservation and the perioperative functional decrease in an analysis of 237 patients who underwent PN from 2007 to 2010.[24] We found that the eGFR at 2 years after PN, regardless of complexity, was not inferior to the preoperative eGFR. To our knowledge, this is the first study to show that the RENAL nephrometry score is not a prognostic factor predicting renal insufficiency and renal function recovery.

This study has several limitations in addition to its retrospective design. Heterogeneity of intraoperative management existed. Patient selection, multiple surgical methods, and techniques influenced by the physician's preference could account for the heterogeneity in our results. We do not have data on the number of cases that underwent radical nephrectomy because PN was not recommended for small renal mass. In addition, measurement of the RENAL nephrometry score and pathologic results were not centrally investigated but were assessed by urologists and pathologists at each institution. Nevertheless, we believe that this effect may reflect real-world clinical practice and is inherent in any retrospective study. Finally, we evaluated the parameters to predict renal function recovery; however, previous studies have investigated renal functional compensation as a phenomenon of renal compensatory adaptation.[21,22] In the future, we plan to evaluate the contribution of ipsilateral atrophy or contralateral hypertrophy to renal functional recovery after partial nephrectomy.

5. Conclusion

Age ≥60 years and preoperative creatinine ≥1.1 mg/ml were risk factors for renal insufficiency following PN. Patients with renal insufficiency whose preoperative creatinine was <1.1 mg/ml were more likely to have renal function recovery.

Author contributions

Conceptualization: Kyo Chul Koo.
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