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Partial and Radical Nephrectomy for Unilateral Synchronous Multifocal Renal Cortical Tumors

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Abstract

Objective—To evaluate clinicopathologic characteristics and treatment outcomes of patients undergoing partial (PN) or radical nephrectomy (RN) for unilateral synchronous multifocal renal tumors.

Methods—We retrospectively reviewed medical records for 128 patients with non-metastatic unilateral synchronous multifocal renal tumors who underwent surgical resection at our institution from 1995 to 2012. Five patients with hereditary renal cell carcinoma were excluded. Differences between patient and tumor characteristics from the two nephrectomy groups were evaluated. Outcomes in terms of recurrence-free survival, overall survival, and chronic kidney disease upstaging were estimated using Kaplan-Meier methods. The log-rank test was used for group comparisons.

Results—The study cohort included 78 PN patients (63%) and 45 RN patients (37%); 17/95 planned PN (18%) were converted to RN. Tumor diameter and R.E.N.A.L. nephrometry scores were greater in RN patients ($p<0.0001$ and $p=0.0002$, respectively). Pathological stage T3 was seen in 40% of RN patients and 10% of PN patients ($p=0.0002$). Histologic concordance was apparent in 60/123 patients (49%).

Median follow-up for patients alive without a recurrence was 4 years. Five-year recurrence-free survival was 98% for PN and 85% for RN. Five-year overall survival was 96% for PN and 86% for RN ($p=0.5$). Five-year freedom from chronic kidney disease upstaging was 74% for PN, and 55% for RN ($p=0.11$).

Conclusion—Partial nephrectomy for the treatment of unilateral synchronous multifocal renal tumors with favorable characteristics was associated with a low recurrence rate. These findings suggest PN is an appropriate management strategy for this group of carefully selected patients.

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Keywords

Renal cell carcinoma; nephrectomy; prognosis; survival rate; multiple primaries

Introduction

Renal cortical tumors are multifocal in 3.5%–25% of patients.[1] Traditionally, patients with unilateral synchronous multifocal disease were treated with radical nephrectomy (RN), thus avoiding possible residual ipsilateral lesions and achieving maximal oncologic benefit, despite the negative effects on renal function and risk of subsequent chronic kidney disease (CKD).[2,3] Recent reports indicate that partial nephrectomy (PN) for multifocal renal cortical tumors offers equivalent cancer-specific survival (CSS) to RN, with the added benefit of preservation of postoperative renal function with a limited complication profile. [3–5]

To our knowledge, only one previous series compared the outcomes of patients with non-hereditary ipsilateral multifocal renal tumors who were treated with either PN or RN.[4,5] While this series showed equivalent CSS, surgical characteristics and complication rates were not compared, and the effect of multiple resections on the preservation of kidney function has not been reported.

The aim of the present study was to evaluate the surgical characteristics and treatment outcomes of patients with unilateral, synchronous, multifocal renal tumors treated with RN or PN. In addition, we compared postoperative complication rates and long-term renal function in these patients.

Material and Methods

After obtaining Institutional Review Board approval, we retrospectively reviewed the medical records of 333 patients who underwent nephrectomy at a single institute from 1995 to 2012 and were found to have multifocal renal tumors with at least one renal cell carcinoma (RCC) component according to their pathology report. We excluded patients with metastatic disease at presentation (n=7). Patients with synchronous bilateral tumors (n=71), a solitary kidney (n=29) and hereditary renal cancer (n=5) were also excluded, as these patients are usually treated with PN under absolute or relative indications. In addition, patients with pathological multifocal lesions undetected on preoperative imaging or during surgery (n=98) were excluded, as these patients were not subject to the same preoperative planning and intraoperative decision making that patients with known multifocal renal tumors are.

Data on patient characteristics including age, gender, race, body mass index, American Society of Anesthesiologists score (I/II or III/IV), presentation status (incidental, local, or systemic), and smoking status (never, former or current) were collected. Preoperative estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[6] based on preoperative serum creatinine levels. The number of tumors detected on preoperative imaging was documented, and the largest tumor was defined as the index lesion. R.E.N.A.L. (radius, exophytic/

endophytic, nearness to collecting system or sinus, anterior/posterior and location relative to polar lines) nephrometry scores were calculated for the most complex renal lesions.[7]

RN was performed using standard procedure. Open PN was performed in most cases using the "mini-flank" supra-11th rib incision.[8] The laparoscopic and robotic approaches were completed via transperitoneal or retroperitoneal access. Vascular control was obtained by occluding the renal vessels with a bulldog clamp, except for selected cases. Cold ischemia, when used, was achieved using ice slush for open procedures and cold intravascular perfusion for minimally invasive procedures. Surgical characteristics including date of surgery, type of surgery (RN or PN), surgical approach (open or minimally invasive), operating time (minutes), type and duration (minutes) of ischemia, and estimated blood loss (EBL, mL) were reported. The conversion rate from PN to RN was also recorded. Postoperative length of stay was determined and early postoperative complications, within 30 days of surgery, were graded according to the Clavien-Dindo classification system.[9]

Surgical specimens were processed by standard pathological techniques and reviewed by genitourinary pathologists. The number of tumors and their histological subtypes were identified on the pathological specimen. All clear cell RCC tumors were graded according to the Fuhrman nuclear grading system.[10] Tumors were measured by their maximal diameter and staged according to the 2010 American Joint Committee on Cancer/Union for International Cancer Control TNM classification system. Surgical margin status was defined as positive or negative. Similar to previous reports, malignant concordance was defined when all tumors in the involved kidney were of malignant nature, and benign concordance was defined when all lesions were benign. Histologic concordance was achieved when all tumors were of the same histology, and histological discordance was defined when the index tumor and the other tumors were of different histological subtype.[3]

Patients were followed semi-annually with physical examination, blood chemistry, and abdominal and chest imaging. CKD was defined as an eGFR <60 mL/min/1.73 m^2, and further categorized as stage 3 CKD (eGFR 30–59 mL/min/1.73 m^2), stage 4 CKD (eGFR 15–29 mL/min/1.73 m^2) and stage 5 CKD (eGFR <15 mL/min/1.73 m^2).[11] CKD upstaging was noted as new onset of stage 3 CKD or above after the procedure, or when the CKD stage at last follow-up was higher than the stage on the preoperative assessment in patients presenting with CKD. Disease recurrence was defined as either local or distant based on imaging study findings.

Kaplan-Meier methods were used to evaluate recurrence free survival (RFS) and overall survival (OS) for PN and RN. Due to a limited number of events, we were unable to perform multivariable analyses adjusting for patient and tumor characteristics. Survival times were calculated from the time of surgery to the time of recurrence, the time of death, or were censored at the last time the patient was recurrence-free or alive. Chi-squared tests were used to assess the differences between categorical variables by type of nephrectomy and Wilcoxon signed-rank tests were used for continuous variables. Univariable regression models were used to evaluate the association between pre-operative patient and tumor characteristics and the outcomes of conversion from PN to RN, complication events, EBL,

and length of hospitalization. Statistical analyses were conducted using Stata 12.0 (StataCorp, College Station, TX).

Results

The study cohort included a total of 123 patients, of which 78 underwent PN (63%), and 45 underwent RN (37%). Patient and surgical characteristics are summarized in Table 1, and tumor characteristics by PN or RN are summarized in Table 2. Patients with more than two tumors on preoperative imaging were more likely to be treated with RN than PN (eight vs. four, respectively, p=0.023). Patients who underwent RN tended to have worse tumor characteristics, including larger median tumor diameters (4.5 cm for RN vs. 2.7 cm for PN, p<0.0001), higher R.E.N.A.L. nephrometry scores (p=0.0002), higher rates of clear cell histology (p=0.024), and higher pathological T-stages (p=0.0002). Patients treated between the years 1995–2000 were more likely to undergo RN 9/11 (82%) than PN 2/11 (18%); however, patients operated between the years 2001–2012 were more often treated with PN 76/112 (68%) than RN 36/112 (32%), (p=0.001). Operating time was shorter in patients undergoing PN (p=0.035). No significant difference was observed in EBL (p=0.7). Cold ischemia was used in 63/71 patients (89%) undergoing PN with a median duration of 39.5 minutes. Warm ischemia was used in 8/71 patients (9%) with a median duration of 33 minutes. The length of postoperative stay was significantly shorter for PN patients, with a median of three days compared to four days for RN, (p=0.014), whereas the rate or grade of complications did not differ significantly (p=0.2). Seventeen of the 45 RN patients were initially slated to undergo PN, thus 17/95 planned PN (18%) were converted to RN. Eleven cases (12%) were converted due to the finding of a multifocal or extensive tumor and three (3%) due to insufficient residual kidney following the resection. Additional reasons for conversion were a large renal cortical defect that could not be effectively closed after resection, hilar structure involvement, and bleeding (one case each, 1%). Table 3 summarizes the results of univariable logistic regression analyses evaluating the association between preoperative patient and tumor characteristics and the outcomes of conversion from PN to RN, and postoperative complications. Patients with a larger tumor were more likely to undergo conversion from PN to RN (OR 1.55, 95% CI 1.12, 2.16, p=0.008). Univariable linear regression analyses evaluating the association between similar patient and tumor characteristics and the outcomes of EBL and length of hospitalization, found high R.E.N.A.L. nephrometry scores (10–12) were associated with increased EBL (p=0.006). However, the significance of these findings is limited due to multiple hypothesis testing.

The number of tumors on final pathology ranged from two to 17. The most common index tumor histology was clear cell RCC in 48/123 patients (39%), followed by papillary RCC in 29/123 patients (24%). Malignant concordance was observed in 63/103 patients with at least one malignant tumor (61%). Only 21/60 patients with at least one benign tumor (35%) had benign concordance. Histologic concordance was apparent in 60/123 patients (49%), and histologic discordance in 63/123 patients (51%).

In total, seven patients had RCC recurrence (five distant, one contralateral kidney, and one local) and 19 patients died, three of whom died of RCC. Median follow-up was four years for those who did not experience recurrence or die. All three patients who died of RCC had

undergone RN. Five year RFS were 98% (95% CI 84%, 100%) and 85% (95% CI 66%, 93%) for PN and RN, respectively. While RN patients had worse tumor features, we were unable to adjust for these factors, nor compare the two groups, because only six RN and one PN patient experienced disease recurrence. Five-year OS were 96% (95% CI 84%–99%) and 86% (95% CI 68%–94%) for PN and RN, respectively (p=0.5). Five-year estimated rates of survival without CKD upstaging were 74% (95% CI 58%–85%) for PN and 55% (95% CI 37%–70%) for RN (p=0.11). Kaplan-Meier curves of RFS in patients with at least one malignant tumor, OS, and survival without CKD upstaging in patients undergoing PN are shown in Figure 1.

Comment

RN has traditionally been used to treat patients with unilateral multifocal renal tumors as long as the contralateral kidney was normal.[2,3] Recent studies suggest PN may be performed for multifocal renal tumors with acceptable oncologic outcomes and preservation of renal function. In the current study, evaluating PN and RN for unilateral multifocal renal tumors detected on preoperative imaging or during surgery, PN was associated with a low recurrence rate, most likely due to careful surgical case selection for patients with more favorable tumor characteristics. Furthermore, while there were no significant differences in the rate of diabetes mellitus and hypertension between the PN and RN groups, fewer PN patients had a worsening of their CKD status, with the 5-year probability of freedom from CKD upstaging being 74% for PN patients compared to 55% for RN patients; however, this difference was not statistically significant (p=0.11).

Occult multifocality, apparent only after pathologic review, comprised 56%–86% of tumors in earlier series.[1] Recent series reported a lower rate of occult multifocality (36%), consistent with the improvement in preoperative imaging.[1] In the current study, occult multifocality was apparent in 98/333 patients (29%), similar to recent reports. We chose to exclude this group of patients as these cases of occult multifocality were found incidentally, and therefore would not be subjected to the same preoperative planning and intraoperative decision-making as patients with multifocal disease identified at preoperative imaging or during surgery. Patients with known hereditary RCC syndromes were also excluded; however, patients with a negative family history may have been included in the cohort despite the presence of an unidentified hereditary syndrome. In most of these patients, PN should be delayed until the largest solid tumor measures 3cm in diameter, in order to preserve renal function, maximize time interval between PN, and minimize the risk of disease progression.[12]

Index tumors in patients with multifocal disease are most commonly conventional clear cell RCC; however the rate of tumor multifocality is higher among patients with papillary RCC.[13,14] While initial reports described a high histologic concordance rate of up to 74%, lower histologic concordance rates of 57%–59% were recently reported.[3–5,14] Similarly, previously reported malignant and benign concordance rates were 77% and 49%, respectively.[3] Consistent with previous reports, clear cell RCC was the most common index tumor in the present study; however, the tumor concordance rates were lower than previously reported. Even after excluding papillary adenomas, malignant, benign, and

histology concordance rates were 66%, 37%, and 57%, respectively, further emphasizing that a malignant or benign pathology in one renal mass does not accurately predict similar tumor characteristics of ipsilateral lesions.

The 5-year RFS, CSS, and OS rates in series reporting RN for multifocal renal tumors were 79.6%–97%, 74.0%–74.6% and 66.7%–75.2%, respectively.[13–15] Furthermore, OS, CSS, and RFS rates after RN for multifocal and unifocal renal masses were not significantly different.[13–16] Similar to previous reports, the 5-year RFS and OS for RN in the current series were 85% and 86%, respectively. In a previous report from our institution, a 7% conversion rate to RN was documented for patients who were scheduled for a PN to treat a solitary renal tumor.[17] In the current report we found a higher rate of conversion to RN (17/95, 18%) reflecting the surgical complexity of multiple PNs. An even higher conversion rate of 51% was documented in a previous series of unilateral multifocal tumors.[5] The relatively high rate of open RN in the current cohort may be attributed to patients converted from PN (16/39, 41%). Patients operated on during earlier years (7/39, 18%), and surgeon preference may have also added to this rate. Large index lesion size may be associated with a higher rate of conversion, however further studies are required to validate this association. While it is our practice to perform PN for stage T1 renal tumors whenever technically feasible, current findings underscore the importance of preoperative counseling on the risk of conversion to RN in patients scheduled for multiple unilateral PNs, especially in patients with large index lesions.

Since RN was found to be a significant risk factor for the development of CKD,[2] the role of PN has expanded, and it is currently the recommended treatment for stage T1 renal tumors whenever technically feasible.[18] Simhan et al. published the largest series of patients who underwent PN for the treatment of unilateral multifocal renal masses (n=76). After a median follow-up of 24 months, metastatic renal cancer developed in 3.9% of patients, and 7.9% had a metachronous renal recurrence, all of which were in the contralateral kidney. Three patients (3.9%) died during the study period, and only one death (1.3%), 4 years after PN, was attributed to RCC. None of these patients required conversion to RN. During follow-up, only three (3.9%) cases were upstaged from CKD stage III to stage IV. Eleven patients (14.5%) experienced eight minor (I/II) and seven major (III/IV) Clavien-Dindo classification graded postoperative complications.[3] Consistent with this report, in our series of 78 patients undergoing PN, similar rates of recurrence and OS were obtained (5-year RFS and OS of 98% and 96%, respectively), with no patients dying of their disease. In addition, blood loss was minor, especially for tumors with low R.E.N.A.L. nephrometry scores, and only 4% of PN patients experienced a Clavien-Dindo classification grade III/IV complication following the procedure. However, we did find a higher rate of CKD upstaging, which may be due to a different definition of CKD upstaging in the current study.

In a series reporting the outcome of both RN and PN for patients with multifocal ipsilateral tumors, Blute et al. observed favorable CSS in 16 patients treated with PN compared to 102 patients treated with RN. Estimated CSS rates at 5 years were 90.1% and 100% after RN and PN, respectively. Metachronous contralateral recurrence occurred in five patients after RN, compared to two patients who had local recurrence and one patient who had a metachronous contralateral recurrence following PN.[4] Krambeck et al. reported an update of

this series with a longer follow-up for 114 RN patients and 26 PN patients. After a median follow-up of 8 years for RN and 6 years for PN, disease recurrence was apparent in 9/114 RN patients (8%) and 3/26 PN patients (12%). Similar to the initial report, estimated 5-year CSS were 90.5% and 95.8% after RN and PN respectively; however these were not compared statistically due to a low number of patients and events.[5] Contrary to our initial expectations, we found lower RFS rates for patients who underwent RN compared to PN. In addition, PN was associated with shorter operating time and equivalent operative blood loss. However, patients who underwent RN tended to have worse tumor characteristics, including larger tumor diameters and higher pathological stages, which are associated with cancer recurrence, likely explaining these results. In addition, patients were more likely to undergo RN in earlier years, while in recent years, PN was performed more commonly. Unfortunately, we were unable to adjust for these factors due to a limited number of events. Clavien-Dindo classification grade III/IV complications occurred only in PN patients in the current study; however, their overall rate was low, and did not differ significantly than that of the RN group. The positive outcome of PN and relatively low complication rate, suggest that patients with few tumors, small tumor diameter, and low RENAL nephrometry scores (<10), who represent the majority of patients treated with PN in the current study, may successfully undergo PN.

The limitations of our study include its retrospective design with an apparent selection bias. Accordingly, patients treated with RN had less favorable tumor characteristics, leading to a higher recurrence rate despite the more extensive surgery. In addition, we were unable to perform multivariable analyses adjusting for patient and tumor characteristic due to the limited number of events in our cohort. Larger cohorts are necessary to compare the two procedures while adjusting for patient and tumor characteristics; however, this may require a multi-institutional study because of the uncommon nature of multifocal tumors. Nevertheless, the favorable outcome and low rate of recurrence in patients treated with PN supports the role of PN in treating carefully selected patients with synchronous unilateral multifocal RCC whenever technically feasible.

Conclusions

PN for the treatment of unilateral synchronous multifocal renal tumors with favorable characteristics was associated with a low recurrence rate, did not lead to a significantly higher postoperative complication rate, and preserved renal function for approximately 75% of patients at a 5-year follow-up. These findings suggest PN is an appropriate and effective management strategy for this carefully selected group of patients.

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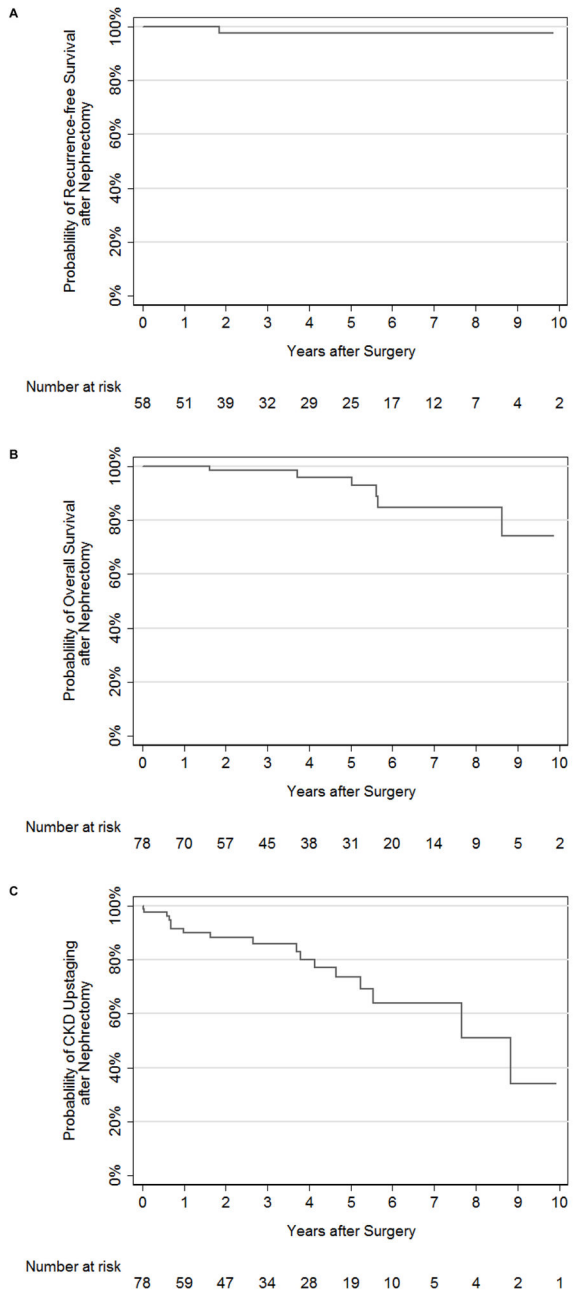

Figure 1.

Kaplan-Meier curves for (A) recurrence-free survival in patients with at least one malignant tumor, (B) overall survival, and (C) survival without chronic kidney disease upstaging, for patients who underwent partial nephrectomy.

Table 1

Patient and treatment characteristics (N=123). All values are median (interquartile range) or frequency (%).

	Partial Nephrectomy (n=78)	Radical Nephrectomy (n=45)	p-value
Age	64 (59–72)	64 (55–68)	0.3
Sex			
Female	33 (42%)	8 (18%)	0.005
Male	45 (58%)	37 (82%)	
Race			
White	72 (92%)	38 (84%)	0.4
Black	5 (6.4%)	6 (13%)	
Asian	1 (1.3%)	1 (2.2%)	
BMI	28.9 (25.3–31.6)	28.1 (26.0–32.4)	0.7
Diabetes	9 (12%)	7 (16%)	0.5
Hypertension	53 (68%)	35 (78%)	0.2
ASA			
I/II	41 (53%)	25 (56%)	0.7
III/IV	37 (47%)	20 (44%)	
Presentation			
Incidental	70 (90%)	33 (73%)	0.026
Local	7 (9.0%)	12 (27%)	
Systemic	1 (1.3%)	0 (0%)	
Smoking Status			
Never	45 (58%)	13 (29%)	0.006
Former	25 (32%)	21 (47%)	
Current	8 (10%)	11 (24%)	
Preoperative eGFR	60 (55–72)	67 (54–75)	0.073
Surgical Approach			
Open	69 (88%)	39 (87%)	0.8
Minimally Invasive	9 (12%)	6 (13%)	
Year of Surgery			
1995 – 2000	2 (2.6%)	9 (20%)	0.001
2001 – 2012	76 (97%)	36 (80%)	
Operating Time	157 (129–195)	185 (142–230)	0.035
Estimated Blood Loss (mL)	300 (200–500)	300 (200–600)	0.7
Length of Stay (days)	3 (2–4)	4 (3–5)	0.014
Highest Complication Grade (within 30 days of surgery)			
None	66 (84.5%)	36 (80%)	0.2
I/II	9 (11.5%)	9 (20%)	
III/IV	3 (4%)	0 (0%)	

Abbreviations: BMI = body mass index, ASA = American Society of Anesthesiologists, GFR =glomerular filtration rate

Table 2

Tumor Characteristics (N=123). All values are median (interquartile range) or frequency (%)

	Partial Nephrectomy (n=78)	Radical Nephrectomy (n=45)	p-value
Maximal Tumor Diameter (cm)	2.7 (2.0–4.0)	4.5 (3.0–5.7)	<0.0001
RENAL Nephrometry Score[a]			
4–6	27 (35%)	5 (11%)	0.0002
7–9	39 (50%)	19 (42%)	
10–12	12 (15%)	21 (47%)	
No. of tumors on imaging			
≤ 2	74 (95%)	37 (82%)	0.023
> 2	4 (5.1%)	8 (18%)	
No. of tumors on pathology			
≤ 2	58 (74%)	29 (64%)	0.2
> 2	20 (26%)	16 (36%)	
Index Tumor[b] **Histology**			
Clear Cell	27 (35%)	21 (47%)	0.03
Chromophobe	3 (3.8%)	6 (13%)	
Papillary	17 (22%)	12 (27%)	
Unclassified RCC	6 (7.7%)	1 (2.2%)	
Other Malignant	3 (3.8%)	2 (4.4%)	
Benign	22 (28%)	3 (6.7%)	
Pathological T Stage			
<= pT1B	69 (88%)	25 (56%)	0.0002
pT2	1 (1.3%)	2 (4.4%)	
pT3	8 (10%)	18 (40%)	
Pathological N Stage			
Nx/N0	78 (100%)	44 (98%)	0.8
N1	0 (0%)	1 (2%)	
Tumor Grade (Clear Cell)			
1	3 (11%)	0 (0%)	0.2
2	20 (74%)	14 (67%)	
3	4 (15%)	6 (29%)	
4	0 (0%)	1 (4.8%)	
Surgical Margin Status			
Negative	68 (87%)	42 (93%)	0.4
Positive	10 (13%)	3 (6.7%)	

[a] R.E.N.A.L. nephrometry score was calculated for the most complex tumor in the specific renal unit.

[b] The index tumor was defined as the largest tumor in the specific renal unit.

Table 3

Univariable logistic regression models of preoperative patient and tumor characteristics for the outcomes of conversion from partial nephrectomy to radical nephrectomy and complication events in patients who underwent partial nephrectomy

	Conversion from RN to PN (n=95)*		Complication events (n=78)	
	OR (95% CI)	p	OR (95% CI)	p
Age (per 10 years)	0.67 (0.41, 1.12)	0.13	1.74 (0.85, 3.55)	0.13
BMI	1.01 (0.90, 1.14)	0.8	0.89 (0.76, 1.04)	0.2
ASA (III/IV vs. I/II)	0.78 (0.27, 2.25)	0.6	4.07 (1.01, 16.43)	0.049
Preoperative eGFR	1.04 (1.00, 1.07)	0.034	0.96 (0.92, 1.01)	0.11
Maximum Tumor Diameter (cm)	1.55 (1.12, 2.16)	0.008	1.19 (0.76, 1.88)	0.4
No. of tumors on imaging (> 2 vs. ≤ 2)	3.96 (0.80, 19.68)	0.092	1.91 (0.18, 20.06)	0.6
RENAL Nephrometry Score		0.6		0.6
4–6	Ref.	-	Ref.	-
7–9	1.90 (0.55, 6.61)	-	1.45 (0.33, 6.40)	-
10–12	1.12 (0.18, 7.00)	-	2.67 (0.45, 15.72)	-

*Calculated for all 95 patients who were planned to undergo partial nephrectomy.

RN, radical nephrectomy; PN, partial nephrectomy; OR, odds ratio; BMI, body mass index; ASA, American Society of Anesthesiologists; eGFR, estimated glomerular filtration rate.