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Contrast-enhanced ultrasonography role in the evaluation of complex cystic masses

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Contrast-enhanced ultrasonography role in the evaluation of complex cystic masses

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Abstract

Introduction: Imaging plays a key role in the diagnosis and follow-up of renal masses. Contrast-Enhanced Ultrasound (CEUS) has gained interest in the evaluation of complex renal cysts. Our purpose was to assess the performance of CEUS in the evaluation of complex cystic renal lesions and, secondarily, compare its results with Computed Tomography (CT) scan. Furthermore, we aimed to determine imaging predictors of malignancy.
Methods: Retrospective study included 254 patients with complex renal cysts, that underwent CEUS for initial imaging or follow-up. CEUS classified lesions as benign or malign according to Bosniak classification. CEUS findings were compared to definitive pathologic diagnosis in 28 patients. Diagnostic accuracy measures were calculated using pathologic diagnosis as the reference standard, as well as lesion stability or downgrading at follow-up. Lesion characteristics on CEUS were evaluated as predictors of malignancy.
Results: CEUS had 100% sensitivity (95% CI: 89.9-100%) and 85% specificity (95% CI: 79.5-90.0%) on the performance analysis. CEUS showed good agreement with CT in terms of nodularity, number of septa and dimensions, but no agreement in contrast enhancement pattern and Bosniak classification. Progression of Bosniak classification and growth during follow-up were associated with malignant histology at resection. Nodularity (OR: 15.0), enhancement (OR: 8.6), and thickness >4mm (OR: 11.0) at CEUS evaluation were predictors of malignancy.
Discussion: CEUS is a useful diagnostic tool for the evaluation and follow-up of renal masses, but its accuracy in predicting malignant histology and its impact on patient management need to be further validated.

Keywords
Ultrasonography; Contrast media; Carcinoma, renal cell; Cystic renal disease.

Abbreviations
CEUS – contrast-enhanced ultrasonography.
CT – computer tomography.
MRI – magnetic resonance imaging.
US – ultrasonography.
RCC – renal cell carcinoma.

Introduction

Imaging plays a key role in the diagnosis and follow-up of Renal Cell Carcinoma (RCC). The demand to diagnose and treat RCC at a curable stage result in many benign neoplasms being resected. This is especially true for cystic masses, which are more likely to be benign and, when malignant, less aggressive.(1,2) These lesions can represent approximately 10% of all RCC, and their differentiation from nonmalignant renal cysts is challenging – due to hemorrhage, infection, inflammation, and ischemia.(2,3)

The Bosniak classification has been used for more than 30 years to stratify the risk of malignancy in cystic renal masses and guide follow-up in such lesions.(4) The consecutive refinements of Bosniak classification aimed to reduce the number of benign masses being classified as Bosniak III, therefore reducing overdiagnosis and overtreatment.(5,6) The most important modifications included the introduction of Bosniak category IIF, to bridge category II and III with the option of radiological follow-up,(1) and more recently, 2019 classification established definitions for previously vague imaging terms, enabling a greater proportion of masses to enter lower risk lesions and improving specificity. These improvements reduced procedural morbidity, loss of renal function, and costs.(6)

Bosniak classification was originally described for computed tomography (CT) and the 2019 version formally incorporates MRI into the classification. Bosniak I and II masses are clearly benign lesions that require no follow-up. Stable Bosniak IIF complex renal cysts show a malignancy rate of less than 1% during radiological follow-up. Nevertheless, there is 12% progression of Bosniak IIF to Bosniak III or IV during radiological follow-up, and 86% of reclassified lesions will be malignant.(1) Bosniak III category shows 51% prevalence of malignancy, which will result in surgical overtreatment of 49% benign cysts. Bosniak IV masses are approximately 90% likely to be malignant.(6)

Recently, the development of ultrasound contrast agents coupled with a superior resolution of ultrasound make contrast-enhanced ultrasound (CEUS) a promising modality to follow-up and diagnose cystic renal lesions.(7) CEUS offers a good approach to effectively characterize renal lesions based on differences between lesion and organ perfusion. (8) Recent European guidelines standardized the application of Bosniak classification to CEUS.(7) Table 1 shows the recent proposal for CEUS Bosniak Cyst Categorization.

Ultrasound contrast agents are composed of gas microbubbles enclosed in a protein, lipid, or polymer shell with the size of a red blood cell.(9) This composition and size allows the agent to be able to last for 5–7 min inside the blood vessels. Therefore, these drugs show no extravascular passage and are regarded as pure blood pool agents.(10) After circulating, microbubbles dissolve in the lungs and the coating shell is metabolized in the liver.(11) The kidneys are not involved in their excretion and microbubbles do not accumulate in the pelvicalyceal system. Due to this metabolic pathway, renal insufficiency is no contraindication for the use of these contrast agents.

Table 1 – CEUS Bosniak classification.

		B-MODE APPEARANCE		CEUS APPEARANCE
NEGATIVE FINDINGS	I	Simple cysts with thin wall Without irregularities, calcifications, anechoic content	CEUS not necessary	Thin wall and septa without irregularities No enhancement
	II	Meet the criteria of simple cysts but are characterized by 1–3 thin septa Calcifications of the wall	CEUS not necessary	Thin wall and septa without irregularities No enhancement
	II	Cysts with internal debris Echogenic content	CEUS necessary	Thin wall and septa without irregularities No enhancement
	IIF	Multiple septa internal debris Echogenic content Calcifications of the wall and/or septa	CEUS necessary	Multiple septa Thin or minimally thickened (2–3 mm) Smooth or minimally thickened wall
	IIF	Totally intrarenal cysts otherwise meeting the category II criteria	CEUS necessary	Thin septa without irregularities No enhancement
POSITIVE FINDINGS	III	Multiple septa Internal debris Echogenic content Mixed appearance	CEUS necessary	Enhancing smooth thick (≥ 4 mm) wall or septa Enhancing irregular (> 3 mm) walls and/or septa. No nodules
	IV	Multiple septa Internal debris Echogenic content Mixed appearance	CEUS necessary	Enhancing smooth thick (≥ 4 mm) wall or septa Enhancing irregular (> 3 mm) walls and/or septa Enhancing soft-tissue protrusions (nodules with obtuse margins ≥ 4 mm or with acute margins of any size)

Adapted from: EFSUMB 2020 Proposal for CEUS Bosniak Cyst Categorization.(7)

The most studied contrast agent, sulphur hexafluoride microbubbles, shows high performance and excellent safety profile.(12) It is relatively inexpensive and can be performed quickly at the patient bedside. Moreover, microbubble contrast agents can be administered safely in those with renal failure without risk of contrast-induced nephropathy, nephrogenic systemic fibrosis, or contrast accumulation in organs.(12) CEUS also eliminates radiation exposure of CT, which constitutes an attractive characteristic for follow-up of complex renal cysts.(13,14) Sulphur hexafluoride microbubbles is contraindicated in patients known to have right-to-left shunts, severe pulmonary hypertension, uncontrolled hypertension, or adult respiratory distress syndrome.(12,14)

Previous studies compared CEUS and CT performance in the classification of cystic renal masses according to Bosniak system. CEUS has shown equal or even superior diagnostic accuracy in most studies.(15) Complete concordance was observed between CEUS and CECT (contrast-enhanced computed tomography) for the differentiation of surgical and nonsurgical lesions.(12,14)

CEUS has high sensitivity for the detection of microbubbles in peripheral wall, intracystic septa and solid enhancing components that do not appear on CT imaging.(16–19) Consequently,

CEUS has been proposed in the characterisation of indeterminate complex renal cysts on CT. In a study conducted on indetermined CT lesions, CEUS resulted in 26% upgrading Bosniak scores. Five of these lesions were correctly diagnosed as Bosniak category III or IV by CEUS but were misdiagnosed as Bosniak category IIF or less by CT, which led to a change in treatment plan.(12) CEUS detected a higher number of septations within a lesion, was superior in detecting the degree of septal wall thickening, septal enhancement, and enhancement of solid components within the lesion.(12) Additional studies also demonstrated superior diagnostic accuracy of CEUS when compared with CT and conventional ultrasound.(8,12,18) CEUS demonstrated higher sensitivity to intralesional characteristics (number of septa, wall and septa thickness, solid components) than CT or US.(8,20)

Inter-reader variation, user dependency and patient biotype are limitations of CEUS use. Recent European guidelines standardized the Bosniak classification to CEUS to eliminate inter-observer variation.

Since CEUS has shown better characterization of cysts than CT and a favourable safety profile, it has been suggested as preliminary method to evaluate lesions with complex cystic appearance on baseline US.(8) CT may be used for staging and hilar anatomy characterization after CEUS. Overall, CEUS can replace CT for evaluation and follow-up of complex renal cysts, especially in patients with renal insufficiency and indeterminate findings on CT or MRI imaging.(14)

In the following work, we aimed to evaluate the utility of CEUS for the evaluation and follow-up of cystic renal masses. We also intended to determine CEUS accuracy as diagnostic tool of malignant renal cystic masses and to determine the image predictors of malignancy. Secondarily, compare the CEUS and CT performance in the patients with malignant disease.

Materials and Methods

Using the approved complex renal cyst institutional database, we selected and retrospectively analysed 240 consecutive patients who underwent CEUS for complex renal cystic masses between 2010 and 2022. Patients were initially referred for CEUS because of indeterminate findings on previous exams or if there were conflicting results on imaging follow-up studies. Written or oral informed consent for CEUS, microbubbles contrast and performance monitoring were requested at time of examination. Patient characteristics (age; sex; symptoms assessment; mass side) and first exam findings were available and gathered at time of contrast-enhanced ultrasound. The initial imaging study could have been CT scan, MRI or US.

All lesions were classified according to Bosniak grading system by a radiologist dedicated to urinary system imaging and contrast-enhanced ultrasound. All findings were interpreted and reported at the time of the contrast-enhanced US exam, without the knowledge of outcome. Lesion characteristics were also reported. Included features were contrast enhancement, wall and septa thickness, number of septa, calcifications, maximal dimensions, and nodularity.

Performance analysis was conducted retrospectively, considering positive and negative findings for malignancy according to Bosniak classification at CEUS report. Bosniak III and IV lesions were considered positive findings for malignancy. Bosniak I, II and IIF were considered negative findings for malignancy.

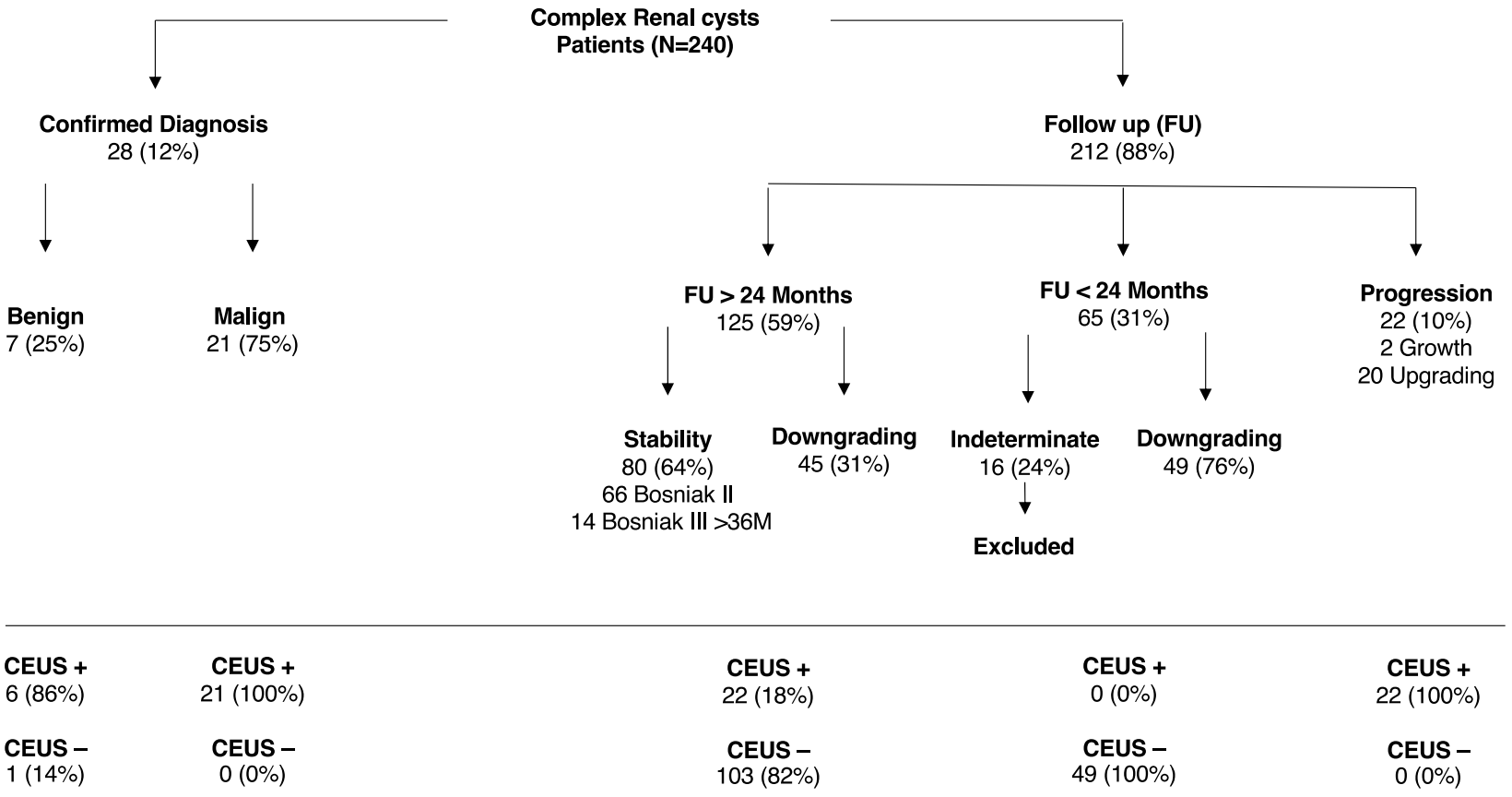
In terms of outcomes, a definitive diagnosis was assigned if there was a histologic exam from a surgical specimen or a biopsy. In the present analysis, 28 (14%) had histologic confirmed diagnosis. The remaining 212 (88%) patients were analysed by imaging (CEUS, CT or MRI) and clinical follow-up. Follow-up time was considered the months between CEUS and last renal cyst assessment by any imaging modality. Progression on follow-up was defined as 30% increase in size of a cystic mass classified as Bosniak III or an upgrading to Bosniak IV on CT and CEUS on follow-up, regardless of follow-up time. Stability and benign evolution were defined by downgrading in follow-up, irrespective of time, stable Bosniak I or Bosniak II in different exams for more than 24 months and stable Bosniak III for more than 36 months. Stable Bosniak IIF or III for less than 36 months were excluded from the analysis. Summary of the analysis is displayed on figure 1.

Performance analysis was conducted in the subgroup with definitive histological diagnosis (gold-standard) and in the global sample.

Agreement between CEUS and CT was performed in the subgroup of patients with definitive diagnosis. CT and CEUS must have been performed in our institution with less than 6 months between the two exams. Agreement was determined for lesion dimensions, enhancement, number of septa and nodularity. CEUS characteristics were evaluated as predictor of malignant disease or progression in follow-up.

Statistical Analysis

Descriptive analyses were performed using standard summary statistics. Sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) where determined to evaluate CEUS performance on determining malignant lesions or progression. McNemar test and Cohen's measurement of agreement were determined for evaluation of agreement between imaging exams. Independent samples T-Test were used to determine the relations between the tumor dimensions at histopathology and imaging exams. Preliminary analyses were performed to ensure no violation of normality and linearity. Binary logistic regression was conducted to analyse predictors of malignancy in CEUS exam. All analyses were performed using SPSS version 25 (SPSS IBM, Armonk, NY, USA). Statistical significance was defined as $p < 0.05$. Medians are reported with corresponding 95% confidence intervals (CIs).



CEUS: Contrast Enhancement Ultrasound; FU: follow-up; +: positive findings; -: negative finding.

Figure 1 – Flowchart of global performance analysis.

Results

A total of 240 patients underwent Contrast Enhanced Ultrasound for complex renal cyst. Participants included 89 female patients (37%) and 151 male patients (63%). Age at examination ranged from 22 to 92 years, with a median age of 71. Most patients presented with incidental findings on routine exams (89%) and 23 patients had symptoms (10%) – lumbar pain or haematuria. The initial imaging study could have been CT scan (40%), MRI (6%) or US (54%).

On the evaluated patients, CEUS classified 41 Bosniak I lesions (17%), 69 Bosniak II lesions (29%), 69 Bosniak IIF lesions (29%), 46 Bosniak III lesions (19%) and 15 Bosniak IV lesions (6%). Lesion size varied from 8 to 140 mm (mean size 42,9 mm $\pm$ 26,3). Contrast enhancement was found in 153 lesions (64%), of those 64 presented with minimal enhancement (27%). Most lesions had 3 or more septa (81%). Septal and wall thickness was also evaluated, with 51 (21%) showing 3 mm thickness and 37 (15%) with $\geq$ 4 mm. Calcifications were found in 58 (24%) lesions. In terms of nodularity, 20 lesions (8%) had irregular wall thickening and 15 (6%) had a nodularity.

Subgroup analysis of patients with confirmed diagnosis

In a subgroup analysis of patients who had definitive diagnosis of anatomopathological specimen, 7 were benign (25%) and 21 were malign (75%). Of those, 5 underwent total nephrectomy, 22 partial nephrectomy and 1 biopsy proven histology. The most frequent malignant histology was Clear Cell (CC) RCC (43%) followed by Chromophobe RCC (29%). Results of histopathologic analysis are shown in table 2. Mean dimensions of resected lesion was 33.8mm ($\pm$ 20,5).

As shown in table 2, the 28 cystic renal masses were categorized by CEUS as follows: 1 Bosniak IIF, 14 Bosniak III and 13 Bosniak IV. Only 18 patients underwent CT within 6 months and were classified as follows: 1 Bosniak I, 4 Bosniak IIF, 9 Bosniak III, and 4 Bosniak IV. Same category was attributed in 11 patients (61%), differing in the other 7 lesions. Of those, 6 lesions were upgraded by CEUS on the follow-up imaging. Upgrading lesions were resected showing malignant histology in 5 patients. One patient classified as category III on CT and IV on CEUS was resect showing a Angiomyolipoma with low fat component. No agreement between exams was met (p=0.06).

Good agreement between the two exams were met in terms of nodularity (K=0.77; p<0.05) and number of septs (K=0.71; p<0.05). The number of septs were similar in both exams in 78% of lesions. No agreement between exams were found in contrast enhancement pattern (p=0.64).

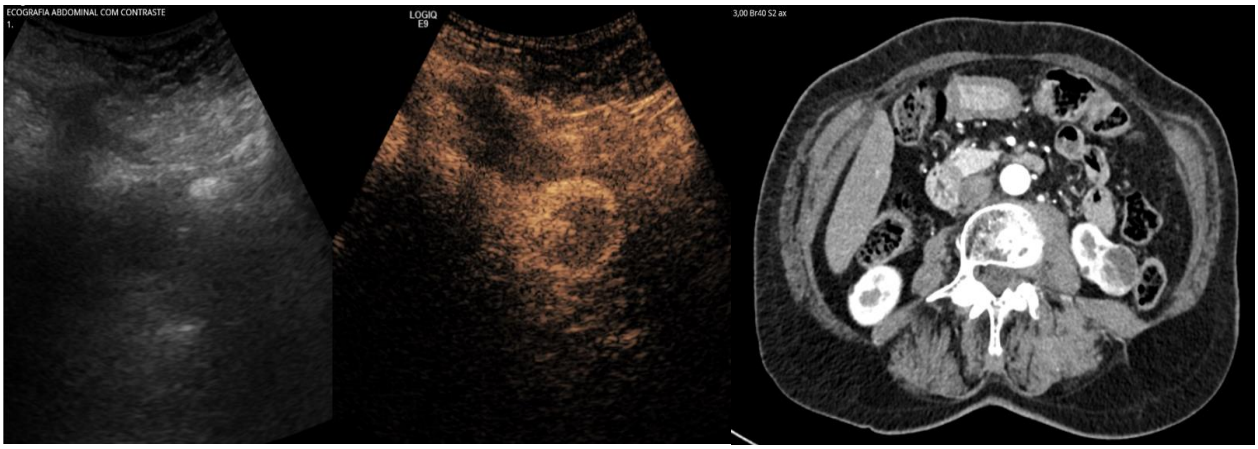
Dimensions were compared between the two imaging modalities without showing significant difference (T(16)=0.69; p=0.49). When comparing CEUS to pathology specimen, there were also no significant difference in terms of dimensions (T(26)=0.85; p=0.40). Mean difference between CEUS dimension and final specimen was 4.1mm, with tendency for overestimation of dimensions.

Diagnostic accuracies of CT and CEUS for malignant renal tumor were 44% and 66%, respectively. CT scan misdiagnosed 4 malignant lesions, that were classified as having positive findings on CEUS. These findings motivated a correct change in the treatment plan.

Performance was analysed using pathology as comparator, showing 21 true positive (TP) scores, 6 false positive (FP) and 1 true negative (TN) score. Sensitivity of CEUS was 100% (95% CI: 83.9-100%) and specificity of 14.3% (95% CI: 0.36-57.9%). Although with 100% negative predictive value (NPV).

CEUS resulted in overtreatment in 6 patients (28%) – benign lesions being resected. One patient underwent partial nephrectomy for a benign lesion because of symptoms and dimensions (with negative CEUS findings). The 6 lesions were classified as potentially malign in CT and CEUS. False positive lesions were cystic nephroma, papillary adenoma, mixed epithelial and stromal tumor and angiomyolipoma.

Progression of Bosniak classification ($p<0.05$) and growth ($p<0.05$) during follow-up are both associated with malignant histology on final specimen. CEUS characteristics (contrast enhancement; nodularity, dimensions, and thickness) were evaluated as predictors of malignant histology, although the model was not statistically significant.



Right to left: Mode-B US with complex cyst. Bosniak IV with nodularity, thickened and irregular wall showing contrast enhancement. Contrast-enhanced CT scan shows complex cyst with septa and irregular thickened wall – Bosniak IV. Partial nephrectomy confirmed a Papillary Renal Cell Carcinoma.

Figure 2 – Bosniak IV lesion on CEUS and CT.

Table 2 – Subgroup analysis of patients with anatomopathological confirmed diagnosis.

N	BOSNIAK		ENHANCMENT		SEPTS NUMBER		NODULARITY		FOLLOW-UP		SURGERY/PATHOLOGY			DIMENSIONS		
	CEUS	**CT**	**CEUS**	**CT**	**CEUS**	**CT**	**CEUS**	**CT**	**PROGRESSION**	**GROUTH**	**TREATMENT**	**OUTCOME**	**DESCRIPTION**	**CEUS**	**CT**	**AP**
1	III	III	Yes	Yes	≥4	≥4	None	None	Yes	Yes	PN	B	CN	30	24	35
2	IIF	IIF	No	ME	≤3	≤3	None	None	No	Yes	PN	B	PA	145	100	30
3	III	IV	Yes	Yes	≤3		None	-	Yes	No	PN	B	CN	40	18	40
4	IV	III	Yes	Yes	≥4	≥4	N/T	Irregular	Yes	Yes	PN	B	Angiomyolipoma	21	45	12
5	III	III	Yes	ME	≥4	None	N/T	N/T	Yes	No	TN	B	MEST	40	35	35
6	IV	IV	Yes	Yes	None	None	N/T	N/T	Yes	No	TN	B	MA	81	81	110
7	IV	IV	Yes	Yes	None	None	N/T	N/T	Yes	Yes	TN	B	Pseudotumor	36	70	35
8	III	III	Yes	Yes	≥4	≥4	N/T	N/T	Yes	No	PN	M	P RCC	28	34	41
9	III	-	Yes	-	≥4	-	Irregular	-	No	No	PN	M	CC RCC	11		22
10	III	III	Yes	Yes	≥4	≥4	None	None	Yes	No	PN	M	T RCC	28	28	32
11	III	III	Yes	Yes	≤3	≤3	Irregular	Irregular	No	Yes	PN	M	CC RCC	40	28	30
12	III	III	Yes	Yes	≥4	≥4	None	None	No	No	PN	M	CC RCC	40	40	32
13	III	IIF	Yes	ME	None	None	N/T	N/T	Yes	No	PN	M	PRCC	16	15	20
14	III	-	Yes	-	≤3	-	N/T	-	No	Yes	PN	M	Chrom RCC	35		30
15	III	-	Yes	-	≤3	-	N/T	-	Yes	No	PN	M	P RCC	25		16
16	III	-	Yes	-	≤3	-	None	-	Yes	No	PN	M	CC RCC	23		22
17	IV	-	Yes	-	None	-	N/T	-	No	No	PN	M	Chrom RCC	12		11
18	IV	IV	Yes	Yes	None	None	N/T	-	No	No	PN	M	CC RCC	16		18
19	IV	IIF	Yes	No	None	≥4	Irregular	-	Yes	No	PN	M	P RCC	43	46	50
20	IV	-	Yes	-	≤3	-	Irregular	--	No	No	PN	M	Chrom RCC	18		20
21	IV	-	Yes	-	≤3	-	N/T	-	No	No	PN	M	CC RCC	38		38
22	IV	-	Yes	-	≥4	-	N/T	-	No	No	PN	M	CCR CC	18		13
23	IV	-	Yes	-	None	-	N/T	-	No	No	PN	M	P RCC	49		50
24	IV	III	Yes	Yes	≤3	≤3	N/T	N/T	No	Yes	PN	M	Chrom RCC	26	30	35
25	IV	-	Yes	-	≥4	-	N/T	-	Yes	No	PN	M	CC RCC	66		70
26	III	IIF	Yes	No	≤3	None	None	None	Yes	Yes	TN	M	Chrom RCC	65	19	18
27	IV	IV	Yes	Yes	None	None	N/T	N/T	No	No	TN	M	CC RCC	38	47	50
28	III	IIF	No	No	None	None	N/T	None	Yes	No	BX	M	Chrom RCC	33	32	
	K=0.28 (p=0.65)		**K=0.09 (p=0.64)**		**K=0.71 (p<0.05)**		**K=0.77 (p<0.05)**								**T-Test (p=0.49)**	**T-test (p=0.40)**

BX: biopsy; CC: clear cells; Chrom: chromophobe; CN: cystic nephroma; Irregular: irregular wall or septa; MA: metanephric adenoma; ME: minimal enhancement; MEST: mixed epithelial and stromal tumor; N/T: nodularity or thickness; P: papillary; PA: papillary adenoma; PN: partial nephrectomy; RCC: Renal cell carcinoma; T: tubular; TN: total nephrectomy.

Global Performance analysis

In the global analysis, we considered 43 patients with positive clinical findings (21 patients with confirmed malignant histology, 20 with progression and 2 with > 30% growth on follow-up). Of the 212 patients managed with follow-up, 174 had stable or downgrading disease (14 Bosniak III with > 36 months follow-up, 66 stable Bosniak II with > 24 months and 94 downgrading lesions). There were 16 patients excluded with indetermined findings on follow-up. Therefore, we considered 181 patients with negative clinical findings and 43 with positive clinical findings. Flowchart of the global analysis is shown on figure 1.

CEUS had positive findings on 71 patients and negative findings on 169 patients. Performance was calculated, showing 100% sensitivity (95% CI: 89.9-100%) and specificity of 85% (95% CI: 79.5-90.0%). Positive predictive value of 53.3% (95% CI: 44.8-61.7%) and negative predictive value of 100%. CEUS accuracy was 87.44% (95% CI: 82.4-91.49%).

Predictors of malignancy according to CEUS characteristics were determined using a logistic regression model. Contrast Enhancement (significant enhancement), wall/septa thickness (>4mm) and nodularity were included in the analysis. The model was statistically significant, $\chi 2$ (3, N = 223) = 81.34, $p<0.05$, indicating that the model was able to distinguish patients who had positive clinical findings for malignancy. Globally, the model has correctly classified 90.1% of cases. Model sensitivity was 78% and specificity was 91%. Nodularity was the strongest predictor of malignancy, showing 15.05 OR (CI 95% of 4.22-53.63). Enhancement (OR: 8.6) and thickness >4mm (OR: 11.0) were also significant predictors of malignant disease. Logistic regression predicting likelihood is displayed on table 2.

Table 3 – Risk factor and treatment groups

	B	SE	Wald	df	p	OR	95% CI	
Thickness	2.15	0.56	14,461	1	<0.01	8.65	2.84	26.32
Nodularity	2.71	0.64	17,493	1	<0.01	15.05	4.22	53.63
Enhancement	2.39	0.66	12,882	1	<0.01	11.00	2.97	40.79
Constant	-4.53	0.65	47,671	1	<0.01	0.01		

Discussion

The number of complex renal lesions that are incidentally found on routine and follow-up exams is increasing dramatically. The differentiation between renal masses that require surgery from those who do not represents a clinical challenge. Cystic renal cell carcinomas and other benign complex cysts are sometimes indistinguishable on cross-sectional imaging. Therefore, complex renal cysts motivate sequential follow-up imaging and definitive resection. The imaging overlap on these lesions can result in many benign neoplasms being resected and occasionally overtreatment.(1,2) Moreover, intense follow-up with CT can induce contrast nephropathy and unnecessary radiation exposure. On the other hand, simple US is not a reliable method to differentiate which cysts require resection, because this method lacks evaluation of contrast enhancement pattern, which is crucial for treatment decision.(21,22) Consequently, the optimal imaging modality should have high sensitivity and specificity, low radiation exposure, contrast enhancement evaluation and safer contrast agents. Therefore, we conducted retrospective clinical analysis of CEUS performance on indeterminate and cystic renal masses due to the characteristics of this promising imaging modality.

Our study was conducted in a urology and radiology reference center, which have accumulated experience with a high number of CEUS performed in the last 10 years. Despite low number of patients who underwent definitive resection, our follow-up time was long and even superior to other similar studies.

This study endorses the potential use of CEUS in the initial evaluation and follow-up of complex renal cysts according to Bosniak Classification system. Considering the global performance analysis, CEUS has 100% sensitivity and high specificity, which endorses the results of similar studies.(12,20) In the subgroup analysis with confirmed histology, this modality was also able to identify all patients with malignant disease. Moreover, 5 patients who underwent CT and CEUS were correctly reclassified by CEUS and resected. These results validate previous studies that proposed that CEUS may replace CT in this setting, due to its high performance and safety.(14) Although high performance was found, we showed carefully analyze the low specificity on the subgroup of patients who underwent surgery. First, only one patient underwent surgery with negative findings on CEUS and, secondly, all false positive findings were classified as potentially malignant by both imaging modalities - CEUS and CT. Furthermore, CEUS resulted in overtreatment in 6 patients (28%), which is approximately the 20-25% benign lesions resected on series of partial nephrectomy.(23)

On our sample, CEUS was superior to CT in terms of accuracy. Bosniak classification and contrast enhancement pattern were different in the two exams, which may be explained by the extreme sensitivity of CEUS in the detection of even few small bubbles of contrast material traveling in a septum or cystic wall.(2,14) CEUS allows real-time imaging, which can be useful in assessing the vascularization of cystic lesion, while CT, on the other hand, provides static images and may not be able to capture the dynamic changes in blood flow that occur during CEUS. (24)

Both exams equally classified the number of septa and nodularity which conflicts with previous results, where CEUS was superior to CT for determination of number of septa,

characterizing wall thickness and solid components of cystic renal lesions.(25) Both CT and CEUS were good estimating the dimensions of the tumor, with tendency for overestimation.

Studies have demonstrated CEUS to be a safe imaging technique. The contrast agents used in this technique are generally well-tolerated and severe allergic reactions are extremely rare when compared to those used in angiographic imaging techniques.(26) In addition, CEUS does not use ionizing radiation, which is a concern, especially when repeated scans are necessary. CEUS can also be performed quickly, more easily repeated and has a reduced cost, making it a valuable toll in dynamic imaging of the kidney. In addition, without renal or hepatic contraindications, CEUS is extremely helpful in patients with renal insufficiency.(20) However, caution should be exercised in patients with severe chronic obstructive pulmonary disease, congestive heart failure (class IV according to the New York Association classification), and recent cardiac infarction.(14)

We should also take in consideration that CT will almost always be performed in case of surgery. Nevertheless, for the advantages mentioned above, CEUS can be extremely helpful in the initial evaluation of renal masses and sequential exams, sparing these patients of a more unfavorable exam.

On the clinical follow-up performance analysis, CEUS demonstrated both high sensitivity and specificity. The 85% specificity, good size estimation, and the identification of size and Bosniak progression make this exam a promising follow-up exam. During follow-up, Bosniak progression and growth were the parameters most associated with a malignant transformation. Moreover, cystic renal cell carcinomas are more likely to be less aggressive.

Our data also shows that nodularity and enhancement are the best predictors of malignancy, which can guide clinal decision-making and management of indetermined renal masses, regarding the need for immediate resection. The combination of contrast enhancement, wall/septa thickness > 4 mm and nodularity in renal cysts can predict malignant lesions with good grade of certainty. Nodularity, individually, increases 15 times the risk of malignancy.

Our study has several limitations. The retrospective design, interobserver variability and the small number of pathologically proven cases that were included the sample. Although follow-up was superior to previous studies, the slow growth rate and progression of cystic lesions may indicate the need of longer follow-up time. Thus, further investigation in surgical cases is needed to support our results.

Conclusion

CEUS seems to be a valuable tool for differentiating benign and malignant renal masses and can also provide valuable information regarding the vascularity and internal architecture of the cyst, particularly important when facing indeterminate lesions. This imaging technique might

also play an important role in the initial work-up diagnosis and follow-up, making an alternative to CT or MRI, considering it is non-invasive, safe, and well-tolerated, with low risk of adverse events.

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