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Original Article

Partial versus Radical Nephrectomy for Small Renal Cancer: Comparative Propensity Score-Matching Analysis of Cardiovascular Event Risk

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Although partial nephrectomy (PN) is preferred over radical nephrectomy (RN) for preserving renal function in patients with cT1 renal cancer, its impact on cardiovascular events (CVe) remains controversial. This study aimed to compare PN and RN in regard to the occurrence of CVe, including cerebrovascular events and exacerbation of hypertension (HT). We retrospectively analyzed 418 consecutive patients who underwent PN or RN for cT1 renal cancer. Propensity score-matching analysis was used to adjust for imbalances between patients who underwent PN and RN, leaving 102 patients in each group. The 5-year probability of cumulative CVe incidence was 6% in the PN group and 12% in the RN group ($p = 0.03$), with a median follow-up of 73.5 months. The statistical significance was retained after propensity score matching for patients without preoperative proteinuria ($p = 0.03$). For all CVe including cerebrovascular events and exacerbation of HT analyzed, PN provided a lower probability of occurrence than RN in patients with small renal cancers.

Key words: chronic kidney disease, hypertension, nephrectomy, proteinuria

Partial nephrectomy (PN) is recommended as the standard treatment for small renal masses, particularly T1 lesions, when technically feasible. PN is considered superior to radical nephrectomy (RN) in terms of preserving renal function and reducing the risk of chronic kidney disease (CKD) progression [1-4], and CKD is a known risk factor for cardiovascular events (CVe) [5, 6]. PN has also been suggested to be more favorable than RN in preventing postoperative CVe [7-10], as supported by several recent cohort studies demonstrating a lower incidence of CVe with PN than with RN in patients with small renal cancers [1, 11]. However, the only randomized controlled trial conducted on this issue failed to confirm an overall survival (OS) advantage of PN over RN [12]. Additionally, the incidence of CVe has not been studied. Therefore, whether PN contributes to a decreased risk of CVe remains controversial [12].

Further complicating this issue, the definitions of CVe have varied among the relevant comparative studies of CVe after PN and RN [1, 2, 13-15]. In several retrospective studies in which only major cardiac events were defined as CVe, no difference was found between PN and RN in terms of the occurrence of postoperative CVe [14, 15]. Our group previously published a retrospective multicenter analysis on multiple outcomes, including CVe occurrence in a cohort of 570 patients who underwent PN or RN. We did not classify hypertension (HT) exacerbation as a CVe in that study and did not observe a significant difference in the occurrence of CVe between the two groups [13]. By contrast,

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another retrospective study in which HT and cerebrovascular events were included in CVe showed a significantly lower incidence of CVe in patients with PN than with RN [1]. Moreover, multiple confounding factors, including age and tumor size affected the occurrence of CVe in patient selection for renal surgery, leading to differences in the results.

In the present study, we aimed to determine the impact of PN and RN on the incidence of CVe after surgery for cT1 renal cancers by including cerebrovascular events and HT exacerbation in the definition of CVe. Additionally, we utilized a propensity score to adjust for imbalances that could affect the outcomes.

Materials and Methods

Study population. After approval from the institutional review board, data from patients who were diagnosed with clinical T1a or T1b renal cancer and who underwent PN or RN from 1997 to 2018 at our institution were retrospectively collected and assessed. The required sample size was estimated by referring to the CVe occurrence rate reported in a previous study [1]. We focused on the CVe occurrence rate at 7 years after the operation because our former study had a five-year median follow-up period of 5 years, and we sought to extend the term [13]. The definition of CVe used in our present analysis was similar to that used in the previous study [1], but with the addition of exacerbation of HT (including new-onset HT). That study reported that approximately 20% of RN patients experienced CVe compared to 10% of PN patients 7 years after the operation [1]. We calculated the required sample size based on the probabilities (by setting the α value to 0.05 and the β value to 0.8), and the result of the calculation was 219 samples for each group.

A total of 418 consecutive patients were enrolled. After excluding patients whose tumor sizes were unrecorded; patients who underwent renal replacement treatment (hemodialysis, peritoneal dialysis, or renal transplantation); patients with multifocal lesions or distant metastases, including lymph node metastasis, given the malignant potential regardless of the primary tumor size; and patients who received adjuvant therapies to avoid any influence of anticancer drugs on renal function in the early postoperative period, especially on vascular endothelial growth factor signaling pathway inhibitors [16], the remaining 204 patients, 102 each undergoing PN or RN, were included in the analysis. The choice between PN or RN for each patient was determined preoperatively during our surgical team's conference, considering patient characteristics such as patient age, tumor size, and tumor complexity.

Ethics. The study protocol was approved by the Institutional Ethics Review Board of Okayama University (approval number #2208-042). Informed consent was not obtained from all the patients included in this study. However, information about the upcoming study was disseminated online, and patients were allowed to opt out.

Clinical evaluation. We collected data on patient characteristics, including age, sex, preoperative renal function, presence of perioperative proteinuria, cardiovascular-related diseases (*e.g.*, diabetes, HT, cardiovascular disease, and cerebrovascular disease), clinical stage, tumor size, and postoperative pathological data from medical records. Preoperative renal function was evaluated based on the presence of proteinuria and estimated glomerular filtration rate (eGFR). Postoperative eGFR (expressed as ml/min/1.73 m^2) was measured three months after the surgeries and was calculated using the abbreviated Modification of Diet in Renal Disease Study equation as follows: 186×serum $Cr^{-1.154} \times age^{-0.203}$ ($\times 0.742$, if female). We also examined preoperative proteinuria, as it has recently been reported to be a prognostic factor for postoperative renal function in patients undergoing surgery for renal cancer [17]. Urine protein levels were determined from the single urine dipstick test results using random spot urine samples. Positive urinary protein levels were defined as proteinuria with a recorded result of (2+) or higher, whereas negative urinary protein levels were defined as proteinuria with a recorded result of (1+), (+/−), and (−).

Outcomes. The primary endpoint was new-onset CVe after renal surgery, as identified from medical records. CVe was defined as one of the following: exacerbation of HT (addition of antihypertensive drugs), arrhythmia, symptomatic aneurysm, myocardial infarction, acute angina, congestive heart failure, or cerebral stroke (including cerebral infarction and cerebral bleeding). The CVe-free survival period was calculated from the date of renal surgery to the date of the first CVe occurrence or censored follow-up. Further events were not considered. The secondary endpoint was OS, defined as the time from renal surgery to all-cause death.

Statistical analysis. Statistical analyses were conducted using EZR software version 1.55 (Saitama Medical Center, Jichi Medical University, Saitama, Japan). Statistical significance was set at $p < 0.05$. Continuous variables were analyzed using the Mann–Whitney *U* test, and categorical variables were analyzed using Fisher's exact test. Propensity scores were calculated using logistic regression models, considering the following variables: age at surgery, sex, tumor size, preoperative eGFR values, and history of cardiovascular diseases, HT, cerebrovascular diseases, and diabetes mellitus.

The two groups were matched using propensity scores to adjust for imbalances in patient characteristics. The propensity scores were matched 1 : 1 according to the nearest neighbor using the nearest neighbor algorithm without replacement. We used a caliper distance of 0.2 times the standard deviation of the logistic regression model of the propensity scores [18]. The data analysis was conducted using available data, and only the patients without missing data were included in each analysis. After matching, OS estimates were calculated using the Kaplan–Meier method. The log-rank test and Cox hazard regression model were used to calculate differences between the two groups. The cumulative incidence was calculated to assess the incidence of CVe in both groups. The Gray test and Fine–Gray hazard regression model were also employed to evaluate differences between PN and RN groups. All-cause deaths were considered competing events for total CVe, CVe except for HT, and HT only. For additional analyses, we subdivided CVe into HT exacerbation only and other CVe and compared the incidence probability of each event between the PN and RN groups. When HT alone was considered, the incidence of other CVe was disregarded. Similarly, HT was disregarded when analyzing the other CVe. Furthermore, we conducted a propensity score-matched analysis of patients with preoperative negative proteinuria. The propensity scores were calculated using the same variables to adjust for imbalance of the entire cohort in additional analysis.

Results

The study cohort comprised 418 patients, of whom 250 underwent PN and 168 underwent RN. The median age of the patients in the PN group was 61 years, while that in the RN group was 66 years. The median tumor sizes in the PN and RN groups were 25 and 40 mm, respectively. The median preoperative eGFR, presence of proteinuria, and number of patients with cardiovascular-related disease were similar between the two groups. The median postoperative eGFR value was 67.8 mL/min/1.73 m^2 in the PN group and 46.2 mL/min/1.73 m^2 in the RN group. Preoperative eGFR levels were not available for 1 patient, and post-operative eGFR levels were not available for 8 patients. The median follow-up periods were 73.5, 60, and 96 months for the entire cohort, the PN group, and the RN group, respectively. Approximately three-quarters of patients in both the PN and RN groups underwent laparoscopic or robot-assisted surgery (Table 1).

Overall, 55 patients (15 and 40 in the PN and RN groups, respectively) experienced at least one CVe postoperatively. The most common event was exacerbation of HT in 15 (27%) patients, followed by cerebral stroke in 12 (22%), arrhythmia in 8 (15%), congestive heart failure in 7 (13%), acute angina in 7 (13%), and other events in 6 (10%) patients. In the matching process, 1 patient was excluded because the preoperative eGFR level was unavailable. The distributions of propensity scores for the two groups in the entire and proteinuria-negative cohorts are shown in Fig. 1A and B. The graphs indicated a wide range of common support. In total, 102 patients were assigned to each group after matching. There was no difference in OS between the two groups (Fig. 2, $p = 0.41$), and the Cox hazard regression model gave a hazard ratio (HR) of 0.73 (95%CI: 0.35-1.54, $p = 0.41$).

The 5-year probability of cumulative CVe incidence was 6% in the PN group and 12% in the RN group (Fig. 3A, $p = 0.03$). Fine-Gray hazard regression revealed a sub-hazard ratio (SHR) of 0.4 (95%CI: 0.2-0.82, $p = 0.01$). When CVe were divided into the exacerbation of HT alone and other CVe, the 5-year probability of the cumulative event incidence was as follows: HT only, 5% in the PN group and 6% in the RN group (Fig. 3B, $p = 0.12$); CVe except HT, 6% in the PN group and 9% in the RN group (Fig. 3C, $p = 0.12$). The Fine-Gray hazard regression revealed an SHR of 0.4 (95%CI: 0.14-1.3, $p = 0.15$) for HT only and 0.5 (95%CI: 0.2-1.2, $p = 0.12$) for CVe except HT. Among patients without significant preoperative proteinuria, 76 were included in each group after the matching process. The 5-year probability of cumulative CVe incidence after surgery was 0% in the PN group and 14% in the RN group

Table 1 Pre- and post-propensity score-matched analysis of the demographic and clinical characteristics of patients

Feature	Pre-propensity score matching				Post-propensity score matching				
	Total	Radical nephrectomy (RN)	Partial nephrectomy (PN)	*P*-value	Total	Radical nephrectomy (RN)	Partial nephrectomy (PN)	*P*-value	SMD
No. of patients (%)	418	168 (40.1)	250 (59.9)		204	102 (50.0)	102 (50.0)		
Median age at surgery [IQR]	63 [54, 71]	66 [56, 74]	61 [53, 69]	< 0.001	62 [55, 71]	63 [54, 71]	64 [55, 71]	0.704	0.053
Median preoperative eGFR [IQR]	72.4 [63.5, 85.5]	71.1 [62.4, 89.8]	73.8 [65.5, 83.5]	0.878	75.7 [62.6, 87.3]	75.0 [60.1, 87.4]	76.5 [67.6, 87.2]	0.597	0.074
Median postoperative eGFR (ml/min/1.73 m^2) [IQR]	59.0 [45.7, 71.7]	46.2 [39.2, 55.5]	67.8 [56.0, 76.6]	< 0.001	57.7 [44.5, 72.2]	45.9 [37.9, 53.2]	69.6 [57.1, 79.2]	< 0.001	1.326
Median clinical tumor size (mm) [IQR]	30 [21, 42]	40 [30, 50]	25 [20, 35]	< 0.001	35 [25, 45]	35 [26, 45]	35 [25, 44]	0.965	0.006
Clinical stage (%)				< 0.001				1.0	0.022
cT1a	309 (73.9)	94 (56.0)	215 (86.0)		145 (71.1)	73 (71.6)	72 (70.6)		
cT1b	109 (26.1)	74 (44.0)	35 (14.0)		59 (28.9)	29 (28.4)	30 (29.4)		
Sex (%)				0.11				0.438	0.131
Female	134 (32.1)	62 (36.9)	72 (28.8)		58 (28.4)	32 (31.4)	26 (25.5)		
Male	284 (67.9)	106 (63.1)	178 (71.2)		146 (71.6)	70 (68.6)	76 (74.5)		
Side (%)				0.765				0.397	0.139
Left	201 (48.1)	82 (48.8)	119 (47.6)		89 (43.6)	41 (46.4)	48 (43.8)		
Right	217 (51.9)	86 (51.2)	131 (52.4)		115 (56.4)	61 (53.6)	54 (56.2)		
Procedure (%)				< 0.001				< 0.001	1.277
Open	101 (24.1)	41 (24.4)	60 (24.0)		61 (29.9)	24 (23.5)	37 (36.3)		
Laparoscopic	195 (46.8)	127 (75.6)	68 (27.2)		108 (52.9)	78 (76.5)	30 (29.4)		
Robot	116 (27.7)	0 (0.0)	116 (46.4)		33 (16.2)	0 (0.0)	33 (32.4)		
Hybrid	6 (1.4)	0 (0.0)	6 (2.4)		2 (1.0)	0 (0.0)	2 (2.0)		
Malignant histological subtype (%)				0.009				0.241	0.189
Clear cell carcinoma	337 (80.6)	146 (86.9)	191 (76.4)		158 (77.5)	83 (81.4)	75 (73.5)		
Other than above	81 (19.4)	22 (13.1)	59 (23.6)		46 (22.5)	19 (18.6)	27 (26.5)		
Cardiovascular-related diseases (%)									
Diabetes	57 (13.6)	17 (10.1)	40 (15.9)	0.11	20 (9.8)	10 (9.8)	10 (9.8)	1	< 0.001
Hypertension	159 (38.0)	69 (40.8)	90 (36.1)	0.357	71 (35.3)	33 (32.4)	38 (37.3)	0.577	0.103
Cardiovascular disease	17 (4.1)	8 (4.7)	9 (3.6)	0.617	9 (4.4)	5 (4.9)	4 (3.9)	1	0.048
Cerebrovascular disease	13 (3.1)	7 (4.1)	6 (2.4)	0.391	10 (4.9)	5 (4.9)	5 (4.9)	1	< 0.001
Median follow-up duration(months) [IQR]	73.5 [49.0, 119.8]	96 [69, 141]	60 [45, 96]	< 0.001	78.00 [52.75, 141.25]	109.8 [70.75, 150.00]	86.9 [41.00, 123.50]	0.007	0.382
Preoperative proteinuria (since 2006) (%)				0.807				1	0.014
Positive	19 (4.5)	6 (3.5)	13 (5.2)		8 (5.6)	4 (5.6)	4 (5.9)		
Negative	304 (72.7)	112 (66.7)	192 (76.8)		136 (94.4)	68 (94.4)	64 (94.1)		
Unknown	95 (27.8)	50 (29.8)	45 (18.0)						
Postoperative proteinuria (since 2006) (%)									
Positive	17 (4.1)	6 (3.6)	11 (4.4)	1	7 (4.6)	4 (5.2)	3 (3.9)	1	0.06
Negative	319 (76.3)	122 (86.8)	197 (78.8)		146 (95.4)	73 (94.8)	73 (96.1)		
Unknown	82 (19.6)	40 (9.6)	42 (16.8)						

eGFR, estimated glomerular filtration rate; IQR, interquartile range; SMD, standardized mean difference.

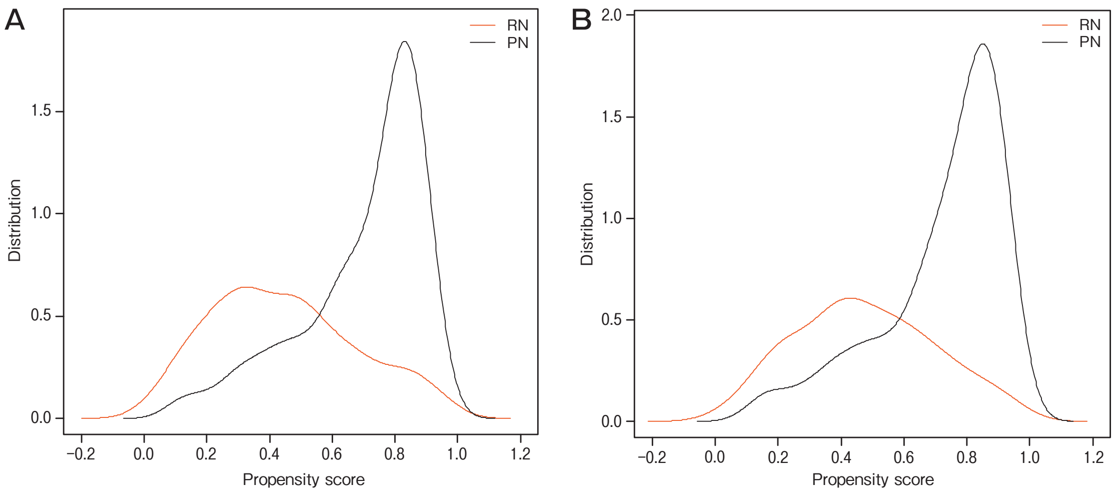


Fig. 1 (A) Density plot of the propensity score in the two groups for the entire cohort. (B) Density plot of the propensity scores in the two groups of patients with negative preoperative proteinuria.

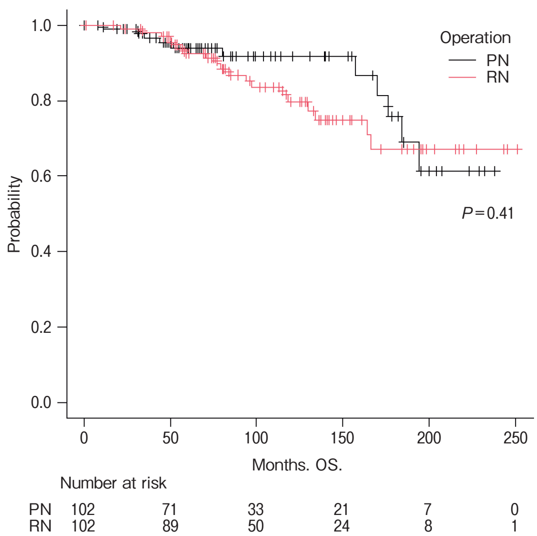


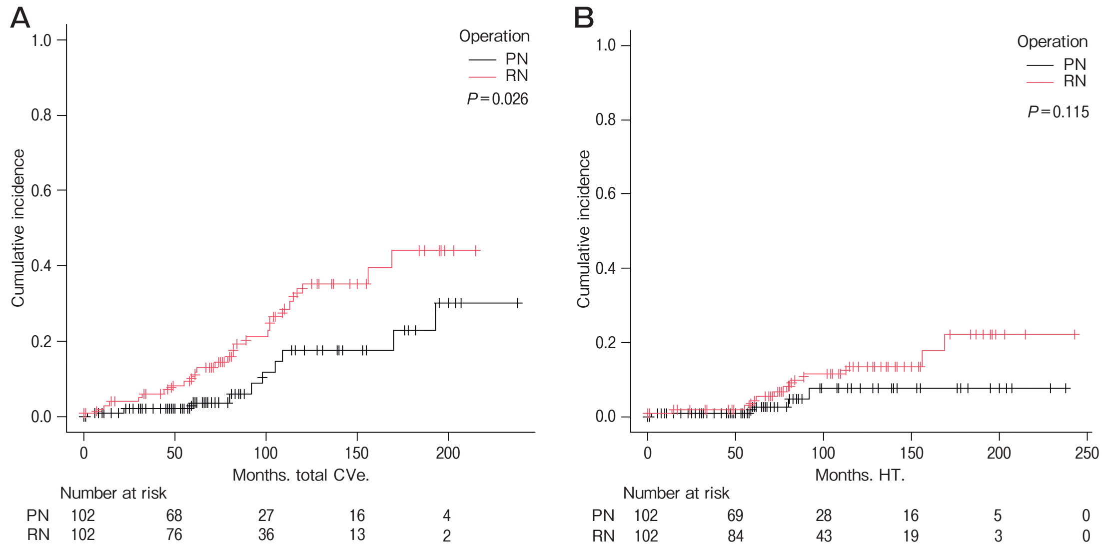
Fig. 2 Kaplan-Meier curve of overall survival time stratified by operation after propensity score matching.

(Fig. 4, $p=0.03$), and the Fine-Gray hazard regression model showed an SHR of 0.2 (95%CI: 0.05-1.0, $p=0.05$).

Discussion

Whether PN reduces the risk of CVe occurrence compared with RN remains a topic of debate. Several confounders can affect CVe post-surgery. Older patients with larger tumors typically undergo RN, and age is a well-known risk factor for CVe [19]. A larger tumor indicates a more advanced tumor; lower nephron volume loss and shorter ischemic time during PN for smaller tumors may affect postoperative renal function and cause differences in the CVe.

This study included HT exacerbation among the CVe since maintaining suitable blood pressure is essential for preserving renal function and preventing other vascular diseases [20]. One study investigated HT alone and other CVe as separate outcomes. Compared to PN, RN was associated with a significantly higher risk of developing postoperative HT, but there was no significant difference in the risk of developing other CVe [14]. This result aligns with our previous study, which did not observe a significant difference in the occurrence of CVe between the two groups [13]. Another potential reason for this discrepancy between the previous study and the present study might be the short observation periods (median 6.1 years and 4.8 years [13]). A meta-analysis of secondary cardiovascular outcomes showed no significant difference between PN and RN (HR, 0.84; 95% CI: 0.70-1.01; $p=0.063$) [2]. Of the six studies that included cardiovascular outcomes in this meta-analysis, the median follow-up range of the extracted studies was short (from 2.0 to 4.3 years); however, several studies have failed to demonstrate this difference despite long-term follow-up. Among the latest studies, the only one to mention the observation period featured a longer follow-up period (median, 6.9



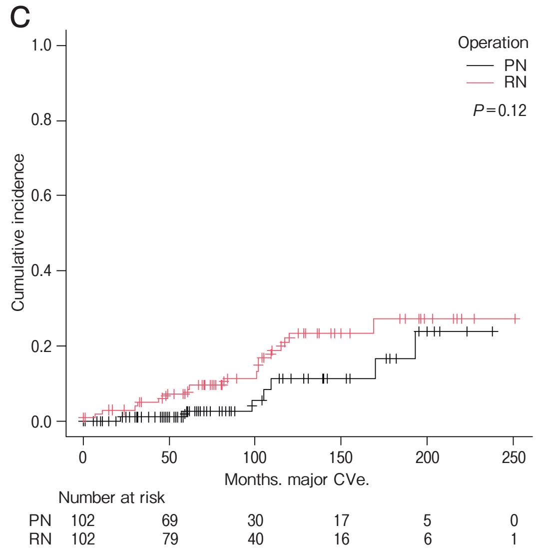


Fig. 3 (**A**) The cumulative incidence of CVe in the two groups after propensity score matching. (**B**) The cumulative incidence of HT only stratified by operation type after propensity score matching. (**C**) The cumulative incidence of CVe except HT stratified by operation type after propensity score matching.

years) than the current study. They, too, found no significant difference in the occurrence of CVe [15]. In this study, the median survival of the PN group was not reached, indicating that further follow-up is necessary to observe these events.

On the other hand, another reason was considered for the disparity between this study and the previous studies [13,15]. In the previous studies, approximately half of the patients in the PN and RN groups underwent open surgery. Other previous study demonstrated that open surgery is significantly associated with CVe onset [21]. Therefore, open surgical techniques could diminish the benefits of PN, given that minimally invasive operative procedures, such as laparoscopy and robot-assisted surgery, remarkably improve surgical outcomes [22,23]. Another retrospective study that used sequential years to define a contemporary cohort revealed that PN had a significant benefit over RN in an analysis of a more recent cohort, suggesting that advancements in surgical technology have improved the outcomes of PN [4]. Indeed, the majority of the cohort in our study underwent laparoscopic or robot-assisted surgery compared to only one-third of the patients in our previous study [13]. Based on these observations, we propose that these innovations and improvements in surgical techniques have led to favorable results for PN.

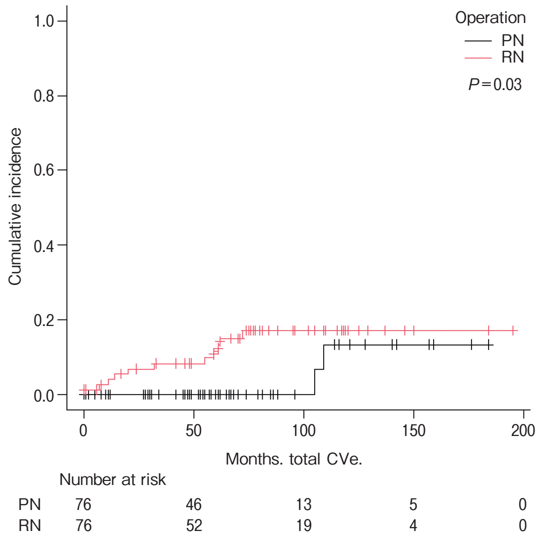


Fig. 4 The cumulative incidence of CVe stratified by operation type in the patients with preoperative proteinuria negative after propensity score matching.
PN, partial nephrectomy; RN, radical nephrectomy; CVe, cardiovascular event(s); HT, hypertension.

PN is desirable for patients with CKD and CKD-related diseases with impaired preoperative renal function. In contrast, RN is considered when PN is technically unfeasible in patients with normal renal function. A previous study with a median follow-up of 6.6 years showed that surgically induced CKD, unlike medical factor-associated CKD, is associated with a relatively lower risk of progressive renal function decline. Additionally, the same study found that preoperative medical factor-associated CKD had a more significant impact on OS [24]. In the present study, we evaluated preoperative proteinuria to examine the medical factors associated with CKD because proteinuria is a risk factor for renal failure [17], and renal failure can lead to CVe, including worsening HT [25]. According to a previous Japanese study, proteinuria ≥ (2+) on dipstick urinalysis is a significant risk factor for developing renal failure compared with proteinuria < (1+) [26]. Therefore, proteinuria (2+) was used as the cutoff value in this study. Despite this added statistical analysis, PN still significantly reduced the risk of CVe compared with RN in patients with preoperative proteinuria, suggesting that PN could be the preferable option even for patients with normal renal function.

This study had several limitations, and the results should be interpreted cautiously. First, it was a retrospective, single-institutional study with a relatively small sample size. Second, there was a significant difference in the median follow-up period between the two groups because the indications for nephron-sparing surgery have expanded with progress in surgical techniques. The treatment algorithm for HT in the guidelines has also changed over the years [27]. Therefore, disparities in the timing of surgery might impact the outcome. Third, several baseline characteristics that could affect the occurrence of CVe, such as sex and history of HT, were not adequately adjusted for, despite propensity score matching. Moreover, several confounders related to the surgery, such as the use of multiple surgical approaches (open or laparoscopic, including robot-assisted surgery), could not be excluded. Moreover, information regarding several surgical procedures was unavailable for most patients, particularly regarding the ischemic time during partial resection. Lower nephron volume loss and shorter ischemic time for smaller tumors may affect postoperative renal function and cause differences in the CVe. Data on several confounders of CVe, such as body mass index and smoking status, were absent. Moreover, not all asymptomatic underlying cardiovascular abnormalities have been adjusted. The results of preoperative cardiac functional examinations, such as cardiac ultrasound, were unavailable for most of the patients in this study. Therefore, adjusting for these factors may yield different results. Fourth, as urinalysis was not routinely performed before 2006, the data for some patients were unavailable. Moreover, the degree of proteinuria determined using the dipstick test does not represent the degree of albuminuria, a risk factor for CKD stage upgrading. Furthermore, tests that are more sensitive than dipstick tests, such as the urine albumin-to-creatinine ratio (ACR) assessment, were unavailable for all patients. Although the dipstick test is reportedly not inferior to ACR, especially in cases with negative or mild proteinuria [28], it might be insufficient to demonstrate a correlation. Lastly, biases resulting from disregarding the incidence of CVe other than HT, or HT alone, were not considered in the additional analyses that separated the types of CVe. This omission occurred because HT and the other CVe might interact with each other.

In conclusion, this study indicates that PN significantly decreases the incidence of CVe, including cerebrovascular events and exacerbation of HT, compared with RN. The significance was retained in patients who were negative for proteinuria on a preoperative dipstick test. The majority of the patients in this study underwent minimally invasive procedures such as laparoscopic or robot-assisted surgeries, reflecting the current trend of surgery for small renal cancers. Despite the aforementioned limitations, this study could provide valuable insights into the cardiovascular prognosis of patients undergoing renal cancer surgery.

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