Cystic renal cell carcinoma: a report on outcomes of surgery and active surveillance in patients retrospectively identified on pretreatment imaging

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Abstract

Purpose—To evaluate the outcomes of surgical intervention and active surveillance in patients diagnosed with cystic renal cell carcinoma at our hypothesized radiologic cutoff of >50% cystic.

Materials and Methods—We identified all patients with a pathologically confirmed cystic renal mass that fit our criteria from 2000 to 2015 (n=430). Patients with lack of CT imaging, tumors <50% cystic on imaging, multifocal tumors and prior renal cell carcinoma were excluded (n=292). Patients were stratified into benign or malignant subgroups, and radiologic, clinicopathologic and oncologic features were obtained. Univariate and multivariate associations between clinicoradiologic parameters in each group were analyzed. A separate cohort of patients managed by active surveillance for cystic renal cell carcinoma was similarly reviewed.

Results—Of the 138 cases of cystic renal cell carcinoma cases identified, 102 (73.9%) were renal cell carcinoma and 36 (26.1%) benign masses. Most tumors were Fuhrman grade 1–2 (77.5%), pT2 stage (83.4%) and clear cell histology (65.9%). On univariate analysis, male gender, a solid component and increasing Bosniak classification were significant for malignancy. In a separate cohort, we identified 38 patients on active surveillance. Growth rate was found to be 1.0 mm/year overall and 2.3 mm/year for the solid component. After a median follow-up of >4 years for all cohorts, there was no evidence of recurrence or metastasis from cystic renal cell carcinoma.

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Conclusions—Patients with unifocal cystic renal cell carcinoma evaluated using a standardized radiologic threshold of >50% cystic have an excellent prognosis on both active surveillance and following surgical resection.

Keywords

Carcinoma; Renal Cell; Cysts; Nephrectomy; Watchful Waiting

Introduction

Complex-cystic renal masses have long posed a challenge to clinicians, as they represent a heterogenous group of entities, both benign and malignant, that share overlapping clinical and radiologic features. Presently, the CT-based Bosniak classification system remains the gold standard utilized to predict malignancy risk in cystic renal masses and guides management and counseling [1]. However, strict adherence to the Bosniak score in the absence of other diagnostic tools may lead to the surgical overtreatment of many cystic lesions[2]. Emerging evidence has suggested AS as an acceptable initial management strategy in this population [2–5], thus improved imaging criteria are required to help guide treatment algorithms in cystic renal masses and allow for increased implementation of AS protocols.

Historically, cRCC has been used to describe an indolent version of RCC composed predominantly of cysts [6]. The threshold of cystic involvement used to define cRCC has traditionally been >75% cystic on pathologic review[7], however this classification provides no contribution to preoperative decision-making. Cross-sectional imaging provides the benefit of assessing tumor morphology without surgical manipulation, allowing for an accurate assessment of the solid and cystic components and classification of cRCC [3, 8]. Recent studies have evaluated radiologic criteria for cRCC diagnosis, suggesting cystic changes in 5–45% of the total mass on imaging to be associated with favorable survival [3, 8]. Given the improved prognostic value that this cystic component yields [8, 9], a consistent and more inclusive classification of cRCC is essential.

Therefore, we aim to advance the preoperative assessment of cystic renal masses by evaluating cRCC as an enhancing renal lesion that is >50% cystic on cross-sectional imaging. We propose that this classification, a simple approach that can be easily be adapted into clinical practice, may yield an improved risk profile allowing for conservative management in the carefully selected patient. The objective of our study is to compare the long-term outcomes of surgery and AS in patients with cRCC using this hypothesized threshold, and to identify any clinicoradiologic parameters that may further predict malignancy risk.

Materials and Methods

Cohorts

After institutional review board approval, all patients who underwent surgery for a renal mass from January 2000 to December 2015 (n=5003) were queried from a prospectively maintained institutional database. All masses that contained a cystic component on final

pathology were identified (n=430). From this cohort we identified 138 cases that met our inclusion criteria (Figure 1).

A separate cohort of 72 complex-cystic masses initially managed by AS from January 2000 to December 2015 was also identified. AS protocols consisted of initial cross-sectional imaging followed by US every 6 months for the first year with annual US studies used thereafter if no growth was present. US studies were included as a part of our follow-up protocol but not for our radiologic assessment. Our final AS cohort consisted of 38 cases (Figure 1). Core biopsies were not utilized given that they are known to have a low diagnostic yield in cystic renal masses [10].

Radiologic review

CT imaging was re-reviewed by one of three genitourinary radiologists (AH, CD, OA), who were blinded to clinical and pathologic characteristics. The solid component of the entire tumor was measured and visually graded into four groups: none, <25%, 25–50% or >50%. Additional imaging characteristics were also recorded, such as the Bosniak classification, maximal diameter (cm), tumor location (>50% exophytic, <50% exophytic, endophytic) and the presence of calcifications (yes/no), septations (yes/no), and other cysts (yes/no).

In our AS cohort, we evaluated the growth rate of the entire lesion calculated by maximal diameter in the first and last CT scan when available. In those patients with a measurable solid component, growth rate of the solid component was also calculated.

Outcomes

Clinical, surgical, radiologic, pathologic [11], and post-operative outcomes were analyzed. Based on final pathology, patients were stratified into either a RCC or benign tumor subgroup. The benign subgroup consisted of mixed epithelial and stromal tumor family, benign multilocular cysts and multilocular cystic renal neoplasm of low malignant potential. In a subset of patients with Bosniak 3 and 4 lesions, associations between the solid component percentage and malignancy risk were similarly assessed. Follow-up was based on last available CT.

Statistical analysis

Univariate analyses of clinical, radiologic and pathologic parameters were evaluated using Fisher's exact test and student's *t*-test. For multivariate analysis, we fitted a logistic model with 5 covariates (sex, Bosniak classification, solid component, solid percentage, calcifications) that we found to be significant in our univariate analysis. Survival analyses were done by constructing Kaplan-Meier curves and log-rank tests. The pre-rejection threshold for all statistical tests was predefined at 0.05. All analyses were performed with the R platform.

Results

Clinicopathologic features

Clinicopathologic and surgical characteristics of our initial cohort of 138 cRCC cases are summarized in Table 1. On pathologic review, 102 (73.9%) were RCC and 36 (26.1%) were benign tumor subtypes. The majority had less aggressive features, presenting with Fuhrman grade 1–2 (77.5%) and pT2 stage (83.4%). Our cohort also had various histopathologic subtypes, with ccRCC (65.9%) being the most common followed by tumors of benign etiology (26.1%). When comparing gender between subgroups, we found that males were more likely to have cystic masses with malignant histology (p=0.006). At a median of follow-up of 5.4 years (IQR 2.8–7.8), there was no evidence of tumor recurrence or metastasis from cRCC. A total of 7 (5.1%) patients died from other causes.

Radiologic and pathologic features

On imaging re-review, the median overall maximal tumor size preoperatively was 3.3 cm (IQR 2.2–4.7). Most cRCC lesions were Bosniak 3 and 4 (93.5%) with a solid component of <25% (83.3%). Figure 2 depicts representative imaging.

Table 2 summarizes the associations of radiologic features between RCC and benign tumor subgroups. The presence of any solid component on imaging (p=0.01), solid component percentage (p=0.01), median solid component size (p=0.004) and calcifications (p=0.02) were all found to be significant between the two subgroups.

On multivariate analysis, we found males to have a significantly higher risk of having malignant disease (p=0.007) and that Bosniak 3 lesions were more likely to be malignant (p=0.01). Although Bosniak 4 lesions also showed an increased malignancy risk, this did not reach statistical significance in our multivariate model (p=0.29).

Bosniak 3 and 4

In a subset of patients with Bosniak 3 and 4 lesions (Table 3), we found no significant difference between the RCC and benign tumor subgroups when comparing the solid component percentage (p=0.12). Even when comparing these differences in Bosniak 3 and 4 lesions individually, we still found no significant difference between the 2 groups (p=0.25 and p=0.71, respectively).

Active surveillance cohort

Overall, 27 (71.1%) remained on AS and 11 (28.9%) went on to receive surgery, of which all underwent partial nephrectomy. The median overall growth rate was 1.0 mm/year (IQR 0–2.8) over 25.3 months (IQR 16.3–44.8). In 15 (39.5%) lesions with a solid component, the growth rate of the solid portion was 2.3 mm/year (IQR 0.3–4.9). In patients who either remained on AS or ultimately underwent surgery, there was no evidence of recurrence or metastasis from cRCC at a median follow-up of 4.3 years (IQR 2.1–5.7) from first imaging diagnosis or 6.9 years (IQR 4.9–8.5) after surgery, respectively. A total of 8 (21.1%) patients died from other causes.

Of the AS cases that underwent delayed surgical intervention, AS was initially chosen due to favorable tumor characteristics on imaging (63.6%) or significant medical comorbidities (54.5%). A change in tumor character (45.4%) and patient preference to no longer remain on AS (18.2%) were noted indications for surgery. On imaging, most lesions were Bosniak 4 (63.6%) with the presence of a solid component (54.5%). On pathologic review, the majority were ccRCC (63.6%), pT1 stage (54.5%) and Fuhrman grade ≤ 2 (63.6%).

Surgery vs. active surveillance cohort

Table 4 summarizes the associations of clinicoradiologic features between patients initially managed with surgery and AS. The median age at diagnosis was significantly higher in the AS subgroup (p=<0.0001). Bosniak classification (p=<0.0001), solid component percentage (p=0.01) and median solid component size (p=0.004) were also found to be significantly different between the subgroups, however median overall tumor size was not (p=0.59).

When comparing patients who initially underwent surgery with those who were initially managed with AS followed by surgery, we found no significant difference between the proportion of tumors with malignant histology (p=0.9). Furthermore, when looking at overall-survival between the same subgroups, we also found no significant difference (p=0.07). Overall, no patients in our entire cohort died of kidney cancer.

Discussion

In this study, we evaluated cRCC as a radiologically distinct subtype of RCC defined by an enhancing renal mass that is >50% cystic on cross-sectional imaging. At this hypothesized threshold, we found that a solitary cRCC lesion in patients with no prior history of RCC has an excellent prognosis on both AS and following surgical resection.

The excellent prognosis of patients with cRCC compared to ccRCC has been recognized in several previous reports, showing that they present with less aggressive pathologic features and have minimal risk of recurrence or metastasis following surgery [3, 9]. Our study consisted of 5 (3%) patients with pT3 disease, like a recent study reporting pT3 disease in 4% of their cohort [12]. Even at higher stage and grade, patients with cRCC have been shown to have better outcomes compared to ccRCC [12]. Given that these lesions are predominantly cystic, the solid portions of these tumors are often significantly smaller than the size of the entire lesion [3, 8]. The median overall tumor size for cRCC cases in our cohort was 3.3 cm, whereas the median solid component size was 0.8 cm. The solid portion is thought to contain the malignant components of these lesions, thus the tumor burden is often significantly less than other tumors of similar size [3, 8].

Similar to other reports, ccRCC was the most common histology in our cohort followed by tumors of benign etiology [3, 13]. Additionally, no patients presented with chromophobe RCC [3, 8]; however, two (1.6%) patients were diagnosed with unclassified RCC, which has not been documented previously in the literature. It has been well established that differentiation of benign and malignant complex-cystic masses by current imaging techniques is difficult, thus any radiologic definition for cRCC will also ultimately include benign tumors and other RCC subtypes.

In a recent study investigating the pathologic and radiologic correlates of complex renal cysts, the authors found that the likelihood of malignancy increased with a rising Bosniak score and the presence of mural nodules [14]. We found a similar trend in our cohort. In addition, we also found that females with cRCC lesions were more likely to have benign pathology (p=0.006), which remained true in our multivariate model (p=0.007). Female gender is associated with a higher probability of benign renal neoplasms overall [15], thus gender may need to be implemented into future diagnostic protocols for cRCC. However, further analyses need to be conducted.

Although it is well established that Bosniak 4 lesions have an increased malignancy risk compared to Bosniak 3 [2], a Bosniak 4 classification did not reach statistical significance in our multivariate model. We attribute this discordant finding to the overlap between the defining criteria of Bosniak 4 lesions[2] and covariates which indicate the presence of a solid component on imaging. Since one of the main criteria to categorize a mass as Bosniak 4 is the evidence of a solid component [1, 2], adding this covariate to the multivariate model results in an overlap of cases and a consequent loss of the association between Bosniak score and malignancy.

In a recent study assessing preoperative growth in cystic renal lesions, the authors found that most tumors (73%) did not show a significant increase in size [13]. In a similar analysis of our AS cohort, we found the median overall growth rate to be 1.0 mm/year. This compared to a mean growth rate of 2.8 mm/year in a meta-analysis of patients with solid renal tumors on AS [16]. Although we also noted the solid portion growth rate to be 2.3 mm/year, this was only in 15 (39.5%) patients and may not be enough to appropriately quantify growth. Given the slow growth rate of cRCC lesions and their more indolent nature, radiologic diagnosis of cRCC allows for AS to be more confidently discussed with appropriately selected patients.

In patients undergoing surgery for a solitary Bosniak 3 or 4 cRCC lesion, partial nephrectomy is recommended when technically feasible[4]. Similarly, most patients in our study underwent partial nephrectomy (90%). Current post-operative surveillance guidelines for RCC are predicated on pathologic TNM staging [11], with more intensive surveillance recommended for high stage disease [17–19]. With the improved outcomes that have been demonstrated in patients with cRCC [3, 9], follow-up care could be optimized and less frequent and aggressive observation could be recommended following surgery with reliance on simple chest imaging and renal US. This could potentially lower health care costs and reduce patient anxiety.

Although most patients with Bosniak 3 and 4 complex-cystic renal masses undergo surgery, AS can be an acceptable initial approach [4]. Recent guidelines on the management of localized renal cancer state that AS can be initially implemented in patients with Bosniak 3 and 4 complex-cystic lesions who have a limited life expectancy, are at higher risk for surgical complications, or have favorable tumor characteristics on imaging [4, 20]. Our data showed that management initially by AS followed by surgery had no difference in either the proportion of malignancy or overall-survival compared to patients initially managed with surgery. Given that cRCC lesions have a smaller overall size, smaller solid component and

lower oncologic risk compared to similar RCC masses, initial AS strategies should be considered [9].

There are several limitations to our study, including its retrospective design, limited follow-up and relatively small cohort. We chose to exclude patients with a history of RCC or other renal lesions to focus exclusively on solitary cystic masses. The cutoff we implemented of >50% cystic on imaging was hypothesis generated and will need to be validated in independent cohorts. We were not able to assess growth rate in our original cRCC cohort given that the majority did not have 2 preoperative CT scans available. In addition, given that patients on AS for cystic renal masses will often be followed with serial US instead of CT, we could only assess growth rate and radiologic characteristics from last available CT. We also could not comment on the incidence of these lesions given that we identified our cohort on retrospective pathology review initially followed by radiologic review, therefore any lesion that did not contain a cystic portion on pathology would not have been included.

Conclusions

Our data suggests that patients with unifocal cRCC evaluated using a standardized radiologic threshold of >50% cystic have an excellent prognosis on both AS and following surgery. In patients with serial imaging, we also noted a similar interval growth rate of cRCC lesions compared to solid renal tumors. We believe that our radiologic definition allows for more inclusive criteria of cRCC and would encourage kidney sparing approaches or implementation of AS protocols when feasible.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations and Acronyms

AS	active surveillance
ccRCC	clear cell renal cell carcinoma
cRCC	cystic renal cell carcinoma
CT	computerized tomography
IQR	interquartile range
RCC	renal cell carcinoma
US	ultrasound

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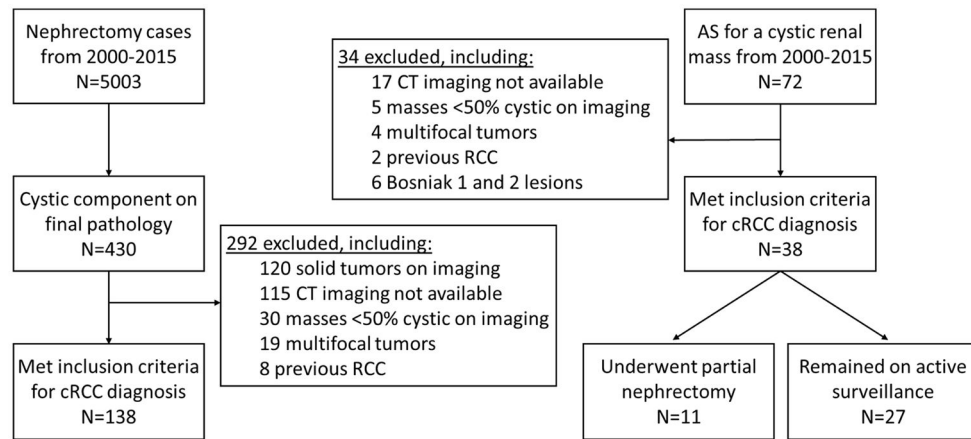
Figure 1.
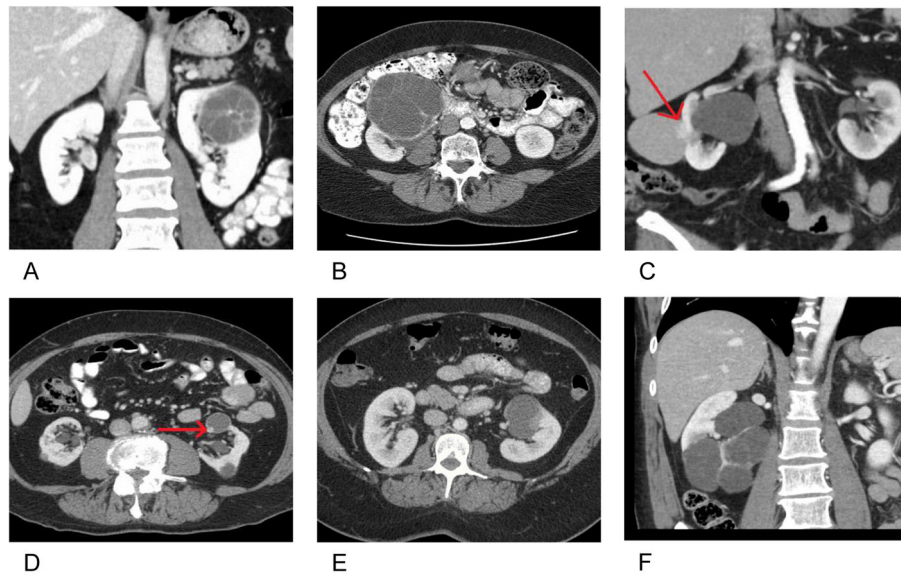Summary of our study cohort and flow chart of exclusion criteria

Figure 2. Radiologic representation of cRCC in various histologic subtypes
A) Clear cell renal cell carcinoma (RCC), B) Multilocular cystic renal cell neoplasm of low malignant potential, C) Papillary RCC, D) Clear cell papillary RCC, E) Unclassified RCC and F) Benign tumor subtype

Table 1

Clinicopathologic and surgical *characteristics of cRCC patients in our surgical cohort*

No. gender (%)	
Male	78 (57)
Female	60 (43)
No. race (%)	
White	132 (96)
Black	2 (1)
Asian	4 (3)
Median age at surgery, years (IQR)	54.1 (45.5–63.9)
No. surgical technique (%)	
Partial	122 (88.4)
Radical	16 (11.6)
Open	113 (81.9)
Laparoscopic	10 (7.2)
Robotic	15 (10.9)
No. presenting symptom (%)	
Incidental, asymptomatic	122 (88.4)
Local	16 (11.6)
No. histologic subtype (%)	
Clear cell renal cell carcinoma	91 (65.9)
Multilocular cystic renal cell neoplasm of low malignant potential	18 (13)
Benign multilocular cyst	16 (11.6)
Papillary renal cell carcinoma	5 (3.6)
Clear cell capillary renal cell carcinoma	4 (2.9)
Unclassified renal cell carcinoma	2 (1.4)
Mixed epithelial and stromal tumor family	2 (1.4)
No. Fuhrman grade (%)	
1	22 (15.9)
2	85 (61.6)
3	9 (6.5)
NA	22 (15.9)
No. pathologic stage (%)	
pT1a	97 (70.3)
pT1b	15 (10.9)
pT2a	3 (2.2)
pT3a	4 (2.9)
pT3b	1 (0.7)

Table 2

Comparison of clinical, surgical and radiologic characteristics between pathologically confirmed renal cell carcinoma and benign tumor subtypes in our surgical cohort

	Renal Cell Carcinoma n=102	Benign Tumors[*] n=36	*P*-value
No. sex (%)			
Male	65 (64)	13 (36)	0.006
Female	37 (36)	23 (64)	
No. race (%)			
White	98 (96)	34 (94)	0.77
Black	1 (1)	1 (3)	
Asian	3 (3)	1 (3)	
No. presenting symptom (%)			
Incidental, asymptomatic	88 (86.3)	34 (94.4)	0.24
Local	14 (13.7)	2 (5.6)	
Median age at surgery (IQR)	53.6 (44.9–63.7)	55.6 (46.7–64.6)	0.50
No. surgical technique (%)			
Partial	91 (89.2)	31 (86.1)	0.76
Radical	11 (10.8)	5 (13.9)	
Open	84 (82.4)	29 (80.6)	0.93
Laparoscopic	7 (6.9)	3 (8.3)	
Robotic	11 (10.8)	4 (11.1)	
Median radiologic tumor size, cm (IQR)	3.3 (2.3–4.7)	2.9 (2.0–4.9)	0.39
No. solid component (%)			
Yes	58 (56.9)	11 (30.6)	0.01
No	44 (43.1)	25 (69.4)	
No. solid component (%)			
25–50%	18 (17.6)	5 (13.9)	0.01
<25%	40 (39.2)	6 (16.7)	
No measurable solid component	44 (43.1)	25 (69.4)	
Median solid component size, cm (IQR)	0.8 (0.6–1.2)	0.6 (0.5–0.9)	0.004
No. Bosniak Classification (%)			
4	49 (48)	10 (27.8)	<0.0001
3	52 (51)	18 (50)	
2F	1 (1)	8 (22.2)	
No. tumor location (%)			
>50% Exophytic	80 (78.4)	26 (72.2)	0.44
<50% Exophytic	7 (6.9)	5 (13.9)	
Endophytic	15 (14.7)	5 (13.9)	
No. presence of calcifications (%)			

	Renal Cell Carcinoma n=102	Benign Tumors[*] n=36	*P*-value
Yes	17 (16.7)	13 (36.1)	0.02
No	85 (83.3)	23 (63.9)	
No. presence of septations (%)			
Yes	92 (90.2)	31 (86.1)	0.54
No	10 (9.8)	5 (13.9)	
No. presence of other cysts (%)			
Yes	57 (55.9)	19 (52.8)	0.85
No	45 (44.1)	17 (47.2)	

[*] Benign tumor subtypes include multilocular cystic renal cell neoplasm of low malignant potential, mixed epithelial and stromal tumor family, and benign multilocular cysts

Table 3

Comparison of solid component percentage and malignancy risk in a subset of patients with Bosniak 3 and 4 lesions in our surgical cohort

Radiologic Solid Component %	Bosniak 3 & 4			Bosniak 3			Bosniak 4		
	Renal Cell Carcinoma	Benign Tumors	*P*-value	Renal Cell Carcinoma	Benign Tumors	*P*-value	Renal Cell Carcinoma	Benign Tumors	*P*-value
Purely cystic	43	18	0.12	43	18	0.25	0	0	0.71
<25%	40	6		6	0		34	6	
25–50%	18	4		3	0		15	4	

Table 4

Comparison of clinical and radiologic characteristics between patients initially managed with surgical intervention and active surveillance in our overall cohort

	Surgical Intervention n=138	Active Surveillance n=38	*P*-value
No. sex (%)			
Male	78 (57)	21 (55)	1.0
Female	60 (43)	17 (45)	
Median age at diagnosis (IQR)	54.0 (45.4–64.2)	67.5 (61.6–73.1)	<0.0001
Median radiologic tumor size, cm (IQR)	3.3 (2.2–4.7)	3.1 (2.3–4.5)	0.59
No. solid component (%)			
Yes	69 (50.0)	13 (34.2)	0.09
No	69 (50.0)	25 (65.8)	
No. solid component (%)			
25–50%	23 (16.7)	8 (21.1)	0.01
<25%	46 (33.3)	5 (13.2)	
No measurable solid component	69 (50.0)	25 (65.8)	
Median solid component size, cm (IQR)	0.8 (0.6–1.1)	1.5 (1.4–3.3)	0.004
No. Bosniak Classification (%)			
4	59 (42.8)	9 (23.7)	<0.0001
3	70 (50.7)	12 (31.6)	
2F	9 (6.5)	17 (44.7)	
No. tumor location (%)			
>50% Exophytic	106 (76.8)	28 (73.7)	0.01
<50% Exophytic	12 (8.7)	9 (23.7)	
Endophytic	20 (14.5)	1 (2.6)	
No. presence of calcifications (%)			
Yes	30 (21.7)	7 (18.4)	0.82
No	108 (78.3)	31 (81.6)	
No. presence of septations (%)			
Yes	123 (89.1)	28 (73.7)	0.03
No	15 (10.9)	10 (26.3)	
No. presence of other cysts (%)			
Yes	76 (55.1)	26 (68.4)	0.19
No	62 (44.9)	12 (31.6)	