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PARTIAL NEPHRECTOMY FOR PRESUMED RENAL CELL CARCINOMA: INCIDENCE, PREDICTORS, AND PERIOPERATIVE OUTCOMES OF BENIGN LESIONS

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ABSTRACT

Background: The aim of this study was to investigate the incidence of benign histology after partial nephrectomy (PN) in patients with presumed malignancy from preoperative imaging. Further, preoperative predictors of benign lesions and perioperative outcomes were also assessed.

Methods: A series of patients undergoing PN for renal masses was identified using a prospectively maintained database. Patients were excluded for known genetic conditions, if more than one renal mass was resected, or if standard preoperative imaging was not suspicious for RCC. Differences in characteristics between patients with benign and malignant pathology were assessed.

Results: A total of 916 patients were identified that underwent PN between 2007-2015, including 129 (14.1%) patients with a final diagnosis of benign disease. The most common types of benign pathology were oncocytoma (n=66, 51.2%), angiomyolipoma (n=37, 28.7%), and complex cysts (n=10, 7.8%). Low BMI [0.96 (0.92-0.99) p=0.02], low R.E.N.A.L. score [0.86 (0.76-0.96) p=0.007], and low preoperative creatinine [0.37 (0.14-0.91) p=0.04] predicted benign histology in multivariate analysis. Tumor size was a significant predictor in additional modeling [0.81 (0.69-0.94) p=0.008].

Patients with benign histology had significantly shorter operative times (p<0.001) and less estimated blood loss (p<0.001), and there was no difference in complication (p=0.93) or blood transfusion (0.24) rates.

Conclusions: In the current study, the rate of benign pathology after PN for presumed RCC is 14.1%. BMI, R.E.N.A.L. score, and preoperative creatinine are predictive of benign histology, but the ability of different variables to predict benign lesions may be influenced by the distribution of benign tumor subtypes, reflecting potential unidentified selection bias.

INTRODUCTION

Over 62,000 new cases of kidney cancer are expected in 2016, representing approximately 4% of all new diagnosed malignancies [1]. Small, localized lesions represent the largest increase in renal cell carcinoma (RCC) incidence rate, and almost half of the new cases of RCC are localized tumors [2]. It is thought that increased utilization of imaging modalities is responsible for the increased incidental finding of small renal masses [2]. Multiple options with comparable oncological outcomes exist for management of these lesions, including both radical and partial nephrectomy (PN) [3], with PN being advantageous for most small lesions [4,5]. As a result, both American and European guidelines recommend nephron-sparing surgery as standard of care for patients with T1 masses that can feasibly be resected [5].

Improvements in preoperative imaging modalities have resulted in smaller lesions being detected, but these imaging techniques are often unable to distinguish benign lesions like oncocytoma or lipid-poor angiomyolipoma (AML) from RCC [6-8]. As with any surgical procedure, there is potential morbidity associated with PN [3]; in patients with lesions more likely to be benign, active surveillance may be more appropriate than PN. Few studies have investigated the incidence of benign lesions after PN [7,9-15]. Reported rates have been between 8.1%-32.6%, but the number of patients in many of these series is limited. Selected studies with >100 patients are summarized in **Supplemental Table 1**. There are few contemporary studies that investigate the benign pathology rate in larger

series of all patients undergoing PN for renal masses presumed to be RCC. Therefore, the purpose of this study was to investigate the incidence of benign renal lesions after PN in a single-center series of patients with presumed malignancy from preoperative imaging. Further, this study aims to investigate perioperative outcomes of patients undergoing PN and identify preoperative predictors of benign pathology.

METHODS

After approval by the Washington University Institutional Review Board, all patients undergoing partial nephrectomy between 2007 and 2015 were retrospectively identified using a consented, de-identified, prospectively maintained database. All patients were included in this study if pre-operative imaging was suspicious for malignancy, which was defined as solid enhancing masses or complicated renal cysts classified as Bosniak category III or IV [16]. For inclusion criteria for this study, all surgical events logged as "partial nephrectomy" were identified. Patient exclusion criteria included the following: von Hippel-Landau syndrome, tuberous sclerosis, Birt-Hogg-Dubé syndrome, resection of more than one renal mass, and preoperative imaging consistent with benign lesions (e.g. lipid-rich AML, excluded calyx). The final cohort of patients underwent a single PN for a solitary renal lesion with curative intent for presumed RCC.

Surgical technique

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Surgical approach was chosen based on history of abdominal surgery, patient habitus, tumor location, and surgeon and patient preference. Laparoscopic operations were performed using a transperitoneal or retroperitoneal approach with clamping of the renal vessels [17]. Open PN was chosen primarily for large, endophytic tumors, and was based on surgeon preference. Robotic-assisted partial nephrectomy (RAPN) operations were performed with a retroperitoneal or transperitoneal approach, as described previously [18]. Off-clamp technique was chosen based on tumor location, patient characteristics, and surgeon preference [19].

Biopsy Procedure and Specimen Evaluation

All biopsies were performed preoperatively in order to help better inform management decisions. Patients receiving anti-coagulants were instructed to discontinue their medication for an amount of time appropriate for the diminution of its effects prior to biopsy. Biopsies were performed by experienced abdominal radiologists and interventional radiologists. Ultrasound (US) guidance is preferred at our institution and was used for all masses that were detectable sonographically. Computed tomography (CT) guidance was reserved for masses not well-demonstrated by US. The number of biopsy cores taken was at the discretion of the radiologist. Immediate post-biopsy imaging with either US or CT was performed to assess for perinephric hematoma formation.

Data collection

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Staff data managers and physicians prospectively collected patient demographics, perioperative outcomes, and tumor characteristics. Preoperative CT or magnetic resonance imaging (MRI) was interpreted by fellowship-trained genitourinary radiologists before the time of surgery, and genitourinary pathologists were responsible for making the final diagnosis. Perioperative complications were defined using the Clavien grading system [20], and major complications were defined as Clavien grade III or IV. Renal biopsy data was queried using a prospectively maintained database, and all biopsies for unilateral renal masses between 2007-2015 were collected.

Statistical analysis

To analyze the association of preoperative variables with benign histology, chi-square analysis, Fisher's exact test, or Mann-Whitney U test were used. Multivariable modeling of predictors of benign histology was performed using logistic regression with the following variables: gender, age, nephrometry score, body mass index, and preoperative creatinine. Tumor size was not included in this multivariate model due to collinearity with the "R" term of R.E.N.A.L. However, a separate model was constructed which included all of the original covariates but included tumor size and excluded R.E.N.A.L. Differences in perioperative outcomes between benign and malignant tumors were assessed using chi-square analysis, Fisher's exact test, or Mann-Whitney U. All analysis was performed using R software (v3.1.3), and a two-tailed p-value <0.05 was considered significant in all analyses.

RESULTS

A total of 916 patients were identified that underwent partial nephrectomy at our institution from 2007-2015, including 59 patients with open procedures, 96 patients with laparoscopic operations, and 754 patients undergoing RAPN. Seven patients were classified as having open procedures after conversion from laparoscopic or robotic-assisted operations. The mean BMI of this patient cohort was 31.1, and the mean age was 57.5 years. Baseline patient demographics are further described in **Table 1**.

Of the 916 patients in this study, 129 (14.1%) patients revealed benign pathology upon final diagnosis (**Table 1**), including 66 (51.2%) patients with oncocytoma, 37 (28.7%) with angiomyolipoma (AML), 10 (7.8%) with complicated cysts, and 16 (12.4%) with miscellaneous other benign pathology. Other benign pathology included metanephric adenoma (4), simple cyst (3), heterotopic adrenal cortex (2), Castleman's disease (1), hemangioma (1), organizing hematoma (1), schwanomma (1), obstructive nephropathy (1), pseudocyst (1), and leimyoma (1). The rate of benign histology after PN specifically for masses ≤4 cm was 15.1%.

From 2007-2015, a total of 92 biopsies were performed of unilateral renal masses ≤10 cm, including 35 biopsies in masses ≤4 cm. Of the 92 patients undergoing biopsy, 10 (10.9%) patients had benign pathology upon biopsy. One patient with benign biopsy

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histology underwent partial nephrectomy, and operative histology confirmed benignity. The remaining 9 patients were managed conservatively.

The association of different preoperative variables with benign histology after surgery was then assessed in univariate analysis (**Table 2**). Compared to patients with a final diagnosis of malignancy, patients with benign histology had significantly lower BMIs (p=0.003), lower nephrometry scores (p=0.01), fewer comorbidities (p=0.04), smaller tumor sizes (p<0.001), and lower preoperative creatinine (p=0.04). Within the R.E.N.A.L. nephrometry scoring system, exophyticity (p<0.001) and a greater distance from the collecting system (p=0.005) were associated with benign pathology, while anterior/posterior location (p=0.31) and tumor relation to polar lines (p=0.14) were not associated. No difference was found between patients with benign and malignant tumors for the following variables: age at surgery, history of diabetes or hypertension, preoperative hemoglobin, and tumor laterality (p>0.05 for all). Female gender approached significance for benign pathology (p=0.053).

A multivariable model was constructed to investigate the independent predictive ability of each variable (**Table 3**). Low body mass index [0.96 (0.92-0.99) p=0.02], low R.E.N.A.L. score [0.86 (0.76-0.96) p=0.007], and low preoperative creatinine [0.37 (0.14-0.91) p=0.04] were independently predictive of benign histology after PN. In the second multivariate model including tumor size and not R.E.N.A.L., tumor size was a significant predictor of benign histology [0.81 (0.69-0.94) p=0.008].

Perioperative outcomes between patients with benign vs. malignant histology after PN were then evaluated (**Table 4**). A total of 17 (13.4%) patients with benign histology had perioperative complications, including 6 (4.7%) patients with Clavien grade III or IV complications (**Supplemental Table 2**). There was no difference in the rate of complications between patients with benign and malignant pathology (p=0.93). Similarly, both set of patients received perioperative blood transfusions at similar rates (p=0.24). Patients with benign histology had significantly shorter operative times (p<0.001) and less estimated blood loss (p<0.001) than patients with malignancy.

DISCUSSION

PN is the gold standard for management of renal masses ≤4 cm in healthy patients, and this is reflected in both American and European guidelines [5]. Renal masses are often found incidentally via imaging modalities [2], and previous groups have reported rates of benign histology after PN for these masses upwards of 30% [14]. Because most previous studies are limited by low patient numbers, the aim of this study was to investigate the rate of PN is a large series of PN patients over the span of 8 years. In this study, we found an incidence of benign lesions of 14.1% in patients undergoing PN for a solitary renal lesion, and an incidence of 15.1% in renal masses ≤4 cm.

The rates of benignity vary across studies, though the results herein are similar to those in most other large-scale reports. In two different series of Japanese patients, pathologic reports revealed benign findings after PN in 8.1% and 11% of patients [7,15]. A

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2004 report by Marszalek et al. found a benign rate of 32.6% in 129 patients. In 2006, a study of 143 patients with presumed malignant renal masses from preoperative imaging found that 16.1% of patients had benign histology [10]. In two recent studies, benign rates of 20-22% were found in lesions ≤4 cm [9,11]. Multicenter results on 873 patients from Mullins et al. are similar with a benign rate of 23.1% for all patients undergoing RAPN [21]. The present study is the largest series of patients to date to investigate the rate of benign histology after PN for patients specifically with presumed malignancy based on preoperative imaging, rather than the benign rate in all PN patients [21].

Despite advancements in radiologic protocols, distinguishing benign lesions with CT or MRI imaging is difficult, and previous studies have investigated whether other preoperative, clinical characteristics can predict benign histology after PN [9,15]. In 2010, Jeon et al. reported that female gender, age at surgery, and year of surgery were independently predictive of benign lesions [9]. Fujita et al. found similar results in 2014, with age, gender, and exophytic properties as significantly predictive [15]. Gender was also significant in a recent paper by Mullins et al., along with tumor complexity [21]. Interestingly, in the cohort of patients included in the present study, neither gender nor age was significantly associated with benign histology. R.E.N.A.L. score, tumor size, preoperative creatinine, and body mass index were the only characteristics independently associated with final histologic diagnosis in this study.

Because the clinical associations with benignity in our study differ from previous studies [9,15], we hypothesized that the reason for discrepancy was based upon the distribution of

benign lesion types between the studies. Indeed, 28.6% of benign masses in our cohort were classified as AML and 49.2% of lesions were oncocytoma, while Jeon et al. had a distribution of 43.2% AML and 13.6% oncocytoma [9], leading to a statistically significant difference in the distribution of benign lesions in our study vs. Jeon et al. ($p<0.0001$; data not shown). Given the known association of AML with middle-aged females [22], it is not surprising that age and gender predict benign pathology in a cohort of patients with high representation of AML.

Mullins et al. evaluated a multicenter series of 873 RAPNs [21]. The authors found a rate of benign lesions of 23.1% and that male gender and tumor complexity by RNS predicted malignancy. Although there are similarities in the described cohorts, our present work represents the findings of all patients undergoing any approach to PN at a single-institution, as opposed to those undergoing specifically RAPN. Moreover, the distribution of benign histology subtypes again differs. For example, the rate of benign cysts in the series by Mullins et al. was 15.8% of benign lesions, compared to 10.1% in the present study; AML was also represented at a higher rate in the report by Mullins et al. than our study ($p=0.053$; data not shown). The results of our single-center experience highlight differences in tumor histology subtypes that may reflect improved detection of lipid-poor AML by radiology and urology staff, leading to fewer surgeries for these patients, and a greater representation of oncocytoma in our cohort.

The differences in the series presented by Jeon et al, Mullins et al., and our present work suggest that models to predict benign histology may be biased by the distribution

of benign lesion subtypes within a population. It is therefore likely a result of an unrecognized selection bias. Strong collaboration with radiology may lead to better identification of certain types of benign lesions such as lipid-poor AML, thus skewing the final distribution of patients undergoing surgery. This presents a potential confounding bias in analysis that has previously been unidentified.

Surgery carries both inherent risk and significant cost, and reducing the number of operations for benign histology may diminish financial burden and the number of patients with complications of surgery. In this study, we investigated perioperative outcomes of patients undergoing PN for benign and malignant lesions. While operative times and blood loss were lower in patients with benign histology, there were similar rates of transfusions and complications between the groups. In particular, 17 (13.2%) patients with benign histology had perioperative complications, including six (4.7%) patients with Clavien grade 3 or 4 complications. The rate of complications for patients with benign lesions in this study is consistent with previous reports and similar to the complication rate for malignant lesions in our population.

The use of imaging and clinically based predictive models for benign histology has the potential to spare some patients from unnecessary operations and resultant complications. There is also provocative evidence that supports routine renal mass biopsies in patients with suspicious masses [23,24]. In patients with equivocal clinical and radiographic findings, renal biopsy may help distinguish benign from malignant histology. Previous authors have pronounced the utility of biopsy in guiding risk

stratification and management decisions, in many cases toward the avoidance of potentially unnecessary surgery (for benign tumors or indolent cancers) [24,25]. Osawa et al. reported on a series of 202 biopsied small renal masses. The authors described the assignment of 53 (26%) of those tumors to active surveillance rather than surgery, although 9/53 (17%) were ultimately determined to have been improperly assigned based on less favorable final pathology [26]. Furthermore, Halverson et al. found a concordance rate between biopsy and final pathology of 92% in a series of 151 tumors [24]. In addition to biopsy, other biomarkers have been shown to effectively discriminate between RCC (clear and papillary subtypes) and benign lesions, such as urinary biomarkers aquaporin 1 and perilipin 2 [27]. Ultimately, better prognostic models will need to be disease-specific (e.g. AML and oncocytoma) and potentially include a combination of clinical and radiographic parameters, as well as urinary biomarkers and biopsy pathology. Such models may help reduce the number of patients undergoing unnecessary PN for benign lesions.

Potential selection bias is a limitation of this study due to the retrospective design. The indications for elective PN at our institution are similar to the indications reported by other institutions. However, it is possible that patients with small renal masses, elevated creatinine, and higher BMIs were considered more preferentially for preoperative biopsy, active surveillance, or image-guided ablation. Renal biopsy can influence management decisions, and in our practice, only 10% of patients with a benign biopsy underwent partial nephrectomy. However, given the overall low number of patients biopsied relative to the total number of partial nephrectomies performed, it is unlikely

that renal biopsy pathology significantly affected the results and conclusions herein. Patient preferences and perceptions regarding the characterization and treatment of their renal mass also add to the selection bias in this population. Our dataset does not delineate such potential management decisions.

CONCLUSIONS

The rate of benign pathology after PN for presumed RCC is 14.1% in all patients and 15.1% in patients with renal masses ≤4 cm. Patients with benign lesions have favorable perioperative outcomes for blood loss and operative time. Body mass index, R.E.N.A.L. score, and preoperative creatinine are predictive of benign histology, potentially reflecting an undetected selection bias. However, the ability of different variables to predict benign lesions may be influenced by the distribution of benign tumor subtypes.

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RCC = renal cell carcinoma
PN = partial nephrectomy
AML = angiomyolipoma
RAPN = robotic-assisted partial nephrectomy
CT = computed tomography
MRI = magnetic resonance imaging
BMI = body mass index
US = ultrasound

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Table 1: Demographics of patients undergoing partial nephrectomy for presumed RCC

Characteristic	*N* (%)
Type of partial nephrectomy	
Open	59 (6.4%)
Laparoscopic	96 (10.5%)
RAPN	754 (82.3%)
Laparoscopic converted to open	1 (0.1%)
RAPN converted to open	6 (0.7%)
History of diabetes	
No	634 (76.7%)
Yes	193 (23.3%)
Unavailable	89
History of hypertension	
No	305 (36.9%)
Yes	522 (63.1%)
Unavailable	89
Tumor laterality	
Left	439 (47.9%)
Right	477 (52.1%)
Perioperative complications	
No complications	728 (86.9%)
Complications	110 (13.1%)
Unavailable	78
Perioperative blood transfusion	
No transfusion	799 (95.0%)
Perioperative transfusion	42 (5.0%)
Unavailable	75
Charlson Comorbidity Index	
0	414 (50.1%)
1	177 (21.4%)
2	113 (13.7%)
≥3	123 (14.9%)
Unavailable	89
Tumor histology	
Benign	129 (14.1%)
Malignant	787 (85.9%)
Histology in tumors ≤4cm	
Benign	110 (15.1%)
Malignant	620 (84.9%)
Age at surgery (years), mean (±SD) (n=916)	57.5 (±12.1)
Body mass index, mean (±SD) (n=882)	31.1 (±7.1)
R.E.N.A.L. score, mean (±SD) (n=678)	7.6 (±1.9)
Radiographic tumor size (cm), *n*, mean (±SD)	911, 3.1 (±1.6)
Preoperative hemoglobin (g/dL), *n*, mean (±SD)	776, 13.8 (1.6)
Preoperative creatinine (mg/dL), *n*, mean (±SD)	833, 0.94 (0.35)

Abbreviations: renal cell carcinoma (RCC), robot-assisted partial nephrectomy (RAPN)

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Table 2: Univariable analysis of preoperative predictors of benign kidney histology

Characteristic	Benign (n=129)	Malignant (n=787)	p-value
Age at surgery (years), mean (±SD)	59.0 (±11.8)	57.3 (±12.2)	0.15
Body mass index, mean (±SD)	29.4 (±5.6)	31.4 (±7.3)	0.003
Gender, *n* (%)			0.053
Female	66 (51.2)	331 (42.1)	
Male	63 (48.8)	456 (57.9)	
History of diabetes, *n* (%)			0.07
No	107 (82.9)	527 (75.5)	
Yes	22 (17.1)	171 (24.5)	
Missing data	0	89	
History of hypertension, *n* (%)			0.90
No	47 (36.4)	259 (37.0)	
Yes	82 (63.6)	440 (63.0)	
Missing data	0	88	
Charlson comorbidity index, *n* (%)			0.04
0	76 (58.9)	338 (48.4)	
1	28 (21.7)	149 (21.3)	
2	15 (11.6)	98 (14.0)	
>=3	10 (7.8)	113 (16.2)	
Missing data	0	89	
R.E.N.A.L. score, mean (±SD)	7.1 (±2.0)	7.7 (±1.8)	0.01
Radiographic tumor size (cm), mean (±SD)	2.7 (±1.5)	3.2 (±1.6)	<0.001
Tumor location relative to polar lines, *n* (%)			0.14
Entirely above/below	40 (40.0)	163 (30.0)	
Crosses polar lines	30 (30.0)	188 (34.6)	
>50% over polar lines	30 (30.0)	193 (35.5)	
Missing data	29	243	
Nearness to collecting system, *n* (%)			
>=7	30 (30.0)	103 (18.9)	0.005
4-7	23 (23.0)	92 (16.9)	
<=4	47 (47.0)	349 (64.2)	
Missing data	29	243	
Exophyticity, *n* (%)			<0.001
>=50%	45 (45.0)	141 (25.9)	
<50%	35 (35.0)	312 (57.4)	
Endophytic	20 (20.0)	91 (16.7)	
Missing data	29	243	
Anterior/posterior location, *n* (%)			0.31
Anterior	46 (40.4)	205 (33.6)	
Posterior	33 (28.9)	214 (35.1)	
Neither	35 (30.7)	191 (31.3)	
Missing data	15	177	
Tumor laterality, *n* (%)			0.82
Left	63 (48.8)	376 (47.8)	
Right	66 (51.2)	411 (52.2)	
Preoperative creatinine (mg/dL), mean (±SD)	0.88 (±0.30)	0.96 (±0.37)	0.04
Preoperative hemoglobin (g/dL), mean (±SD)	13.6 (±1.5)	13.9 (±1.6)	0.10

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Table 3: Multivariable analysis of preoperative predictors of benign kidney histology

Characteristic	Odds ratio [95% CI]	p-value
Gender (ref=female)	0.98 [0.61-1.56]	0.92
Age at surgery (per yr.)	1.02 [1.00-1.04]	0.08
R.E.N.A.L. score (per unit)	0.86 [0.76-0.96]	0.007
Body mass index (per unit)	0.96 [0.92-0.99]	0.02
Preop. creatinine (per 1.0 mg/dL)	0.35 [0.13-0.85]	0.03

Table 4: Perioperative outcomes of patients with benign and malignant kidney histology after PN

Characteristic	Benign	Malignant	p-value
Perioperative complications, *n* (%)			0.93
No complications	110 (86.6)	618 (86.9)	
Complications	17 (13.4)	93 (13.1)	
Missing data	2	76	
Blood transfusion rate, *n* (%)			0.24
No perioperative BT	118 (92.9)	681 (95.4)	
Perioperative BT	9 (7.1)	33 (4.6)	
Missing data	0	75	
Operative time (min), mean (±SD)	146.9 (±51.8)	165.6 (±54.5)	<0.001
Estimated blood loss (ml), mean (±SD)	158 (±233)	223 (±284)	<0.001

Abbreviations: partial nephrectomy (PN), blood transfusion (BT)

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Supplemental Table 1: Reports rates of benign lesions in recent large series of patients undergoing partial nephrectomy

Author	Year	Renal Masses N	Benign Masses n, % total	AML n, % total	Oncocytoma n, % total	Cyst n, % total	Other n, % total
Fujii et al.	2008	176	19 (11%)	10 (5.7%)	5 (2.8%)	2 (1.1%)	1 (0.6%)
Jeon et al.	2010	376	81 (21.5%)	35 (9.3%)	11 (2.9%)	26 (6.9%)	9 (2.4%)
Kutikov et al.	2006	143	23 (16.1%)	10 (7.0%)	8 (5.6%)	3 (2.1%)	1 (0.7%)
Pederson et al.	2014	151	23 (15.2%)	7 (4.6%)	12 (7.9%)	NR	4 (2.6%)
McKiernan et al.	2002	291	64 (22.0%)	12 (4.1%)	31 (10.7%)	14 (4.8%)	7 (2.4%)
Pahernik et al.	2006	504	123 (24.4%)	33 (6.5%)	53 (10.5%)	23 (4.6%)	13 (2.8%)
Marszalek et al.	2004	129	42 (32.6%)	7 (5.5%)	10 (7.8%)	18 (13.9%)	7 (5.4%)
Fujita et al.	2014	149	12 (8.1%)	5 (3.4%)	5 (3.4%)	0 (0%)	2 (1.3%)

Abbreviations: NR = not reported , AML = angiomyolipoma

Supplemental Table 2: Postoperative complications of patients undergoing partial nephrectomy with a final diagnosis of benign pathology

Clavien Grade	n (%)	Complications
Clavien I	3 (17.6)	fever (1), urinary retention (2)
Clavien II	7 (41.2)	blood transfusion (2), hypertensive crisis (1), deep vein thrombosis (1), fever (1), atrial fibrillation (1), pulmonary embolism (1), shortness of breath (1)
Clavien III	6 (35.3)	pseudoaneurysm (5), reintubation due to hypoxia (1), acute kidney failure (1)
Clavien IV	1 (5.9)	myocardial infarction (1), hematoma (1)