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Multi-Institutional Analysis of Robot-Assisted Partial Nephrectomy for Renal Tumors >4 cm Versus ≤4 cm in 445 Consecutive Patients

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Abstract

Background and Purpose: Robot-assisted partial nephrectomy (RPN) has emerged as a viable approach to minimally invasive surgery for small renal tumors. There are few reports of RPN for tumors >4 cm. Our objective was to evaluate outcomes of RPN for tumors >4 cm compared with RPN for tumors ≤4 cm in a large multi-institutional study.

Patients and Methods: We reviewed data for 445 consecutive patients who underwent RPN by experienced surgeons at four academic institutions from 2006 to 2010. Patients were stratified into two groups according to radiographic tumor size. Patient demographics, perioperative outcomes, and oncologic outcomes were recorded.

Results: A total of 83 of 445 (18.7%) patients had tumors >4 cm with a median radiographic tumor size of 5.0 cm (4.1–11 cm). Patients with tumors >4 cm had a higher proportion of hilar tumors (9.8% *vs* 4.7%, $P<0.001$), a higher mean R.E.N.A.L. nephrometry score (8.0 *vs* 6.3, $P<0.01$), longer warm ischemia time (WIT) (24 *vs* 17 min, $P<0.001$), and an increased rate of collecting system repair (72.2% *vs* 51.6%, $P=0.006$) compared with patients with tumors ≤4 cm. Functional outcomes and complications were similar between groups. There were no positive margins in patients with tumors >4 cm and only one recurrence.

Conclusions: In the largest multi-institutional series of RPN for tumors >4 cm, we demonstrate safety, feasibility, and efficacy of RPN for tumors >4 cm. Patients with tumors >4 cm had a higher nephrometry score, longer WIT, and slightly higher estimated blood loss compared with patients who had tumors ≤4 cm, but there was no increased risk of adverse outcomes in the hands of experienced surgeons.

Introduction

Partial nephrectomy (PN) is the standard of care treatment option for small renal tumors that offers equivalent oncologic efficacy to radical nephrectomy (RN)[1,2] with preservation of renal function and improved survival.[1,3] Larger tumors pose additional technical challenges during PN, particularly with a minimally invasive approach. The technical feasibility of laparoscopic partial nephrectomy (LPN) for tumors >4 cm has been described,[4,5] but considerable surgeon experience is necessary, and complication rates may be higher. Reports of robot-assisted partial nephrectomy (RPN) for tumors >4 cm are limited to a few small single institution series.[6,7] We report outcomes of RPN for tumors >4 cm compared with tumors ≤4 cm in a large multicenter study.

Patients and Methods

Data acquisition and patient evaluation

After approval from our respective Institutional Review Boards, we reviewed data for 445 consecutive patients who underwent RPN by renal surgeons who were experienced in minimally invasive techniques (SB, MS, JK, CR) at four institutions between June 2006 and April 2010. Maximum tumor diameter was assessed radiographically by a board-certified radiologist. Nephrometry score was assigned to renal tumors using the R.E.N.A.L. (radius; exophytic/endophytic; nearness; anterior/posterior; location) tumor classification system.[8] For no patients was there preoperative suspicion of localized or distant metastatic disease.

Patients were stratified into two groups based on radiographic tumor size >4 cm and ≤4 cm. Demographic and

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perioperative variables were assessed, including patient age, body mass index (BMI), American Society of Anesthesiologists (ASA) score, operative time, warm ischemia time (WIT), estimated blood loss (EBL), collecting system repair, complications (Clavien classification system[9]-Clavien II or greater complications reported), length of hospital stay, histology, tumor stage. and margin status. Estimated glomerular filtration rate (eGFR) was assessed preoperatively, at 1-month follow-up, and at the most recent follow-up using the Modification of Diet in Renal Disease equation.[10] A urine leak was defined as biochemically proven urine drainage >7 days postoperatively or the need for an intervention (ie, ureteral stent, nephrostomy, percutaneous drainage of urinoma, etc.). All patients who were amenable for a minimally invasive nephron-sparing procedure under warm ischemia, including three patients with a solitary kidney, underwent RPN.

Surgical technique

The technique of RPN was similar among all surgeons and has been described.[11–14] The da Vinci robot system (Intuitive Surgical Inc., Sunnyvale, CA) was used in all cases. Laparoscopic ultrasonograpy was used to evaluate tumor location and extent. Hilar occlusion was performed in most cases, and the tumor was resected using cold resection with robotic scissors. A limited number of cases were performed without hilar clamping for small tumors. For larger or endophytic tumors, both the artery and the vein were clamped for improved visualization during tumor resection.

Statistical analysis

We compared demographic, clinical, and tumor characteristics of patients with tumors >4 cm *vs* tumors ≤4 cm. The assumption of normality was tested using the Shapiro-Wilk normality test. All variables with the exception of maximum tumor size were normally distributed. Variables were compared between groups with tumors >4 cm *vs* tumors ≤4 cm using the Student *t* test and the Mann-Whitney *U* test. Significance was set at 0.05 for each analysis. To control for confounding and to examine the learning curve, a comparison of categorical and continuous covariates was performed between the cases in the first (n = 222) and second half (n = 223) of the study. All statistical analyses were performed using SAS v9.2 for Windows (SAS Institute Inc, Cary, NC).

Results

A total of 83 (18.7%) patients had tumors >4 cm, with a median tumor size of 5.0 cm (4.1–11 cm). Nine of these patients had tumors >7 cm (clinical stage T_2); 362 (81.3%) patients had tumors ≤4 cm, with a median tumor size of 2.3 cm (0.7–4 cm). Patient demographics and radiographic tumor characteristics are summarized in Table 1. Patients with tumors >4 cm had a higher BMI (30.4 *vs* 28.2 kg/m^2, $P = 0.01$) and a higher proportion of tumors in a hilar location (9.8% *vs* 4.7%, $P < 0.001$). Patients with tumors >4 cm had a higher mean nephrometry score of 8.0 (n = 60 patients, range 4–11) compared with a median nephrometry score of 6.3 for smaller tumors (n = 228, range 4–10), $P < 0.01$.

Table 2 demonstrates operative outcomes by tumor size. Patients with tumors >4 cm had a longer mean WIT (24 *vs* 17 min, $P < 0.001$), a higher operative time (194 *vs* 180 min, $P = 0.017$), EBL (200 *vs* 150 mL, $P = 0.001$), length of hospital stay (3 *vs* 2.5 days, $P = 0.005$), and higher rate of collecting system repair (72.2% *vs* 51.6%, $P = 0.006$). Most cases in both groups were performed with hilar clamping (93% *vs* 88%, $P = 0.25$). There were no significant differences in functional outcomes measured by eGFR between groups. The mean percent decrease in eGFR at 1 month postoperatively was greater for tumors >4 cm (9% *vs* 4.5%), but this did not reach statistical significance ($P = 0.09$). Preoperatively, 17.2% of patients with tumors >4 cm and 13% of patients with tumors

Table 1. Patient Demographics for Robot-Assisted Partial Nephrectomy by Tumor Size

Variables	*Tumors >4 cm (n = 83)*	*Tumors ≤4 cm (n = 362)*	P *value*
Mean age, y (SD)	61 (12)	60 (11)	0.69
Sex, N (%)			
Male	52 (62.7)	245 (67.7)	0.44
Body mass index, kg/m^2[a]	30.4 (26.8–35.2)	28.2 (25.4–32.9)	0.01
ASA score	2 (2–3)	2 (2–3)	0.45
Mean preoperative creatinine, mg/dL, (SD)	1 (0.39)	0.98 (0.32)	0.68
Mean preoperative eGFR, (SD)[b]	81.7 (31.4)	82 (23)	0.94
Radiographic characteristics, N, (%)			
Tumor size, cm (range)	5 (4.1–11)	2.3 (0.7–4)	< 0.001
Upper pole	26 (32.1)	82 (23.8)	0.26
Midpolar	32 (39.5)	163 (47.2)	
Lower pole	23 (28.4)	100 (29)	
Endophytic	16 (25)	68 (25.7)	0.75
Mean nephrometry score (range)[c]	8.0 (4–11)	6.3 (4–10)	< 0.01
Anterior, N (%)	23 (38.4)	99 (43)	
Posterior	16 (26.6)	72 (32)	
Neither	21 (35.0)	57 (25)	
Hilar	5 (9.8)	9 (4.7)	

[a]Continuous values are expressed as median (interquartile range) unless mentioned otherwise.
[b]Calculated using the Modification of Diet in Renal Disease equation.
[c]Nephrometry score available in 60 patients with tumors >4 cm and 228 patients with tumors ≤4 cm.
SD = standard deviation; ASA = American Sociaty of Anesthesiologists; eGFR = estimated glomerular filtration rate.

Table 2. Operative Outcomes for Robot-Assisted Partial Nephrectomy by Tumor Size

Variables	*Tumors >4 cm (n=83)*	*Tumors ≤4 cm (n=362)*	P *value*
Operative time, min[a]	194 (153–240)	180 (147–220)	0.017
Mean warm ischemia time, min (SD, range)	24 (10, 0–45)	17 (9, 0–60)	< 0.001
Estimated blood loss, mL	200 (100–400)	150 (100–250)	0.001
Hilar clamping, N (%)	77 (93)	319 (88)	0.25
Collecting system repair, N (%)	39 (72.2)	114 (51.6)	0.006
Blood transfusions, N (%)	10 (12)	10 (3)	0.001
Conversions, N (%)			
Robot-assisted RN	0 (0)	2 (0.55)	1.00
Conventional laparoscopic PN	2 (2.4)	2 (0.55)	0.16
Open RN	0 (0)	1 (0.28)	1.00
Length of stay, d	3 (2–4)	2.5 (2–3)	0.005
Mean percent decrease eGFR at 1 month (SD)	9% (11)	4.5% (15)	0.09
Mean percent decrease eGFR at last follow-up (SD)	8.6 % (16.5)	3.9 % (17.4)	0.11

[a]Continuous values are expressed as median (interquartile range) unless mentioned otherwise.
SD = standard deviation; RN = radical nephrectomy; PN = partial nephrectomy; eGFR = estimated glomerular filtration rate

≤4 cm were classified as having chronic kidney disease stage 3 or greater; the corresponding values in the postoperative period (1 month) were 40.4 % and 27.6% for the two groups, respectively.

There were no differences in complications between groups (Table 3), and complications were either Clavien II or IIIa. Postoperative complications of patients with tumors >4 cm included two urine leaks necessitating stent placement, one bleed necessitating angioembolization, and a pulmonary embolism in two patients. Two patients in the >4 cm tumor group underwent conversion to LPN because of equipment malfunction early in our experience, but there was no difference in conversions between groups.

Table 3 lists pathologic characteristics of the tumors. There was no difference in the rate of malignancy between groups. The mean pathologic tumor size was 4.8 cm *vs* 2.2 cm ($P<0.001$), similar to the comparison of radiographic tumor size. There were no positive surgical margins in patients with tumors >4 cm. There were seven focally microscopic positive margins on final pathologic evaluation in patients with tumors ≤4 cm, resulting in a positive margin rate of 1.9%. Two of these tumors were benign (lipid-poor angiomyolipomas not clearly evident on preoperative radiographic imaging). There was only one local recurrence in a patient with a tumor >4 cm and high-grade pT_{3a} renal-cell carcinoma (RCC) with negative margins. No other patient had evidence of recurrence or metastatic disease at a maximum of 45 months follow-up (mean 10 months).

When comparing outcomes in the first and second half of our RPN experience, there was no difference in the percentage of tumors >4 cm (15.7% *vs* 17.0%, $P=0.46$). There were no statistically significant differences in operative parameters, such as WIT or positive margin rate, except for a slightly shorter operative time in the later cohort (189 *vs* 175 min, $P<0.05$).

Discussion

As the role of nephron-sparing surgery (NSS) expands minimally invasive techniques of PN have been applied to

Table 3. Postoperative Outcomes of Robot-Assisted Partial Nephrectomy by Tumor Size

Variables	*Tumors >4 cm (n=83)*	*Tumors ≤4 cm (n=362)*	P *value*
Tumor histology, N (%)			
Clear-cell RCC	40 (48.2)	180 (50.3)	0.41
Other RCC	18 (21.7)	81 (22.6)	
Other malignant	2 (2.4)	11 (3.1)	
Benign	23 (27.7)	86 (24)	
Tumor stage			
T_{1a}	12	257	< 0.001
T_{1b}	38	6	
T_2	4	0	
T_{3a}	4	8	
T_{3b}	2	1	
Positive margins, N (%)	0 (0)	5 (1.4)	0.35
Complications, N (%)	5 (8.4)	14 (3.9)	0.37
Urine leak necessitating intervention	2 (2.4)	3 (0.83)	0.23
Postoperative bleed/pseudoaneurysm necessitating intervention	1 (1.2)	5 (1.38)	1.00
Pulmonary embolism/DVT	2 (2.4)	6 (1.66)	0.65

RCC = renal-cell carcinoma; DVT = deep vein thrombosis.

more complex renal tumors. Recent guidelines[15,16] for RCC have recommended the use of NSS for T_1 renal tumors whenever feasible, regardless of tumor diameter. Open PN has been shown to be safe and feasible in selected patients with 4 to 7 cm renal tumors with outcomes comparable to those of RN[2,17] and with evidence suggesting reduced cardiovascular events and improved survival over RN,[18] similar to what has been demonstrated with T_{1a} tumors. Large tumors may present additional technical challenges even for surgeons experienced in minimally invasive techniques. RPN has been demonstrated to be safe and feasible for challenging renal tumors, such as large and hilar renal masses.[6,7,19]

The aim of our study was to demonstrate the feasibility of RPN for tumors >4 cm and to emphasize that robotic assistance may offer advantages even for surgeons who are experienced in minimally invasive techniques.

Our multicenter study includes 83 patients who underwent RPN for tumors >4 cm, making it the largest study of minimally invasive PN for tumors >4 cm by any approach. Patients with tumors >4 cm had a longer WIT (24 *vs* 17 min). The WIT in our series, however, was well below the targeted goal of ≤30 minutes in both groups. The longer mean WIT observed for large tumors is consistent with previous smaller single institution reports of RPN for tumors >4 cm.[4,6] The increased complexity of the group with tumors >4 cm as evidenced by the higher nephrometry score and higher rates of collecting system repair likely influenced the differences seen in WIT. Although tumors >4 cm had higher operative times and EBL in comparison with tumors ≤4 cm that achieved statistical significance, the clinical significance is debatable.

The feasibility of PN for tumors >4 cm has been described for LPN[4,5] by experienced laparoscopic surgeons. A series by Simmons and associates[4] included 58 patients who underwent LPN for tumors >4 cm with a mean WIT of 38 minutes. Another series that included 34 patients who underwent LPN for tumors >4 cm did not include data on WIT, but patients with tumors >4 cm had a higher rate of complications than patients with tumors ≤4 cm (37% *vs* 21.8%).[5] Robotic assistance may help surgeons achieve shorter WIT. Results of a large comparative study of RPN *vs* LPN found that WIT was shorter in the RPN group (19.7 *vs* 28.4 min) even for surgeons who were experienced in minimally invasive techniques, and this trend continued with more complex tumors.[13] We did not routinely use early unclamping techniques in our study, which has been shown to reduce WIT during LPN,[20] but we would expect the WIT for RPN to further decrease with application of this technique.

Two small single-institution studies have evaluated RPN for tumors >4 cm. Patel and colleagues[6] reported on RPN for 15 patients with tumors >4 cm and compared outcomes with 56 patients with tumors ≤4 cm. Patients with tumors >4 cm had a longer median WIT (25 *vs* 20 min, $P=0.011$). Gupta and coworkers[7] reported on 17 patients with tumors >4 cm (median tumor size, 5 cm), with a median EBL of 500 mL, median operative time of 390 minutes, and median WIT of 36 minutes. They attributed these outcomes to a higher median nephrometry score of 9 (6–11), a multifocality rate of 42%, and the fact that 89.5% of tumors were >50% endophytic. In our study of 83 patients with tumors >4 cm, we achieved a WIT of 24 minutes despite equivalent median tumor size (5 cm) and tumors that were also complex (median nephrometry score, 8; collecting system repair rate, 72%) and with no positive surgical margins.

Surgeon experience and patient selection likely contribute to successful RPN, particularly for tumors >4 cm. Learning curve effects did not appear to have a major impact on our results, as surrogate end points such as the proportion of tumors >4 cm attempted, positive surgical margins, and WIT did not change significantly between the first and second half of the study. The lack of a learning curve detection in our study may be in part because all surgeons were experienced in laparoscopic and robotic techniques, and all surgeons performed complicated cases early in the series.

Limitations of our study include the retrospective nature and selection biases of a nonrandomized surgical cohort. R.E.N.A.L nephrometry scores and estimated creatinine clearance were available for most, but not all patients. There is emerging interest in controlling for case complexity with nephrometry scoring systems, but these systems await validation and may be of limited utility in a cohort selected for homogeneity such as ours, in which all patients with tumors >4 cm had tumors amenable to RPN. We used a measurement of tumor size based on the maximum tumor dimension on preoperative imaging. Although this size measurement has inherent limitations and does not include tumor volume, this was the variable collected in our prospective database. Long-term follow-up was not available for all patients in our dataset because many patients were referred to our respective tertiary medical centers and received long-term follow-up by their local urologists. Further studies to evaluate the long-term outcomes of RPN for tumors >4 cm are warranted.

Conclusions

In the largest multi-institutional series of RPN for tumors >4 cm, we demonstrate safety, feasibility, and efficacy of RPN for tumors >4 cm. Tumors >4 cm had a higher nephrometry score, longer WIT, and a slightly higher EBL compared with tumors ≤4 cm, but there was no increased risk of adverse outcomes in the hands of experienced surgeons.

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Disclosure Statement

Dr. Rogers is a member of the Speakers' Bureau and is a consultant for Intuitive Surgical. For the remaining authors, no competing financial interests exist.

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Abbreviations Used

ASA = American Society of Anesthesiologists
BMI = body mass index
EBL = estimated blood loss
eGFR = estimated glomerular filtration fate
LPN = laparoscopic partial nephrectomy
NSS = nephron-sparing surgery
PN = partial nephrectomy
RCC = renal-cell carcinoma
RN = radical nephrectomy
RPN = robot-assisted partial nephrectomy
WIT = warm ischemia time