

# Survival benefit of nephron-sparing surgery for patients with pT1b renal cell carcinoma: A population-based study

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**Abstract.** The use of partial nephrectomy (PN) to treat patients with large renal cell carcinoma (RCC) remains controversial, particularly among elderly patients. The present study compared the improvement in cancer-specific survival (CSS) in patients with pT1b RCC who underwent either PN or radical nephrectomy (RN) and investigated the effects of age and sex on CSS. A total of 20,343 patients were identified in the Surveillance, Epidemiology and End Results database. Kaplan-Meier curves and Cox regression analysis were used to compare the CSS of patients who received PN vs. those who received RN. In total, 5,375 (26.42%) and 14,968 (73.58%) patients with pT1b RCC received PN and RN, respectively. Kaplan-Meier and Cox regression analysis indicated that PN resulted in an improved CSS compared with RN ( $P<0.001$ ). In addition, PN was observed to be beneficial in male ( $P<0.001$ ) and female patients  $<75$  years of age. However, it was not beneficial for female patients of  $\geq 75$  years of age ( $P=0.197$ ). These preliminary results warrant further investigation in clinical trials.

## Introduction

Renal cell carcinoma (RCC) accounts for ~90% of all renal malignancies (1). For clinically localized RCC, nephrectomy remains the treatment method of choice (2). Numerous studies demonstrated that partial nephrectomy (PN) may provide a recurrence-free and long-term benefit to patients with tumors  $<4$  cm in diameter compared with radical nephrectomy (RN) (3-6). PN is thus becoming a main alternative to RN for treating T1a disease (RCC tumors  $<4$  cm) (7-9), and the European Association of Urology (EAU) guidelines

recommended PN as the standard surgical procedure for tumors measuring  $<4$  cm (10).

However, for tumors measuring  $>4$  cm, the EAU guidelines do not recommend PN (10). Achieving patient benefit without damaging renal function is the most important purpose of RCC treatment. Mir *et al* (11) observed that PN may provide oncological outcomes similar to those of RN in clinical stage T1b patients (RCC tumors  $\geq 4$  and  $<7$  cm). In addition, other studies reported equivalent outcomes regarding cancer control (individuals with no disease recurrence or progression) for PN and RN (tumors  $>4$  cm) (12,13). The majority of those previous studies mostly focus on PN function, regardless of age. Tan *et al* (14) observed similar long-term survival in patients with T1 stage RCC who were treated with PN and RN; however, subgroup analysis revealed improved survival in patients  $>75$  years of age treated with PN compared with RN.

The purpose of the present study was to investigate the benefit of PN vs. RN on the cancer-specific survival (CSS) in patients with T1b RCC, and to further assess the effects of age and sex on the benefit of PN vs. RN. For that purpose, data from a population database were analyzed.

## Materials and methods

**Data source.** Case details were retrieved from the Surveillance, Epidemiology, and End Results (SEER) database (<https://seer.cancer.gov>; code: kidney C64.9), which covers ~28% USA population. The SEER program contains cancer epidemiology information (15).

**Study population.** Patients who were histologically confirmed to have RCC (stage pT1b N0M0) between the years 2004 and 2015 were identified using SEER\*Stat software (version 8.3.2; <https://seer.cancer.gov/data-software/>). Variables including marital status, ethnicity, age at diagnosis, sex, surgical method, tumor size, laterality and months of follow-up were identified. TNM classification of RCC was based on the 6th edition of the American Joint Committee on Cancer staging system (16). In total, data from 20,554 patients with pT1b RCC who received PN or RN were collected. Patients of unknown ethnicity ( $n=121$ ), laterality ( $n=4$ ), tumor size ( $n=5$ ) or survival months ( $n=67$ ) were excluded. The remaining 20,343 patients were included in the present cohort study (Fig. 1). For data

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analysis, subgroups of patients were created as follows: Males <75 years; males  $\geq 75$  years; females <75 years; and females  $\geq 75$  years.

**Statistical analysis.** Frequencies and proportions were used to describe categorical variables. Means, medians and ranges were reported for continuous variables. The  $\chi^2$  test was used to assess statistical significance in proportion differences, while the t-test was used to evaluate statistical significances in the means (Table I). The effect of surgery (PN vs. RN) on the CSS was evaluated by Kaplan-Meier survival curves with log-rank tests. Differences in CSS were assessed by multivariate Cox proportional hazards regression analyses.  $P < 0.05$  was considered to indicate a statistically significant difference. Statistical analyses were performed using the statistical package MASS for R (version 3.4.1; <https://www.r-project.org/>) or Empower software version 1.1 ([www.empowerstats.com](http://www.empowerstats.com)).

## Results

In total, 5,375 (26.42%) and 14,968 (73.58%) patients with pT1b RCC received PN and RN, respectively. The baseline characteristics of the patients are presented in Table I. Of all patients, 45.73% were diagnosed between 2004 and 2008 (mean follow-up time, 91 months), while 54.27% were diagnosed between 2009 and 2015 (mean follow-up time, 35 months). The mean follow-up time was 92 months (range, 0-143 months) for PN and 90 months (range, 0-143 months) for RN. The mean overall age was 61.4 years [standard deviation (SD), 12.5 years], while the mean age for male patients was 61.2 years (SD, 12.1 years) and 61.7 years (SD, 13.0 years) for female patients.

Regardless of their age or sex, there was an improvement in CSS in all patients treated with PN ( $P < 0.001$ ; Fig. 2). There was an improvement in CSS in males ( $P < 0.001$ ) and females ( $P < 0.001$ ) regardless of their age. Multivariable Cox regression analyses revealed that PN was an independent predictor factor of CSS [hazard ratio (HR), 1.35; 95% confidence interval (CI), 1.13-1.62;  $P = 0.001$ ]. In addition, multivariate Cox regression analyses revealed that age at diagnosis, marital status, tumor size and grade were associated with outcomes (Table II).

Considering the age of the patients, male patients <75 and  $\geq 75$  years of age exhibited an improvement in CSS following PN ( $P = 0.017$ ; Fig. 3). Among females, only patients <75 years exhibited a notable CSS improvement ( $P = 0.002$ ) following PN. In patients treated by PN  $\geq 75$  years of age, no CSS improvement was observed ( $P = 0.197$ ; Fig. 4). Male and female patients  $\geq 75$  years of age exhibited the same prognostic data for RN and PN, regardless of their sex (Fig. 5). All male and female patients <75 years exhibited improved CSS following PN. Female patients <75 years exhibited improved CSS following PN ( $P = 0.029$ ) compared with male patients <75 years. There were no statistically significant differences for RN ( $P = 0.066$ ; Fig. 6).

The contradistinction of the follow-up of patients treated with PN (group 1, 2004-2008 and group 2, 2009-2015) is presented in Fig. 7 ( $P = 0.091$ ). The comparison of CSS following PN and RN during different periods of time is presented in Figs. 8 and 9 (Fig. 8, 2004-2008;  $P = 0.002$ ; and Fig. 9, 2009-2015;  $P < 0.001$ ).

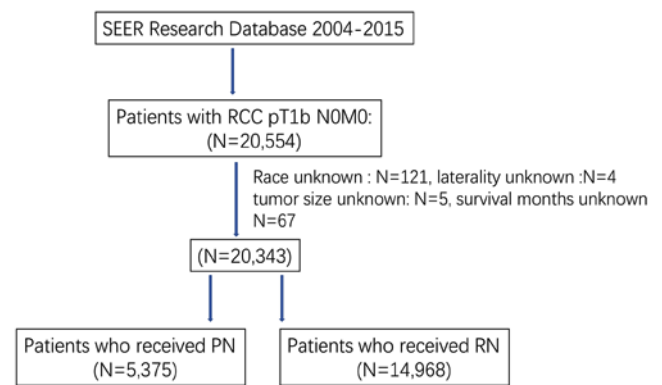


Figure 1. Consort flow diagram of patient selection in SEER. SEER, Surveillance, Epidemiology, and End Results; RCC, renal cell carcinoma; RN, radical nephrectomy; PN, partial nephrectomy.

## Discussion

The present study conducted a population-based analysis with 20,343 cases to compare the benefits of PN vs. RN in the treatment of pT1b RCC. The results obtained may clarify the benefit of PN and aid evidence-based surgical decision-making. Regardless of age and sex, a notable improvement in survival was observed for all patients treated with PN, compared with those treated with RN (HR, 1.35;  $P = 0.001$ ).

In terms of the improvement in CSS observed following PN in patients with T1 clinical stage RCC across all age groups, the results obtained in the current study are in accordance with the literature (17-19). Tan *et al* (14) reported improved survival only in patients with T1a RCC treated with PN who were <75 years of age. Previously, PN was considered to be associated with an increased probability of complications (20). Thus, elderly patients with multiple comorbidities were deemed to be more likely to suffer serious complications. However, according to a study by Roos *et al* (21), PN may be performed with acceptable complications on selected  $\geq 65$ -year-old patients with a single, small, unilateral, localized RCC. Similar studies revealed that selected  $\geq 80$ -year-old patients with RCC may benefit from PN (22-24). However, the aforementioned studies did not investigate the differences in the benefits of PN between age groups according to sex. In the current study, in the male group, patients <75 and  $\geq 75$  years of age experienced an improved CSS ( $P = 0.017$ ) following PN compared with RN. Notably, in the female group, only patients <75 years of age exhibited a marked CSS improvement ( $P = 0.002$ ) following PN compared with RN, which may be due to bias introduced by the small sample number. Dulabon *et al* (25) revealed that female patients had lower probability of undergoing PN compared with males, and that female patients, particularly the elderly, may prefer being subjected to active surveillance for renal disease rather than to surgical extirpation. In a previous study, PN decreased chronic kidney disease as well as nononcologic morbidity and mortality compared with RN, and the complication rate did not differ between the young and old patients (26).

To exclude bias introduced by the implementation of new technologies, including laparoscopic robot-assisted procedures, compared with open surgery (22,27,28), different time periods

Table I. Baseline characteristics and pathological characteristics of patients.

Characteristics	Partial nephrectomy	Radical nephrectomy	P-value
n	5,375 (26.4%)	14,968 (73.6%)	
Tumor size, (mm)	50.9±7.6	54.5±8.5	<0.001
Marital status, n (%)			0.211
Single/widowed/divorced/unmarried	1,859 (34.6%)	5,319 (35.5%)	
Married	3,516 (65.4%)	9,649 (64.5%)	
Age at diagnosis (years), n (%)			<0.001
≥75	4,713 (87.7%)	12,446 (83.2%)	
<75	662 (12.3%)	2,522 (16.8%)	
Period diagnosed, n (%)			<0.001
2004-2008	1,545 (28.7%)	7,758 (51.8%)	
2009-2015	3,830 (71.3%)	7,210 (48.2%)	
Sex, n (%)			<0.001
Male	3,600 (67.0%)	9,158 (61.2%)	
Female	1,775 (33.0%)	5,810 (38.8%)	
Ethnicity, n (%)			0.001
Caucasian	4,327 (80.5%)	12,337 (82.4%)	
African-American	722 (13.4%)	1,726 (11.5%)	
Other (American Indian/AK Native, Asian)	326 (6.1%)	905 (6.1%)	
Histology type, n (%)			<0.001
Non-clear cell RCC	2,457 (45.7%)	5,562 (37.2%)	
Clear cell RCC	2,918 (54.3%)	9,406 (62.8%)	
Grade, n (%)			<0.001
I+II	3,034 (56.4%)	8,939 (59.7%)	
III+IV	1,561 (29.1%)	4,264 (28.5%)	
Unknown	780 (14.5%)	1,765 (11.8%)	
Laterality, n (%)			0.170
Left	2,612 (48.6%)	7,437 (49.7%)	
Right	2,763 (51.4%)	7,531 (50.3%)	

Statistical significance was determined by  $\chi^2$  tests, with the exception of a t-test being used to determine statistical significance for tumor size.

Table II. Multivariable cox regression model in the cohort of patients with renal cell carcinoma.

Variables	Hazard ratio (95% confidence interval)	P-value
Surgery type	1.35 (1.13-1.62)	0.0010
Marital status	0.87 (0.76-0.99)	0.0370
Age at diagnosis	2.34 (2.03-2.69)	<0.0001
Period diagnosed	0.87 (0.75-1.02)	0.0958
Sex	0.88 (0.77-1.01)	0.0698
Ethnicity		
Caucasian	Reference	
African-American	1.01 (0.83-1.24)	0.9126
Other (American Indian/AK Native, Asian)	1.09 (0.84-1.41)	0.5207
Histology type	0.98 (0.86-1.11)	0.7168
Grade		
I+II	Reference	
III+IV	1.97 (1.72-2.24)	<0.0001
Unknown	1.09 (0.88-1.35)	0.4355
Laterality	1.05 (0.92-1.18)	0.4814
Tumor size	1.03 (1.02-1.04)	<0.0001

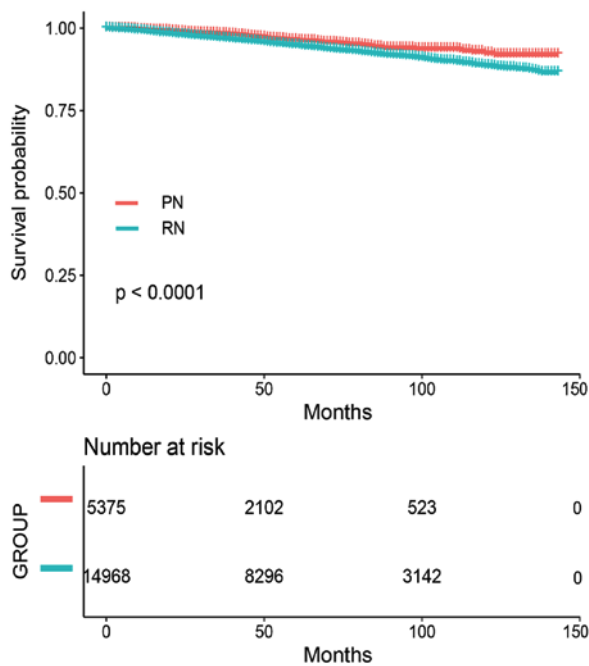


Figure 2. Cancer-specific survival of all patients with pT1b renal cell carcinoma following RN and PN. Regardless of their age or sex, there was an improvement in CSS in all patients treated with PN. RN, radical nephrectomy; PN, partial nephrectomy.

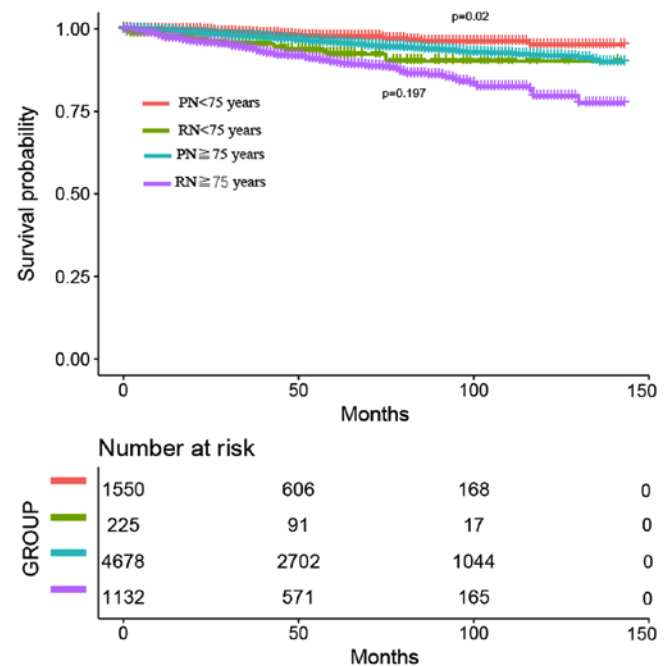


Figure 4. Cancer-specific survival of female patients <75 and ≥75 years. Patients of <75 years of age exhibited a notable CSS improvement upon PN. RN, radical nephrectomy; PN, partial nephrectomy.

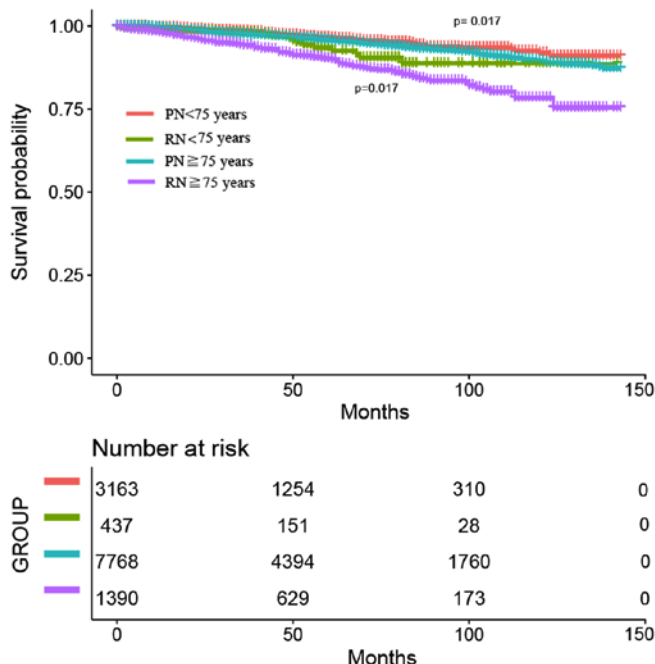


Figure 3. Cancer-specific survival of male patients <75 and ≥75 years. Both male patients of <75 and ≥75 years of age exhibited a CSS improvement. The P-value shown applies to the following comparisons: Male patients <75 treated by PN vs. treated by RN; male patients ≥75 treated by PN vs. treated by RN. RN, radical nephrectomy; PN, partial nephrectomy.

were assessed for the PN group in the present study. Notable differences in CSS following PN were not observed between the groups treated during the periods 2004-2008 and 2009-2015 ( $P=0.091$ ). According to these results, the implementation of new technologies had no effect on CSS following PN.

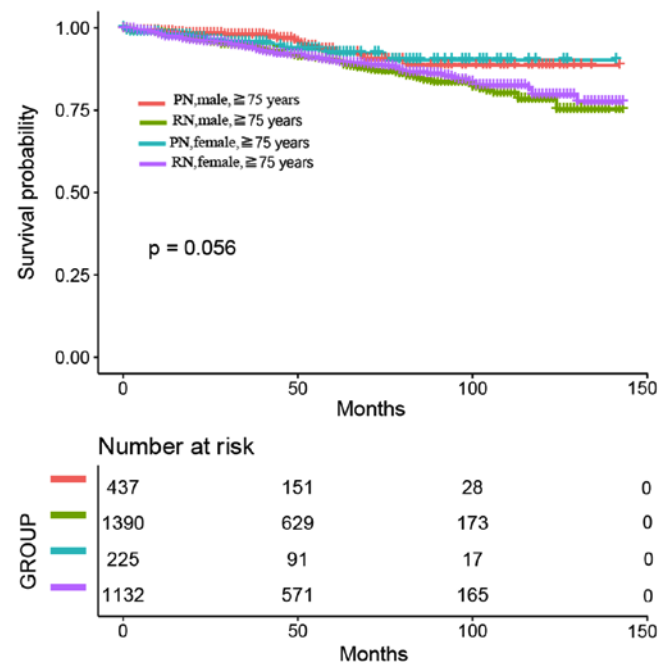


Figure 5. Cancer-specific survival of male and female patients ≥75 years. Male and female patients of ≥75 years of age exhibited the same prognostic data for RN and PN. RN, radical nephrectomy; PN, partial nephrectomy.

A statistically significant improvement in CSS following PN was observed in patients treated during 2004-2008 who were followed up for a long period (mean follow-up time, 91 months;  $P=0.003$ ). This was also observed in patients treated during the 2009-2015 period (mean follow-up time, 35 months;  $P<0.001$ ). Thus, it appears that CSS improvement following PN may not be associated with follow-up time.

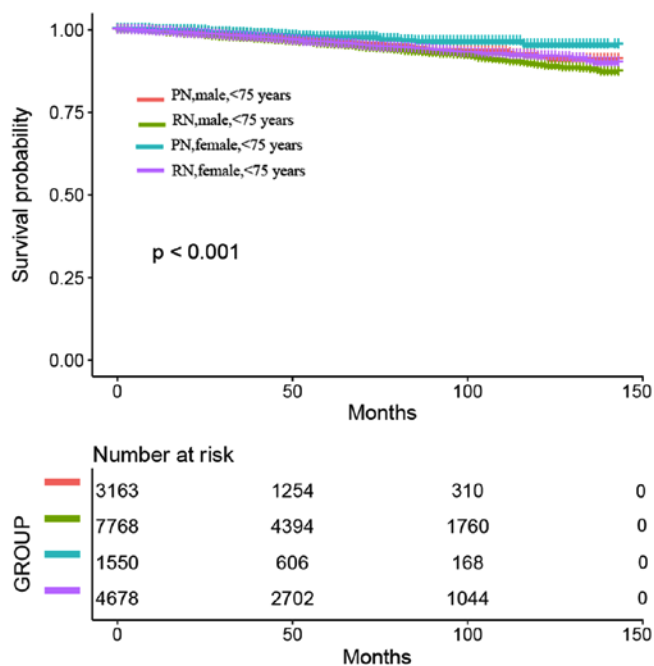


Figure 6. Cancer-specific survival of male and female patients <75 years. There were no statistically significant differences for RN. The P-value shown is the value obtained by comparing male patients <75 with the remaining groups. RN, radical nephrectomy; PN, partial nephrectomy.

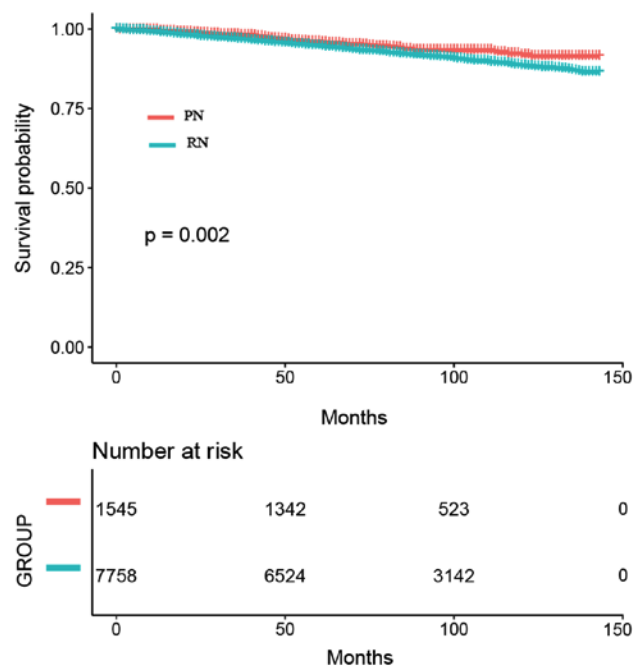


Figure 8. Cancer-specific survival of all patients with pT1b renal cell carcinoma following radical and partial nephrectomy during 2004-2008. A statistically significant CSS improvement upon PN was observed in patients treated during 2009-2015 period. PN, partial nephrectomy.

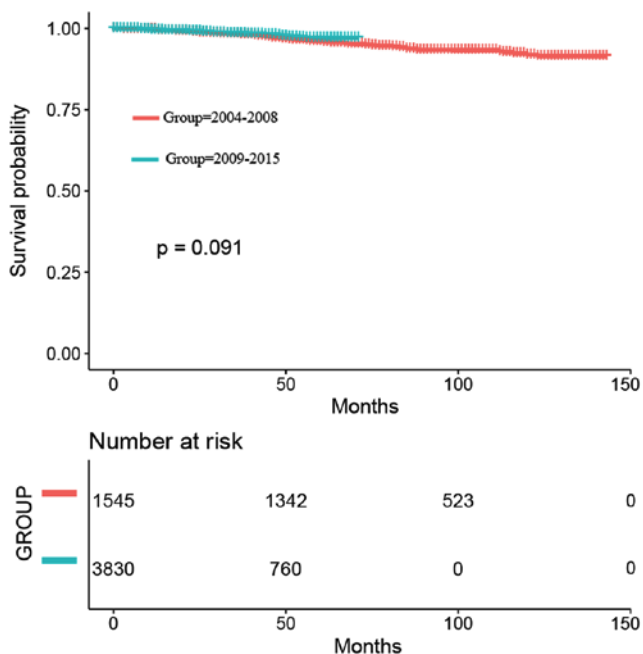


Figure 7. Cancer-specific survival of all patients with pT1b renal cell carcinoma following partial nephrectomy between 2004-2008 and 2009-2015. Notable differences in CSS upon PN were not observed between the groups treated during the periods 2004-2008 and 2009-2015. PN, partial nephrectomy.

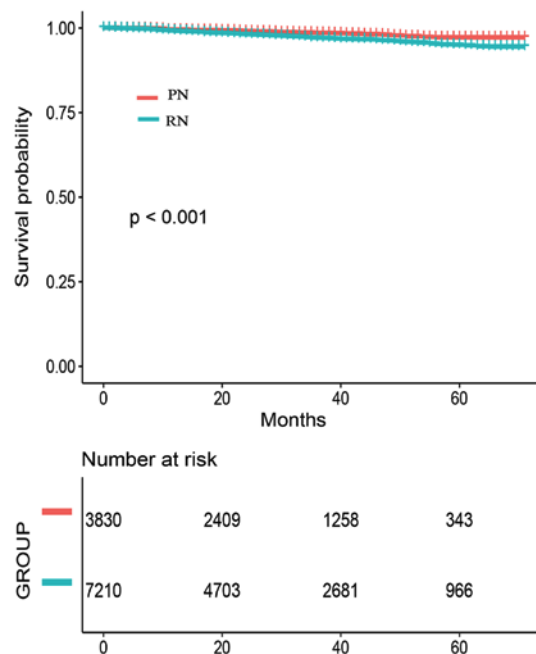


Figure 9. Cancer-specific survival of all patients with pT1b renal cell carcinoma following both radical and partial nephrectomy during 2009-2015. A statistically significant CSS improvement upon PN was observed in patients treated during 2009-2015 period. PN, partial nephrectomy.

Tobert *et al* (29) reported that loss of kidney function caused by surgery may have less effect on survival than chronic kidney disease (CKD). Thus, the protective role of PN against long-term complications such as cardiovascular disease in the elderly may be overestimated (29,30). However, Huang *et al* (31) reported that patients who received PN had lower rates of damaging glomerular filtration rate and CKD

than those receiving RN. However, other criteria, including tumor features, patients' wishes and social support, remain important when deciding to perform PN or RN surgery in elderly patients (21).

The present study had several limitations. The analyses were based on an observational study design, and this result obtained are limited by retrospective nature of the study.

Moreover, the impact of competing risk bias on PN was not investigated (32). The SEER database does not contain information on preoperative renal function, which affects the selection of patients receiving partial resection. Since poor renal function is associated with increased risk of severe cardiovascular disease (33), if a large proportion of patients with poor preoperative renal function is included in the PN group, this may undervalue the role of PN. Furthermore, it is difficult to select appropriate patients to receive partial resection due to the absence of knowledge on the exact tumor location (34,35).

Altogether, the results obtained in the present study, which was conducted on a large cohort, indicated that PN is beneficial for patients with pT1b RCC compared with RN. Future studies are required to clarify whether the patient age should be taken into account when planning to perform PN in patients with T1b RCC. According to the present study, female patients  $\geq 75$  years of age appear to have limited benefit from PN. These results should be corroborated in clinical trials.

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### Availability of data and materials

The datasets analyzed during the present study were downloaded from the Surveillance, Epidemiology, and End Results (SEER) database (<https://seer.cancer.gov>; code: kidney C64.9).

### Authors' contributions

PaZ and PeZ analyzed the data and confirmed the results' authenticity. XDL wrote the manuscript. XMH produced the tables and figures, and together with XDL, interpreted the results obtained. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

Not applicable.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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