

# Efficacy of Partial Nephrectomy for Renal Tumors >4 cm: Comparison With Renal Tumors ≤4 cm

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Partial nephrectomy has become a treatment of choice for clinical T1a renal masses. Some international guidelines suggest that partial nephrectomy can be applied also in clinical T1b tumors. The aim of this study was to evaluate the feasibility of partial nephrectomy for tumors larger than 4 cm. We reviewed the medical records of 1280 patients who underwent partial nephrectomy and had pathologically confirmed malignancy. Patients were categorized into two groups by the size of tumors on computed tomography image, with a cutoff value of 4 cm. The oncologic and functional outcomes were compared between the two groups. Recurrence-free survival after surgery was estimated using the Kaplan-Meier method. Of the 1280 patients, 203 patients (15.9%) had renal tumors larger than 4 cm. There were significantly more exophytic tumors ( $P < 0.001$ ) and the R.E.N.A.L. scores were significantly higher ( $P < 0.001$ ) in partial nephrectomy >4 cm. Mean ischemic times were significantly different ( $P < 0.001$ ). After 24 months, mean creatinine level between partial nephrectomy >4 cm and partial nephrectomy ≤4 cm was not different significantly ( $P = 0.554$ ). And the percent changes of glomerular filtration rate after partial nephrectomy were not different at last follow-up ( $P = 0.082$ ). The 5-year recurrence-free survival rates were 96.6% in partial nephrectomy ≤4 cm, and 94.5% in partial nephrectomy >4 cm ( $P = 0.416$ ). Based on the present findings, partial nephrectomy for tumors larger than 4 cm showed comparable feasibility and safety to partial nephrectomy for tumors ≤4 cm considering oncologic and functional outcomes, despite longer operative and ischemic time.

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*Key words:* Glomerular filtration rate – Kidney neoplasms – Nephrectomy – Partial – Size

Historically, radical nephrectomy has been established as the standard treatment for localized renal cell carcinoma.<sup>1</sup> Renal cancer does not represent a single disease, but a compendium of a complex family of tumors, with variable metastatic potential ranging from benign tumor to clear cell carcinoma.<sup>2</sup> Therefore, the rationale of radical nephrectomy for 20% to 30% of patients with benign or low malignant potential renal tumors has been questioned. Partial nephrectomy (PN), or nephron-sparing surgery, has become a treatment of choice for clinical T1a renal masses and has been shown to provide comparable oncologic outcomes.<sup>3</sup> In addition, PN offers lower renal function impairment compared with radical nephrectomy.<sup>4</sup> As a result, the prevention of chronic kidney disease possibly helps to obtain a better overall survival, and constitutes a wider use of PN. And some international guidelines suggest that PN can be applied also in clinical T1b tumors.<sup>5,6</sup> The European Association of Urology guidelines have recommended PN as an alternative treatment for single renal mass larger than 4 cm, if possible.<sup>5</sup> The American Urological Association guidelines have suggested that PN could be helpful for T1b tumors in patients whose renal function needs to be preserved.<sup>6</sup> Furthermore, a recent study was reported providing evidences that PN could be performed for renal tumors even larger than 7 cm without increase of complication rates and without compromising oncologic outcomes compared with those of radical nephrectomy.<sup>7</sup> Therefore, in the present study we investigated the oncologic and functional outcomes of PN for tumors >4 cm compared with those of PN for tumors ≤4 cm. The aim of this study is to demonstrate the feasibility of PN for tumors larger than 4 cm.

## Materials and Methods

This study was approved by the Committee on the Ethics of the Seoul National University Bundang Hospital (permit no. B-1408/262-106). Because the study was of a retrospective nature, there was no informed consent, and all data were analyzed anonymously. We reviewed the medical records of 1360 patients who underwent partial nephrectomy at our institution between April 1991 and December 2012. Of the 1360 patients, patients with pathologically confirmed malignancy were selected, and

those who were followed up more than 6 months after surgery were included. The patients with bilateral renal masses or benign tumors were excluded in this study. A total of 1280 patients were included, and among these patients, 203 patients (15.9%) had tumors larger than 4 cm in longest diameter on computed tomography or ultrasonography.

Demographics of patients with tumors >4 cm were compared with patients with tumors with ≤4 cm. To assess the operative technical differences, we compared the operative time, ischemic time, and estimated blood loss. And the pathologic reports were reviewed. The tumor size was measured as a maximal diameter of the surgical specimen, and tumor stage was reassessed according to the 2010 TNM classification system.<sup>8</sup> Renal function was evaluated by a serum creatinine level and a glomerular filtration rate (GFR) calculated by the Modification of Diet in Renal Disease equation.<sup>9</sup> Nephrometry scores were calculated to renal tumors using the R.E.N.A.L. (radius; exophytic/endophytic; nearness; anterior/posterior; location) tumor classification system.<sup>10</sup>

All statistical analysis was performed with commercially available statistical software (IBM SPSS version 19.0, IBM, Armonk, New York). Demographics and clinical parameters were compared with  $\chi^2$  test for categoric variables and Student *t*-test for continuous variables. Kaplan-Meier plots and the log-rank test were performed to assess recurrence-free survival. For all statistical analysis, a 2-tailed *P* value lower than 0.05 was considered statistically significant.

## Results

Of the 1280 patients who underwent PN, 203 patients (15.9%) had renal tumors larger than 4 cm. Preoperative demographics are shown in Table 1. Underlying medical diseases like diabetes and hypertension were similar in both patient groups (*P* = 0.214 and 0.704, respectively). Preoperative parameters of the blood test were not different (all *P* > 0.05). Although the laterality of tumors was similar between both groups, the locations and R.E.N.A.L. scores were significantly different. There were more endophytic tumors in PN ≤4 cm than in PN >4 cm, and more exophytic tumors in PN >4 cm than in PN

Table 1 Preoperative characteristics of patients

	PN >4 cm	PN ≤4 cm	P value
No. (%) of patients	203 (15.9)	1077 (84.1)	
Age, y, mean age ± SD	53.6 ± 12.7	54.8 ± 12.8	0.201
Male, n (%)	144 (70.9)	787 (73.1)	0.530
BMI, kg/m <sup>2</sup> , mean ± SD	24.7 ± 3.2	24.6 ± 3.2	0.702
Diabetes, n (%)	19 (9.4)	134 (12.4)	0.214
Hypertension, n (%)	69 (34.0)	381 (35.4)	0.704
Mean preoperative hemoglobin, g/dL	14.1	14.1	0.785
Mean preoperative creatinine, mg/dL	1.04	1.01	0.507
Mean preoperative GFR, mL/min/1.73 m <sup>2</sup>	81.5	82.6	0.508
Laterality, n (%)			0.160
Right	93 (45.8)	568 (52.7)	
Left	110 (54.2)	506 (47.3)	
Tumor size on CT, cm, mean (range)	5.02 (4.1–12.0)	2.33 (0.5–4.0)	<0.001
Location, n (%)			<0.001
Endophytic	36 (17.7)	333 (30.9)	
Exophytic	108 (53.2)	403 (37.4)	
Hilar	14 (6.9)	50 (4.6)	
Mesophytic	45 (22.2)	291 (27.1)	
R.E.N.A.L. score, mean (range)	7.85 (4–11)	6.82 (4–9)	<0.001
Low, n (%)	43 (21.2)	449 (41.7)	<0.001
Moderate, n (%)	114 (56.2)	560 (52.0)	
High, n (%)	46 (22.6)	68 (6.3)	
Follow-up period, mo, mean (range)	30.0 (6–137)	34.0 (6–162)	

BMI, body mass index; CT, computed tomography.

≤4 cm ( $P < 0.001$ ). In addition, R.E.N.A.L. scores were significantly higher in PN >4 cm ( $P < 0.001$ ).

Table 2 shows the results of postoperative outcomes in patients who underwent PN. Operative technique and ischemic type were similar between both groups. But mean operative time and ischemic time were significantly different ( $P = 0.001$  and  $P < 0.001$ , respectively). But the changes of renal function were not significantly different. Mean postoperative creatinine level after 3 months in PN >4 cm was significantly higher than that of PN ≤4 cm ( $P = 0.011$ ), but after 12 and 24 months, mean creatinine levels between PN >4 cm and PN ≤4 cm were not different significantly ( $P = 0.800$  and  $0.554$ , respectively). And the percent changes of GFR after PN were not different (after 3 months, 12 months, and at last follow-up,  $P = 0.130$ ,  $0.726$ , and  $0.082$ , respectively).

In Table 3, the pathologic results and postoperative complications were analyzed. Renal cell carcinoma was the most common histologic type in PN >4 cm (97.0%) and PN ≤4 cm (99.1%). And the rates of margin positivity were higher in PN ≤4 cm ( $P < 0.003$ ). Additionally, the complication rates of PN >4 cm were comparable with those of PN ≤4 cm ( $P = 0.603$ ). Figure 1 shows the Kaplan-Meier curves that compare the recurrence-free survivals of the patients. The 5-year recurrence-free survival rates

were 96.6% in PN ≤4 cm, and 94.5% in PN >4 cm ( $P = 0.416$ ).

## Discussion

In this study, we compared the clinicopathologic characteristics and postoperative outcomes of PN between tumors larger than 4 cm, and 4 cm or smaller. Baseline demographics were not different between the two groups. However, there were significantly more tumors that were endophytic and that had low R.E.N.A.L. scores in the group of PN ≤4 cm. Mean operative time and mean ischemic time were longer in the group of PN >4 cm, but the time differences did not affect postoperative changes of renal function. Also, larger tumor size did not increase postoperative complications compared with the group of PN ≤4 cm.

Initially attempted for small, exophytic, and easily accessible renal tumors, the indications for elective PN have expanded to tumors of a larger size and in difficult locations with growing experience. The technical challenge and ensuing morbidity of a PN is dictated by the tumor size, its growth pattern (endophytic versus exophytic), and its location (lower pole versus upper pole versus hilar and centrally located). Given the lack of an objective, reliable, and reproducible index encompassing size,

Table 2 Postoperative outcomes

	PN >4 cm	PN ≤4 cm	P value
Operative method, n (%)			0.146
Laparoscopic	5 (2.5)	66 (6.1)	
Open	163 (80.3)	809 (75.1)	
Robot-assisted	35 (17.2)	202 (18.8)	
Operative time, min, mean (range)	170.7 (70–325)	155.5 (50–280)	0.001
Ischemic type, n (%)			0.468
Warm	163 (80.3)	817 (75.9)	
Cold	34 (16.7)	206 (19.1)	
None	6 (3.0)	54 (5.0)	
Clamping, n (%)	197 (97.0)	1023 (95.0)	0.203
Ischemic time, min, mean (range)	30.5 (0–86)	24.1 (0–81)	<0.001
Warm ischemic time, min, mean (range)	28.8 (9–55)	24.2 (0–75)	<0.001
Open	27.5 (9–55)	21.9 (0–75)	<0.001
Robot	31.7 (13–49)	26.9 (6–55)	0.018
Mean estimated blood loss, mL	307.5	248.1	0.002
Blood transfusion, n (%)	21 (10.3)	53 (4.9)	0.009
Open conversion, n (%)	0 (0)	4 (1.5)	0.241
Hospital stay, d	7.80	7.85	0.903
Mean postoperative first day hemoglobin, g/dL	12.4	12.6	0.094
Mean postoperative creatinine after 3 mo, mg/dL	2.49	1.09	0.011
Mean postoperative creatinine after 12 mo, mg/dL	1.11	1.09	0.800
Mean postoperative creatinine after 24 mo, mg/dL	1.12	1.08	0.554
Intraoperative complication, n (%)	31 (15.3)	98 (9.1)	0.021
Mean percent change of GFR after 3 mo	−5.2	−4.2	0.130
Mean percent change of GFR after 12 mo	−3.2	−2.4	0.726
Mean percent change of GFR at last follow-up	−3.3	−1.8	0.082

Table 3 Pathologic outcomes and complications

	PN >4 cm	PN ≤4 cm	P value
Histology, n (%)			<0.010
Clear cell RCC	157 (77.3)	908 (84.3)	
Non-clear cell RCC	40 (19.7)	159 (14.8)	
Other malignancy	6 (3)	10 (0.9)	
Specimen size, cm, mean (range)	4.84 (1.4–13)	2.19 (0.4–5.5)	<0.001
T stage, n (%)			<0.001
pT1a	70 (34.5)	1033 (95.9)	
pT1b	112 (55.2)	17 (1.6)	
pT2a	6 (3)	0 (0)	
pT2b	1 (0.4)	0 (0)	
pT3a	14 (6.9)	27 (2.5)	
Positive margin, n (%)	2 (0.99)	11 (1.02)	<0.003
Recurrence, n (%)	6 (3)	28 (2.6)	0.067
Complications, n (%)	23 (11.3)	109 (10.1)	0.603
Clavien-Dindo grading, n			0.245
1	8	42	
2	1	21	
3a	11	40	
3b	3	6	
≥3, n (%)	14 (6.9)	46 (4.3)	0.105
Urine leakage, n (%)	2 (1)	7 (0.6)	
Bleeding/pseudoaneurysm, n (%)	6 (3)	24 (2.2)	
Wound dehiscence/infection, n (%)	5 (2.4)	12 (1.1)	
Acute renal failure, n (%)	1 (0.5)	3 (0.4)	

RCC, renal cell carcinoma.

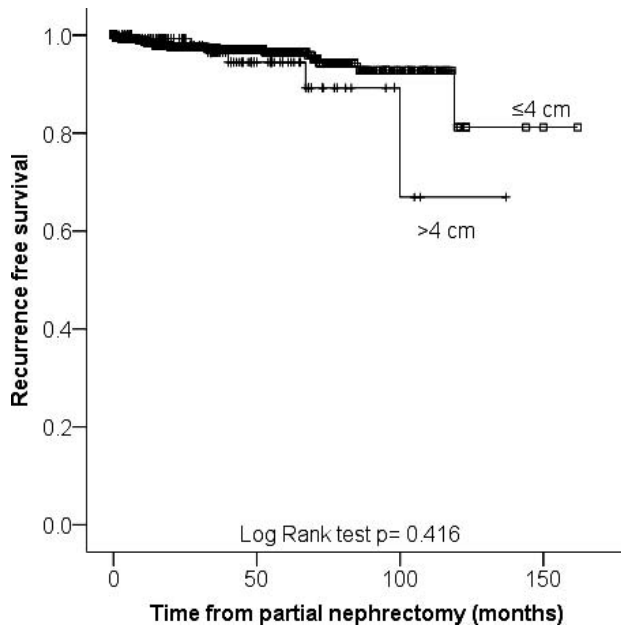


Fig. 1. Kaplan-Meier estimates of recurrence-free survival.

location, and growth pattern to measure the technical complexity of a PN, tumor size is the default parameter and has been widely used in the literature. The use of tumor size is justified by the fact that it is objective, reproducible, and correlates with oncologic outcomes. The 4-cm cutoff as the upper limit of acceptability of PN was determined on the basis of its significant correlation with cancer-specific survival favoring tumors of the smaller size.<sup>11,12</sup> In this category, PN was established by retrospective methodologies as a noninferior therapeutic option to radical nephrectomy with regard to oncologic outcomes. Several reports have shown long-term 5- and 10-year cancer-free survival rates of 92% to 100%, and acceptably low local recurrence rates.<sup>13–16</sup>

In a retrospective analysis based on 662 patients undergoing elective partial or radical nephrectomy for a <4-cm renal mass, Huang *et al*<sup>17</sup> demonstrated that with a normal preoperative serum creatinine and a healthy-appearing contralateral kidney on imaging, 171 patients (26%) had preexisting chronic kidney disease at baseline before surgery (GFR <60 mL/min per 1.73 m<sup>2</sup>).<sup>17</sup> After surgery, the 3-year and 5-year probabilities of freedom from chronic kidney disease were 80% [95% confidence interval (95% CI), 73%–85%] and 67% (95% CI, 57%–75%), respectively, after PN, and 35% (95% CI, 28%–43%) and 23% (95% CI, 16%–30%), respectively, after radical nephrectomy ( $P < 0.0001$ ). For more severe

chronic kidney disease, the 3- and 5-year probabilities of freedom from new-onset GFR <45 mL/min per 1.73 m<sup>2</sup> were 95% (95% CI, 91%–98%) and 93% (95% CI, 87%–96%), respectively, for patients treated by PN, compared with the respective values of 64% (95% CI, 56%–70%) and 57% (95% CI, 50%–64%) for those who underwent radical nephrectomy ( $P < 0.0001$ ). Multivariable analysis indicated that radical nephrectomy remained an independent risk factor for the development of new-onset chronic kidney disease (hazard ratio, 3.82; 95% CI, 2.75–5.32;  $P < 0.0001$ ).<sup>17</sup> The mechanism by which PN offers an advantage over radical nephrectomy in preventing chronic kidney disease in patients with renal masses <4 cm is certainly due to a greater preservation of the nephron capital. Studies looking at the independent predictors of renal function outcome after partial nephrectomy have shown that larger renal volume reduction, or percent of parenchyma resected is adversely influencing renal function after partial nephrectomy. Other predictors are either patient dependent (preoperative estimated GFR, solitary kidney status, older age, and male sex) or technique dependent (length of ischemia time).<sup>18–20</sup>

Avoiding local recurrences has been paramount to the concept of nephron-sparing surgery. The initially recommended negative surgical margin width was 1 cm.<sup>21</sup> However, with the expansion of indications to larger and centrally located tumors, wider safety margins were no always technically feasible, and simple tumor enucleation has been proposed as an alternative.<sup>22,23</sup> In a retrospective review by Carini *et al*,<sup>24</sup> 71 patients with renal cortical tumors between 4 and 7 cm were treated by simple enucleation of the tumor and followed with a median follow-up of 51 months; the 5- and 8-year cancer specific survival rates were 85.1% and 81.6%, respectively. The local recurrence rate, however, was 4.5%; the histologic distribution in this series was 85.9% clear cell, 8.5% chromophobe, and 5.6% papillary.<sup>24</sup> In a smaller study of 44 patients treated by PN for renal cortical tumors with a mean follow-up of 49 months (range: 8–153 months), none of the 41 patients with negative surgical margin developed local recurrence at the excision, the mean and median sizes of the healthy renal parenchymal rim surrounding the tumor and ensuring a negative margin were 2.5 and 2 mm, respectively.<sup>25</sup> In a retrospective review of 777 PNs performed at a single center, Kwon *et al*<sup>26</sup> reported a positive surgical margin rate of 7%. With a median follow-up of 22 months, the detected local recurrence rate was 4% in patients with positive margin versus 0.5%

in those with a negative surgical margin. Recurrence after a positive surgical margin was seen only in patients with what the authors determined as high malignant potential tumors (clear cell, collecting duct, or presence of sarcomatoid features).<sup>26</sup> A report combining the PN experience from 2 tertiary care centers in the United States examined 77 cases of positive surgical margins out of 1390 PNs (5.5%) and did not find any significant difference between patients with positive and negative surgical margins with regard to local recurrence and metastatic disease. The authors concluded that a positive surgical margin after PN does not portend an adverse prognosis.<sup>27</sup> As a result, a 1-cm margin of healthy parenchymal rim throughout the specimen is not always possible, particularly at the deep margin of excision. In light of the available information, such a wide margin is not needed. With PNs offered for larger and more endophytic, centrally located, and juxtahilar tumors, the excision at the deep margin may often be limited to an enucleation.

The limitations of this study include the retrospective aspect and selection bias from nonrandomized surgical series. However, the tumor sizes and medical records were reviewed by one clinician, so the discrepancies during measurements of tumor sizes have been decreased. Estimated GFRs were available for most but not all patients. But the follow-up was continued for more than a year and even for 10 years in some patients, so the follow-up period was enough to compare long-term outcomes of the surgery.

Based on the present findings, PN for tumors >4 cm has similar recurrence-free survival rates and renal functional changes compared with PN for tumors ≤4 cm. And, postoperative complications did not increase in PNs for tumors >4 cm. However, operative and ischemic times were longer in tumors >4 cm. So, we can conclude that PN for tumors >4 cm is feasible and safe without compromising oncologic and functional outcomes compared with PN for tumors ≤4 cm. In addition, efforts to shorten operative and ischemic time are needed to decrease potential risk posed by longer operative and ischemic time.

## Acknowledgments

No sources of funding have to be declared. The authors declare that they have no conflict of interests.

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