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Original Article

Renal Function after Nephrectomy Influences the Risk of Cardiovascular Events

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We retrospectively analyzed the factors related to postoperative cardiovascular (CV) events in patients undergoing partial nephrectomy (PN) or radical nephrectomy (RN) for clinical T1 renal cell carcinoma (RCC). We identified 570 patients who underwent PN or RN for T1 renal cell carcinoma between January 1998 and December 2009 at our institution and related hospitals. We determined the cumulative incidence rate of CV events and overall survival (OS) using Kaplan-Meier survival curves with a log-rank test, and we evaluated the risk for an increase in CV events and OS using Cox proportional hazard regression. Of the 570 patients, 171 underwent PN and 399 underwent RN. The type of surgery was not significantly related with CV events. The only factor that significantly increased the risk of CV events in both the univariate (HR 2.67, $p=0.006$) and multivariate analyses (HR 2.14, $p=0.044$) was a postoperative estimated glomerular filtration rate (eGFR) <45 ml/min/1.73 m^2. Postoperative eGFR was also a significant risk factor for OS in the univariate analysis (HR 2.38, $p=0.0104$), but not in the multivariate model. Postoperative renal function was a significant independent predictor of the incidence of subsequent CV events.

Key words: renal cell carcinoma, nephrectomy, partial nephrectomy, renal function

Chronic kidney disease (CKD) is known to increase the risk of cardiovascular (CV) events and the overall death rate [1-3]. Radical nephrectomy (RN) for renal cell carcinoma (RCC) has been shown to be associated with an increased risk of new-onset CKD compared to a partial nephrectomy (PN) [4]. Many researchers thus agree that PN is the preferred surgical option for RCCs, even in patients with a normal contralateral kidney [5-9]. The rationale for the wider use of PN is based on evidence that suggests a similar level of cancer control can be achieved with PN compared to RN, while preserving renal function with a PN [5-7, 10-12]. Although several studies investigated the

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impact of PN and postoperative renal function on CV events and overall survival (OS) [10-15] the question of whether preserving a patient's postoperative renal function lowers the risk of CV events remains unanswered. The objective of this study was to determine the factors related to postoperative CV events in patients undergoing a partial or radical nephrectomy for localized RCC.

Patients and Methods

Patients who underwent either an RN or a PN for newly diagnosed localized RCC at our institution and related hospitals between January 1998 and December 2009 were enrolled in this study. A total of 700 consecutive patients fulfilled the following criteria: (1) The cohort was restricted to a localized RCC; (2) the preoperative radiological examination did not find lymph node metastasis or distant metastasis; (3) postoperative adjuvant chemotherapy had not been performed. Seventy-two patients with clinical T2 RCC were excluded from the study because all but one of the patients who underwent a PN had clinical T1a or T1b RCCs. Fifty-eight patients were excluded from the analysis because they were on dialysis or had only one kidney. A total of 570 patients were eligible for this retrospective study. The surgical approach (open or laparoscopic approach) in each case was determined by considering the complexity of the renal mass and the preference of the surgeon.

The patients' demographics, clinical stage, perioperative and pathological data were obtained from our kidney cancer patient registry. CV-related diseases such as diabetes, hypertension, cardiovascular disease, and cerebrovascular disease were defined as the respective diagnosis identified in medical records. This study was approved by our institutional review board (IRB# 1607-012). The estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) study equation as: $186 \times sCr^{-1.154} \times age^{-0.203} \times (0.742$ if female), expressed as ml/min/1.73 m^2 [16]. The postoperative eGFR was calculated using the serum creatinine level measured 3 months after surgery.

The primary endpoints of the analysis were the onset of at least one new CV event after renal surgery and the cumulative CV incidence rate. The secondary endpoint of the analysis was OS. The CV events were defined as one of following: myocardial or cerebral infarction, ischemic stroke, transient ischemic attack, percutaneous coronary intervention, coronary artery bypass graft surgery, and hospitalization for the diagnosis of acute angina, congestive heart failure, coronary artery disease, peripheral vascular disease, or cerebral stroke as identified in medical records. The incidence of CV events and the OS were determined as the interval from the date of renal surgery to the occurrence of the event.

Unadjusted associations between the type of surgery (PN vs. RN) and patient characteristics were examined using chi-square statistics. The relationship between the type of surgery and each primary endpoint was evaluated in a time-to-event framework. Kaplan-Meier survival curves were constructed for cumulative CV incidence, and the differences in survival were compared using a log-rank test. We set eGFR < 45 mL/min/1.73 m^2 as the cut-off value for postoperative renal dysfunction. Multivariate Cox proportional hazards regression was used to assess the effect on the hazards at each endpoint, controlled for demographic and clinical characteristics.

We also examined the interactions between the type of surgery and patient characteristics, including preexisting comorbidities. All of the analyses were performed using the JMP ver. 9 statistical package (SAS Institute, Cary, NC, USA), with p-values < 0.05 considered significant.

Results

Patient characteristics and predictors of treatment. The study cohort included 570 patients who had undergone definitive surgery for clinical T1 RCC diagnosed between 1998 and 2009. Of these patients, 171 had undergone a PN and 399 had undergone an RN (Table 1). The RN patients were significantly older ($p = 0.0021$) and had significantly larger tumors ($p = 0.0270$). The median postoperative eGFR values were 50.6 vs. 68.8ml/min/1.73 m^2 for the RN and PN groups, respectively ($p < 0.0001$). The median follow-up duration was 57 months. PN preserved renal function better than RN, as seen by the median rate of change in eGFR of −12.4% in the PN group and −35.2% in the RN group.

A subgroup analysis of the patients with a preoperative eGFR ≥ 60 ml/min/1.73 m^2 showed that the proportions of patients with a postoperative eGFR ≥ 60 or 45-60 were 76.4% and 18.8% in the PN group, and 33.4% and 40.2% in the RN group, respectively.

Cardiovascular events. A total of 34 patients had at least one CV event after surgery, including 6 (3.5%) in the PN group and 28 (7.0%) in the RN group. The 3- and 5-year probabilities of cumulative CV event incidence were 1.2% and 3.1% in the PN group and 2.6% and 4.8% in the RN group, respectively (Fig. 1A), with no significant difference between the 2 groups. When the patients were stratified into 2 groups with a postop-

Table 1 Demographic and clinical characteristics of the patients

Feature	Total	PN	RN	*P*-value
No. of patients	570	171	399	
Median age at surgery (IQR)	65 (54–73)	61 (52–72)	66 (56–74)	0.0021
Median preop eGFR (IQR)	79.0 (63.5–92.7)	79.4 (64.1–93.7)	78.8 (62.8–91.2)	0.5120
Preop eGFR ≥60 (ml/min/1.73 m^2) (%)	470 (82.5)	144 (84.2)	326 (81.7)	0.4709
Median postop eGFR (ml/min/1.73 m^2) (IQR)	54.9 (43.6–70.5)	68.8 (54.8–83.7)	50.6 (41.6–62.1)	<0.0001
Median clinical tumor size (cm) (IQR)	3.3 (2.3–4.5)	2.2 (1.7–3.0)	4.0 (3.0–5.0)	0.027
Clinical stage:				<0.0001
cT1a	356 (62.5)	157 (91.8)	199 (49.9)	
cT1b	214 (37.5)	14 (8.2)	200 (50.1)	
No. (%):				0.0020
Female	178 (31.1)	38 (22.2)	140 (35.1)	
Male	392 (68.8)	133 (77.8)	259 (64.9)	
No. laparoscopic (%):	189 (33.2)	38 (22.2)	151 (37.8)	0.0003
No. malignant histological subtype (%):				0.1502
Clear cell carcinoma	489 (85.8)	141 (82.5)	348 (87.2)	
Non-clear cell carcinoma	81 (14.2)	30 (17.5)	51 (12.8)	
CV-related diseases (%):				
Diabetes	82 (14.4)	25 (14.6)	57 (14.3)	0.8972
Hypertension	187 (32.8)	63 (36.8)	124 (31.1)	0.2057
Cardiovascular disease	45 (7.9)	13 (7.6)	32 (8.0)	1.0000
Cerebrovascular disease	29 (5.1)	8 (4.7)	21 (5.3)	0.8385
Median follow-up duration (months) (IQR)	57 (37–84)	54 (35–80)	58 (38–86)	0.1729

IQR, Inter-quartile range; preop, preoperative; postop, postoperative.

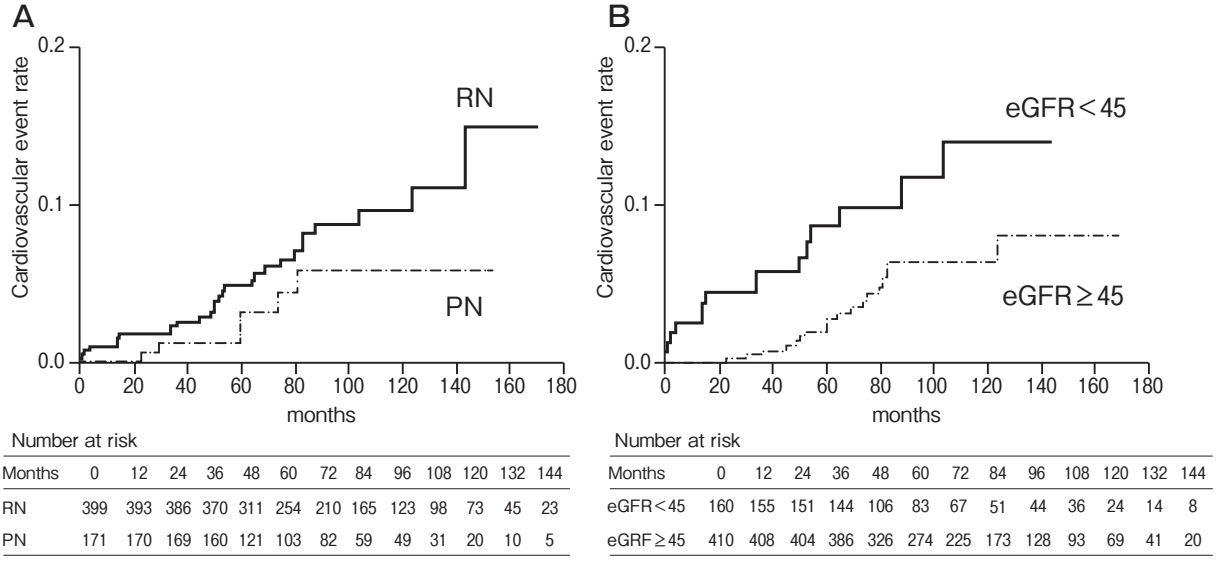


Fig. 1 **A**, Cumulative incidence of cardiovascular events stratified according to type of surgery ($p = 0.1806$). Blue: partial nephrectomy, red: radical nephrectomy; **B**, postoperative eGFR ≥45 vs. eGFR <45 ($p = 0.0030$). Solid line: <45, Dashed line: ≥45.

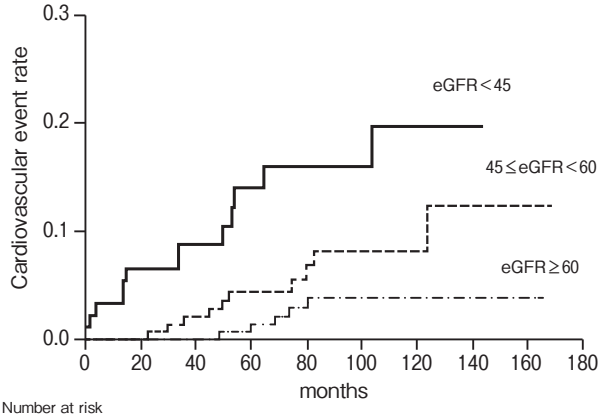
erative eGFR < 45 or ≥ 45 ml/min/1.73 m^2, the cumulative CV event incidence differed significantly ($p = 0.0030$) (Fig. 1B). The multivariate analysis showed that postoperative eGFR was the only factor that significantly increased the risk of CV events ($p = 0.0444$) (Table 2).

In the patients with a preoperative eGFR ≥ 60, the cumulative incidence rate of CV events showed a significant inverse correlation with postoperative eGFR ($p < 0.0001$) (Fig. 2).

Overall survival. Thirty-seven patients died during the study period, including 5 (2.9%) in the PN group and 32 (8.0%) in the RN group. Only three (0.5%) patients died of cardiovascular disease, whereas 11 (1.9%) patients died of RCC and 23 (4.0%) patients died of causes other than RCC or CV-related disease. The univariate analysis showed higher age, lower (45 > ml/min/1.73 m^2) preoperative and postoperative eGFR, type of surgery (RN), and T stage were factors that significantly increased the risk of death. The multivariate analysis showed age, preoperative eGFR, and higher T stage (T1b) were significant determinants of OS but not postoperative eGFR (Table 3).

Discussion

Our study demonstrated that the type of surgery was not a significant risk factor for postoperative CV events, in contrast to 2 recent large retrospective studies that



Number at risk

Months	0	12	24	36	48	60	72	84	96	108	120	132	144
< 45	102	102	100	91	67	50	42	31	26	21	15	10	5
45–60	175	175	172	168	141	120	99	75	53	42	34	21	15
≥ 60	246	245	239	227	193	164	139	108	83	57	42	27	10

Fig. 2 Cumulative incidence of cardiovascular events stratified according to postoperative eGFR ≥ 60, 45–60, and < 45 in patients with a preoperative eGFR ≥ 60 ($p < 0.0001$).

Table 2 Risk factors predicting cardiovascular events

	Univariate		Multivariate	
Parameters	HR (95% CI)	*p*	HR (95% CI)	*p*
Male vs. Female	1.82 (0.83–4.54)	0.1363		
Age Unit risk	1.03 (0.99–1.06)	0.0505	1.01 (0.98–1.04)	0.4500
CV-related diseases:				
Preoperative diabetes Yes vs. No	0.62 (0.15–1.74)	0.4015		
Preoperative hypertension Yes vs. No	1.70 (0.85–3.34)	0.1315		
Preoperative cardiovascular disease Yes vs. No	2.71 (1.08–5.90)	0.0346	2.20 (0.60–3.84)	0.4486
Preoperative cerebrovascular disease Yes vs. No	0.69 (0.04–3.22)	0.7030		
Preoperative eGFR < 45 vs. ≧ 45	1.71 (0.41–4.80)	0.4100		
Postoperative eGFR < 45 vs. ≧ 45	2.67 (1.34–5.24)	0.006	2.14 (1.02–4.47)	0.0444
Operation type: PN vs. RN	0.55 (0.21–1.25)	0.1611	0.71 (0.26–1.66)	0.4486
pT stage: pT1b vs. pT1a	1.46 (0.73–2.87)	0.2762		

preop, preoperative; postop, postoperative; PN, partial nephrectomy; RN, radical nephrectomy.

Table 3 Risk factors predicting overall survival (OS)

Parameters	Univariate		Multivariate	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Sex Male vs. female	0.69 (0.36–1.35)	0.2699		
Age Unit risk	1.06 (1.03–1.10)	0.0001	1.05 (1.01–1.09)	0.0100
CV-related diseases				
Preoperative diabetes Yes vs. No	0.86 (0.26–2.17)	0.7723		
Preoperative hypertension Yes vs. No	1.29 (0.65–2.49)	0.4552		
Preoperative cardiovascular disease Yes vs. No	0.63 (0.10–2.05)	0.4882		
Preoperative cerebrovascular disease Yes vs. No	2.79 (0.83–7.06)	0.0849	1.76 (0.50–4.81)	0.3433
Preoperative eGFR <45 vs. $\geqq 45$	4.88 (2.08–10.18)	0.0007	3.45 (1.33–8.34)	0.0120
Postoperative eGFR <45 vs. $\geqq 45$	2.38 (1.23–4.55)	0.0104	1.00 (0.45–2.14)	0.9981
Operation type PN vs. RN	0.40 (0.04–0.14)	0.0350	0.78 (0.25–2.00)	0.6245
pT stage pT1b vs. pT1a	2.94 (1.52–5.94)	0.0013	2.89 (1.41–6.23)	0.0033

preop, preoperative; postop, postoperative; PN, partial nephrectomy; RN, radical nephrectomy.

showed that PN decreased the risk of postoperative CV events compared to RN [15]. Those 2 earlier studies analyzed patients who underwent RN and PN for clinical T1 RCC, with 3,103 patients in the SEER-Medicare database and 1,331 patients in a multi-institutional collaboration study. The proportions of patients (PN vs. RN) who had experienced a CV event at 5 years were 9.9% vs. 15.6% and 18% vs. 25% in the 2 studies, respectively. On the other hand, a meta-analysis including these 2 studies showed no significant differences in the pooled hazard ratio between PN and RN for CV events (HR = 0.86, $p = 0.238$) [17].

An analysis of data from a large, integrated system of healthcare delivery reported a nonlinear relationship between CV events and eGFR, which rose sharply with an eGFR < 45 [1]. Takeshita *et al.*, who demonstrated that postoperative renal function after an RN influenced CV events, also showed that CV event-free survival differed significantly when the patients were stratified into 3 groups (eGFR ≥ 60, 45-60, and < 45 ($p < 0.001$) [13]. Nakagawa *et al.* analyzed the relationship between eGFR estimated using the MDRD equation and the severity of arterial stiffness using brachial-ankle pulse wave velocity in 647 adult Japanese patients, and they suggested that eGFR < 45 might be a crucial cut-off value for predicting arterial stiffness in CKD. [18] We therefore set eGFR < 45 as a cut-off in the present study, and our analyses revealed that the incidence of CV events became significantly different when the cohort was stratified into postoperative eGFR < 45 and ≥ 45 ($p = 0.003$). In addition, when the cohort was limited to those who had normal renal function (eGFR ≥ 60), the incidence of CV events increased as postoperative eGFR decreased. Our findings confirmed that postoperative renal function was significantly better with a PN than with a RN and that postoperative renal function correlated significantly with the incidence of CV events.

These findings raise the question as to why PN did not significantly reduce the incidence of CV events in our study cohort. The meta-analysis of CV events comparing PN and RN grouped according to publication year showed significant differences between the years 2008-2010 versus 2011-2015. The pooled hazard ratio (HR) published after 2011 indicated that PN significantly reduced the risk of CV events (HR = 0.76, $p = 0.035$) [17]. This finding may reflect the development of surgery using robotic systems. In our PN cohort, 22% of the patients had undergone a laparoscopic PN, and the remainder had an open PN. Shiroki *et al.* compared robotic-assisted partial nephrectomy

with other approaches and concluded that ischemia time appeared to be shorter in robotic-assisted PN than in laparoscopic PN, in which postoperative renal function may vary [3].

We did not observe a relationship between OS and postoperative eGFR or demonstrate CV-related survival in the present study, because only 3 patients in the study cohort died from cardiovascular disease.

Because CV events are critical, preventing postoperative renal insufficiency and maintaining cancer control should be considered in all patients presenting with clinical T1 RCC. Since 2016, robot-associated PN has been covered by public healthcare insurance in Japan, and its use is increasing rapidly. This technology may enable safe and effective operations and lead to more stable postoperative renal function [3]. It is important that efforts be made to minimize the iatrogenic renal insufficiency associated with renal surgery by minimizing ischemia time and by implementing surgical techniques such as early declamping and superselective artery clamping to maintain postoperative eGFR as much as possible.

Our study has several limitations. First, it was a nonrandomized, retrospective design. Second, inherent selection bias may exist when comparing patients with small renal tumors who underwent different surgical procedures. Third, we did not evaluate the widely used indices such as the Karnofsky Performance Status Index or Charlson Comorbidity Index. Fourth, we defined the presence of underlying CV-related diseases according to medical records, and did not evaluate the disease factors such as duration of suffering and medication in detail. Lastly, renal mass complexity including the RENAL nephrometry score must be evaluated in future studies because of the wider range of eGFR changes, especially in the PN group. The only way to overcome this latter limitation would be to prospectively randomize patients to either RN or PN; however, such a design would be considered unethical.

To date, PN appears to be technically feasible in many patients with clinical T1 RCC. Our study suggests that renal dysfunction after surgery may present an independent risk of CV events. It is therefore important to preserve renal function in patients with clinical T1 RCC under cancer control.

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