Original Article

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The diagnostic value of contrast-enhanced ultrasound in differentiating small renal carcinoma and angiomyolipoma

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Summary **The aim of this study was to explore the value of contrast-enhanced ultrasound (CEUS) in differentiating small renal masses. A total of 102 small renal masses (≤ 3 cm) in 99 patients were examined using conventional ultrasound (CUS) and CEUS, and the findings were reviewed and evaluated in comparison to pathology. Significant differences between renal cell carcinomas (RCCs) and angiomyolipomas (AMLs) were noted in terms of the orientation and echogenicity on CUS ($p < 0.05$ for both), but the location, shape, margins, homogeneity, and blood flow signals of RCCs on color Doppler flow imaging (CDFI) were similar to those of AMLs ($p > 0.05$ for all). On CEUS, however, the enhancement intensity, washout in the late phase, and perilesional rim-like enhancement differed significantly for RCCs and AMLs ($p = 0.000$ for all). Significant differences between CEUS and CUS in terms of sensitivity (88.9% *vs.* 55.6%), the negative predictive value (68.0% *vs.* 29.5%), the false negative rate (9.9% *vs.* 44.5%), and accuracy (88.3% *vs.* 58.9%) were noted ($p < 0.05$ for all). CEUS, with its unique features, has value in diagnosing small RCCs and AMLs and outperforms CUS in differentiation of small RCCs and AMLs.**

Keywords: Ultrasonography, contrast agent, renal cell carcinoma, angiomyolipomas

1. Introduction

Renal cell carcinoma (RCC), the most common malignancy involving the kidney, originates in the renal tubular epithelium of the urinary system. Its incidence in China is 2% to 3% in adults, making it second only to bladder cancer (*1*), but its mortality is the highest of all tumors in the urinary system (*2*). Fortunately, the high incidence of small renal masses (SRMs) over the past few decades can be partly attributed to increased sensitivity and widespread use of imaging modalities such as computed tomography (CT), ultrasonography (US), and magnetic resonance imaging (MRI) (*3*). Detection and treatment in the earliest possible stage is key to reducing mortality. Conventional ultrasound (CUS) is a readily available, inexpensive, non-invasive, and non-ionizing imaging modality to detect renal masses, but it has limited use when attempting to differentiate between RCC and renal angiomyolipoma (AML). A safe and accurate imaging modality is needed to differentiate between RCC and AML, and contrast-enhanced ultrasound (CEUS) using microbubble-based contrast agents has garnered increasing attention in this regard (*4,5*).

Dynamic observation of enhancement features on CEUS provides an accurate characterization of lesions, and this helps to determine other examinations that are needed for a faster and more precise diagnosis. Some studies have reported that CEUS is useful in detecting and diagnosing RCC (*6-7*), but there is a dearth of literature investigating its value in the differential diagnosis of SRMs.

The aim of this study was to evaluate the characteristics of SRMs on CEUS and to determine

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whether CEUS is better than US at diagnosing small RCC.

2. Materials and Methods

2.1. *Patient selection*

Between September 2011 and March 2015, a total of 268 renal masses in 261 consecutive patients were examined with CEUS after detection with baseline CUS. Of 268 renal masses, 166 (in 162 patients) were excluded either because they were large in size (> 3 cm) or because subsequent pathology results were unavailable. Patients with a pathologic diagnosis of a simple cyst, oncocytoma, a metastatic tumor, an adenoma, or and a *Wilm's* tumor were also excluded. Thus, this study examined 102 masses in 99 patients, 79 patients with RCC (ages ranging from 25-87, mean 56.6 ± 16.5 years), and 20 patients with AML (ages ranging from 25-87, mean 56.6 ± 16.5 years). An open or laparoscopic partial nephrectomy was performed for all of the masses that were studied. Table 1 shows the baseline characteristics of patients.

This study was approved and supervised by this Hospital's institutional review board, and informed consent was obtained from each patient.

2.2. *CUS*

CUS was performed using an Acuson S2000 ultrasound system (Siemens Medical Solutions, Mountain View, CA, USA) with a 4C1 convex transducer (frequency range: 1.0-4.0 MHz). All examinations were performed by a single radiologist (C.L.) with 13 years of experience in abdominal US and 9 years in CEUS. The long-axis view of the kidney was obtained by placing the probe over the lower back with the patient in the lateral position. Imaging settings such as time gain compensation (TGC), total gain, depth, and focal zone were optimized to ensure adequate image quality. CUS, both gray-scale ultrasound and color Doppler flow imaging (CDFI), was performed to detect and reveal renal masses. After CUS, all patients underwent CEUS.

2.3. *CEUS*

CEUS was performed using contrast pulse sequencing (CPS) technology integrated in the Acuson S2000 unit at a mechanical index of 0.05-0.07. CEUS was performed by the same radiologist who performed CUS (C.L.). CPS allows continuous low-mechanical-index (MI) imaging with a high microbubble tissue ratio. The depth of focus was 7 to 10 cm at the bottom of the lesion. The US contrast agent used in this study was SonoVue (Bracco, Milan, Italy), which consists of sulfur hexafluoride (SF_6) -filled microbubbles stabilized with phospholipids. Before use, an ampoule of 5 mg of SonoVue was shaken with 5 ml of normal saline to serve as a microbubble suspension. A bolus of 1.2 ml of SonoVue suspension was injected intravenously followed by a 5-ml saline flush. A timer and video recorder were activated at the same time the contrast agent was administered. The tumor and renal cortex were observed continuously for at least 3 min., and the images and video clips for each detected mass were saved to a local hard drive for subsequent analysis.

2.4. *Image review and data evaluation*

Two radiologists (D.X.H. and F.L.), both blinded to the pathologic diagnosis, independently reviewed all renal images and video clips of CUS and CEUS saved on the local hard drive. The two radiologists, one with 7 and the other with 9 years of experience in abdominal US, had over 4 years of experience in reading CEUS images. The CUS characteristics that were documented and described included location, shape, orientation, margins, echogenicity, homogeneity, and vascularity. Characteristic changes in enhancement on CEUS were evaluated and recorded, including the initial enhancement time, the extent and pattern of enhancement, and dynamic changes in enhancement. The echotexture or signal intensity from the tumor was identified as hyperechoic, isoechoic, or hypoechoic in

Table 1. Baseline characteristics of patients

Characteristics	Description	RCC (n = 81)	AML (n = 21)	χ^2	p
Gender	Male	56 (69.1)	12 (57.1)	1.079	0.299
	Female	25 (30.9)	9 (42.9)		
Laterality	Left kidney	45 (55.6)	10 (47.6)	0.123	0.516
	Right kidney	36 (44.4)	11 (52.4)		
Tumor location	Upper pole	17 (22.2)	6 (28.6)	0.551	0.759
	Middle part	43 (49.4)	10 (47.6)		
	Lower pole	21 (28.4)	5 (23.8)		
Surgical methods	Open PN	28 (34.6)	5 (23.8)	0.882	0.343
	Laparoscopic PN	53 (65.4)	16 (76.2)		

AML, angiomyolipoma; RCC, renal cell carcinoma; PN, partial nephrectomy. Values are presented as the number (%).

comparison to the adjacent renal cortex, and the pattern was identified as homogeneous and inhomogeneous. CEUS was divided into a wash-in phase (7-15 s to 35-40 s after contrast injection) and a wash-out phase (41-46 s to 180 s) in conjunction with vascular perfusion of the renal cortex. The wash-in and wash-out of contrast in renal masses were described as faster than, slower than, or in sync with perfusion of the adjacent renal cortex. "Pseudocapsule enhancement" around the tumor on CEUS was defined as rim-like enhancement that became more distinct in the late phase. Masses were classified as malignant or benign depending on the image characteristics and the radiologists' experience. On CUS, masses with hypoechogenicity or iso-echogenicity and that were oriented outward from the renal capsule were defined as RCC, and those with hyperechogenicity or iso-echogenicity and that were oriented inward at the renal capsule were defined as AML. On CEUS, masses with hyperenhancement or iso-enhancement and with fast wash-in and/or fast wash-out or rim-like enhancement were defined as RCC, and those with hypoenhancement, iso-enhancement, or synchronous enhancement in the wash-in phase and wash-out phase were defined as AML.

The two radiologists made independent diagnoses and conclusions. In the event their conclusions differed, they consulted to reach a mutually acceptable final conclusion.

2.5. *Statistical analysis*

Continuous data were expressed as a percent or mean ± standard deviation (SD). An *Independent-Sample t* test was used to compare the size of the RCCs and AMLs. A *chi-square* test was performed to compare the image characteristics of RCCs and AMLs and to analyze the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of CUS and CEUS. $P < 0.05$ was considered significant. Statistical analysis was performed using SPSS software version 13.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. *Pathologic findings*

A pathologic diagnosis was obtained for all masses *via* a laparoscopic or open partial nephrectomy. One single nodule was detected in 77 patients with RCC and 19 patients with AML, and multiple nodules were detected in the remaining 3 patients. Of the patients with multiple nodules, 2 had RCC; 1 had 2 masses (1 in each kidney) and 1 had 2 nodules in the left kidney. One patient had AML with 2 nodules in the right kidney. Of the 102 renal masses, 81 (79.4%) were RCCs and 21 (20.6%) were AMLs. The 81 RCCs were clear cell carcinoma (68, 84.0%), papillary carcinoma (8, 9.9%), chromophobe carcinoma (4, 4.9%), or collecting duct carcinoma (1, 1.2%).

3.2. *CUS features of small RCCs and AMLs*

The mean maximum diameter of the renal masses, obtained from CUS, was 1.81 ± 0.59 cm (1.0 to 3.0 cm) for RCCs and 1.77 ± 0.52 cm (1.2 to 3.0 cm) for AMLs ($p > 0.05$). Significant differences between RCCs and AMLs in terms of the orientation and echogenicity on CUS were noted ($\chi^2 = 4.646$, 20.560; $p = 0.031$, 0.000, respectively). However, there were no significant differences between RCCs and AMLs in terms of location ($\chi^2 = 0.424$; $p = 0.809$), shape ($\chi^2 = 0.981$; $p = 0.322$), margins ($\chi^2 = 0.293$; $p = 0.588$), homogeneity ($\chi^2 = 0.036$; $p = 0.850$) and blood flow signals in CDFI (χ^2

Table 2. Characteristics of small RCC and AML in CUS

Lexicon	Description of lesions	RCC ($n = 81$)	AML ($n = 21$)	χ^2	p
Shape	Round/Oval	75 (92.6)	18 (85.7)	0.981	0.322
	Irregular	6 (7.4)	3 (14.3)		
Margins	Circumscribed	76 (93.8)	19 (90.5)	0.293	0.588
	Indistinct	5 (6.2)	2 (9.5)		
Orientation	Inward at the renal parenchyma	54 (66.7)	19 (90.5)	4.646	0.031
	Outward from the renal capsule	27 (33.3)	2 (9.5)		
Echogenicity	Hypoechoic	41 (50.6)	2 (9.5)	20.560	0.000
	Iso-echoic	25 (30.9)	5 (23.8)		
	Hyperechoic	15 (18.5)	14 (66.7)		
Homogeneity	Homogeneous	67 (82.7)	17 (81.0)	0.036	0.850
	Heterogeneous	14 (17.3)	4 (19.0)		
Blood flow signals in CDFI	With	18 (48.1)	4 (23.8)	0.099	0.753
	Without	63 (51.9)	17 (76.2)		

AML, angiomyolipoma; RCC, renal cell carcinoma. Values are presented as the number (%).

Table 3. Characteristics of small RCC and AML in CEUS

Enhancement pattern	Enhancement of lesions	RCC (n = 81)	AML (n = 21)	χ^2	p
Intensity	Hyperenhancement	64 (79.0)	3 (14.3)	32.062	0.000
	Iso-enhancement	10 (12.3)	13 (61.9)		
	Hypoenhancement	7 (8.7)	5 (23.8)		
Homogeneity	Heterogeneous	27 (33.3%)	3 (14.3)	2.914	0.088
	Homogeneous	54 (66.7%)	18 (85.7)		
Wash-in phase	Faster	37 (45.7)	3 (14.3)	7.917	0.019
	Synchronous	32 (39.5)	11 (52.4)		
	Slower	12 (14.8)	7 (33.3)		
Wash-out phase	Faster	63 (77.8)	2 (9.5)	37.227	0.000
	Synchronous	13 (16.0)	9 (42.9)		
	Slower	5 (6.2)	10 (47.6)		
Rim-like enhancement	Without	36 (44.4)	19 (90.5)	8.700	0.003
	With	45 (55.6)	2 (9.5)		

AML, angiomyolipoma; RCC, renal cell carcinoma. Values are presented as the number (%).

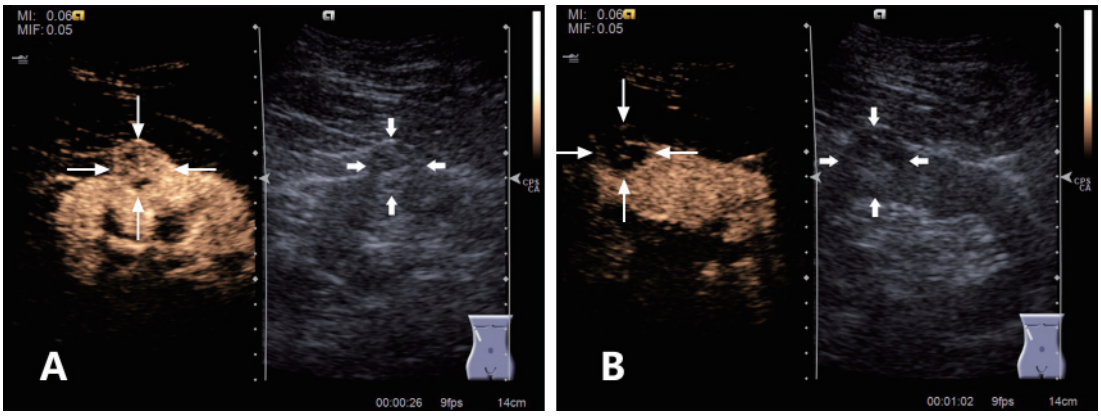

Figure 1. A 57-year-old man with clear cell renal carcinoma. CUS revealed a hypoechoic small renal mass located in the middle of the right kidney (short arrows). **(A)** CEUS imaging in the early phase revealed heterogeneous hyperenhancement. Peritumoral rim-like enhancement was observed (long arrows); **(B)** CEUS imaging in the late phase indicated that the region of the tumor was washed out with heterogeneous hypoechogenicity (long arrows).

= 0.099; p = 0.753). Table 2 details the image features of RCC and AML on CUS.

3.3. *CEUS features of RCCs and AMLs*

RCCs and AMLs differed significantly in enhancement intensity, wash-out in the late phase, and perilesional rim-like enhancement (p = 0.000 for all), but there were no significant differences in homogeneity and wash-in in the early phase (p > 0.05 for both) (Table 3). The typical characteristics of RCCs were hyperenhancement (64/81, 79.0%), homogeneous enhancement (54/81, 66.7%), wash-out of contrast earlier than that in the peripheral cortex in the late phase (63/81, 77.8%), and peripheral rim-like enhancement (45/81, 55.6%) (Figure 1), whereas the dominant features of AMLs were iso-enhancement (13/21, 61.9%), homogeneous enhancement (18/21, 85.7%), wash-in of contrast in sync with perfusion of the peripheral cortex in the early phase (11/21, 52.4%) and wash-out of contrast later than that in the peripheral cortex in the late phase (10/21, 47.6%) (Figure 2).

3.4. *Comparison of the diagnostic value of CUS and CUES*

Of the 102 masses, 51 were diagnosed as malignant and 51 were diagnosed as benign based on CUS, while 77 masses were diagnosed as malignant and 25 were diagnosed as benign based on CEUS. CEUS significantly outperformed CUS in differentiating SRMs (Table 4). Although CEUS and CUS were similar in terms of their specificity (80.9% *vs*. 71.4%), positive predictive value (94.8% *vs*. 88.3%), and false positive rate (19.1% *vs*. 28.6%) (p > 0.05 for all), they differed significantly in terms of their sensitivity (88.9% *vs*. 55.6%), negative predictive value (68.0% *vs*. 29.5%), false negative rate (9.9% *vs*. 44.5%), and accuracy (88.3% *vs*. 58.9%) (p < 0.05 for all).

4. Discussion

RCC is a malignant neoplasm that requires total or partial nephrectomy, and thus definite differentiation

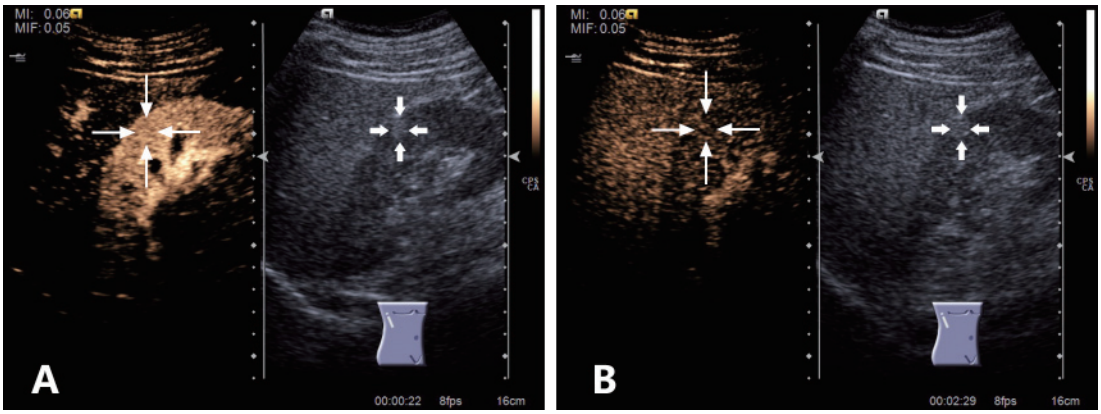

Figure 2. A 65-year-old man with angiomyolipoma. CUS revealed a hyperechoic small renal mass located in the middle of the right kidney (short arrows). **(A)** CEUS imaging in the early phase revealed homogeneous hyperenhancement similar to the peritumoral renal cortex (long arrows). There was no distinct boundary between the mass and the renal cortex; **(B)** CEUS imaging in the late phase showed that the region of the tumor was washed out in sync with perfusion of the peritumoral renal cortex (long arrows).

Table 4. Diagnostic performance of CUS and CEUS in comparison to pathology results

Modality	Sensitivity	Specificity	PPV	NPV	FPR	FNR	Accuracy
CUS	45/81(55.6)	15/21(71.4)	45/51(88.3)	15/51(29.5)	6/21(28.6)	36/81(44.5)	60/102(58.9)
CEUS	73/81(88.9)	17/21(80.9)	73/77(94.8)	17/25(68.0)	4/21(19.1)	8/81 (9.9)	90/102(88.3)
χ^2	3.883	0.071	0.075	3.878	0.324	14.276	7.080
p	0.049	0.790	0.784	0.049	0.569	0.000	0.008

CUS, conventional ultrasound; CEUS, contrast-enhanced ultrasound; PPV, positive predictive value; NPV, negative predictive value; FPR, false positive rate; FNR, false negative rate. Values are presented as the number (%).

between RCCs and benign masses is essential. Imaging studies such as CT, MRI, and US are essential to surgery to treat renal carcinomas. Among these modalities, CUS is usually the first choice for the diagnosis of RCC in China because it is readily accessible, inexpensive, noninvasive, and provides images in real time. However, CUS may be limited because of its lower accuracy in the characterization of some renal masses, and particularly small masses. The current study showed that, among all of the characteristics on CUS, only orientation and echogenicity allowed the differentiation of RCCs and AMLs. To the extent known, hypoechoic renal masses are mostly considered to be malignant while hyperechoic and iso-echoic renal masses are often referred to as benign. However, RCCs that were hyperechoic were noted in 15 masses (18.5%) and RCCs that were iso-echoic were noted in 25 masses (30.9%). Two AMLs (9.5%) were hypoechoic on gray-scale US in this study. Forman *et al*. (*8*) reported that approximately 30% of small RCCs appear as hyperechoic, which is how small benign renal masses similarly appear. In the current study, 6% of the benign renal masses were atypically iso-echoic and 29% of those masses were slightly hyperechoic. Moreover, small RCCs were similar to small AMLs in shape, margins, and homogeneity; both were mostly round/oval, circumscribed, and homogeneous in the present study. Just as US echogenicity is unreliable in differentiating solid renal masses, conventional color Doppler US may have limited ability to detect intratumoral vascularity in RCCs, with a sensitivity of 41% according to one source (*9*). The present study found that CDFI was not effective in the differentiation of the SRMs because of its low sensitivity. Therefore, further imaging studies are needed for patients with uncharacterized SRMs.

As a result of the recent development of microbubble contrast media and imaging techniques, CEUS has been actively used in the detection and differentiation of lesions in parenchymatous organs. Microbubble contrast agents, with a diameter ranging from 1-10 μm (median 2 μm), cannot be filtered by the lungs or enter interstitial fluid. Therefore, they are considered to be pure blood pool agents (*10*). Under US, microbubbles alternately contract and expand with the same resonance frequency as US waves by amplifying the ultrasound signal. Advantages of CEUS imaging include the ability to detect microvasculature that can be overlooked by CDFI. In addition, CEUS allows continuous dynamic imaging after injection as opposed to the intermittent static acquisitions possible with CECT and MR. SonoVue has been used to successfully detect and characterize focal liver lesions and their vascularity (*11*). SonoVue microbubbles consist of a sulphur hexafluoride gas with a phospholipid shell. This contrast agent is metabolized by the liver, and the sulphur hexafluoride gas is exhaled *via* the lungs. Therefore, it is relatively harmless with a lower incidence of adverse reactions,

such as nephrotoxicity (*12*). In addition, CEUS has advantages over CT and MRI including unmatched temporal resolution due to continuous real-time imaging and potential cost savings (*13*). Moreover, CEUS is suitable for patients with a metal implant who cannot undergo MRI. Updated in 2011, the guidelines of the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) recommend kidney CEUS for patients with renal artery stenosis, renal ischemia, and focal renal lesions, for the differentiation of solid renal masses and pseudotumors, and for the characterization of complex cystic masses and renal infections (*14*). Previous studies have found that CEUS is useful in differentiating malignant renal masses from benign ones (*6,7*). However, few studies have focused on the usefulness of CEUS in differentiating SRMs. The purpose of the present study, therefore, was to investigate the value of CEUS in the differential diagnosis of small RCCs and AMLs.

This study showed that CEUS outperformed CUS in the diagnosis of small renal tumors, as is evident in Table 4. The current findings were consistent with the results of previous studies. In a prospective study of 49 lesions (38 RCCs and 11 AMLs), Oh *et al*. (*15*) reported that CEUS had a sensitivity of 86.8%, a specificity of 63.6%, an accuracy of 81.6%, a positive predictive value of 89.2% and a negative predictive value of 58.3%. In a study of 137 lesions (117 RCCs and 20 AMLs), Ignee *et al*. (*6*) reported that CEUS had a sensitivity of 97%, a specificity of 45%, an accuracy of 90%, a positive predictive value of 91%, and a negative predictive value of 75%. The high diagnostic accuracy of CEUS can be ascribed to its performance in assessing vascular morphology and its enhancement patterns that allow evaluation of the micro- and macro-circulation of tumors.

Dynamic observation of blood perfusion with CEUS can provide more useful diagnostic information for the differentiation of RCCs and AMLs. The present study noted rapid accumulation of contrast media in the form of hyperenhancement in the early phase (64/81, 79%), followed by early washout in the late phase for most RCCs (63/81, 77.8%). In contrast, most AMLs (13/21, 61.9%) mainly had slow accumulation of contrast agents in the form of iso-enhancement, followed by a slow wash-out (10/21, 47.6%). Such findings may be related to the pathologic changes produced by RCCs and AMLs. RCC is characterized by numerous immature thin-walled blood vessels with widespread arterio-venous fistulas (*16*), whereas AML is a mesenchymal tumor consisting of a variable proportion of fat tissue, spindle and epithelioid smooth muscle cells, and abnormally thick-walled blood vessels (*17*).

Previous studies reported that RCCs often demonstrated heterogeneous enhancement on CEUS, which can be attributed to the fast growth of those malignant tumors. When the blood supply to the RCC cannot satisfy the growth of the tumor, intratumoral necrosis may result (*18*). AML, a benign tumor with slow growth, is unlikely to develop necrosis and it displays inhomogeneous enhancement. In the present study, there were no significant differences between RCCs and AMLs in terms of the frequency of homogeneous enhancement (66.7% *vs*. 85.7%; $p > 0.05$). This might be explained by the fact that the masses included in this study were smaller than those in previous studies and that there is a relatively low incidence of necrosis in small masses. Lu *et al*. (*19*) reported that CEUS resulted in homogeneous enhancement for all AMLs ($n = 18$) and for 34.3% of RCCs ($n = 105$). However, the maximal diameter of the masses ranged from 1.0 cm to 11.5 cm (mean 4.3 ± 2.1 cm). Jiang *et al*. (20) analyzed CEUS features of clear cell renal cell carcinoma in relation to tumor size, and they found that tumors ≤ 3 cm (72%) had a significantly higher frequency of homogeneity than did tumors > 3cm (9%) ($p < 0.05$).

Rim-like enhancement around the tumor might represent the tumoral pseudocapsule resulting from compression, ischemia, and necrosis produced by tumor growth in the adjacent normal parenchyma, with subsequent deposition of fibrous tissue (*21*). The present study noted significant differences between the rim-like enhancement of RCCs and AMLs ($p = 0.000$). However, rim-like enhancement was observed in only 55.6% (45/81) of RCCs, which is similar to the figure (56.7%, 34/60) reported by Jiang *et al*. (*20*) in clear cell RCCs ≤ 3 cm. However, this figure is significantly lower than that in other studies. Xu *et al*. (*22*) reported noting rim-like enhancement in 79.6% (74/93) of RCCs. This difference may be due to the small size of the masses in the current study and the study by Jiang *et al*. (*20*). The current study found that 2 (9.5%) AMLs displayed incomplete rim-like enhancement. This might be related to the distribution of blood vessels in AMLs. Rim-like enhancement of AMLs needs to be investigated further.

The current study has several limitations. First, this study examined fewer AMLs than RCCs, so a larger sample size is needed for further evaluation. Second, this study included few papillary RCCs, chromophobe RCCs, or chromophobe RCCs. A larger set of samples is needed to further confirm the enhancement features of these RCCs. Finally, CEUS has limited ability to image the kidneys because of the interference of bowel gas, the ribs, and large body habitus (obesity), and CEUS can be influenced by the lesion location, as is true of CUS. In such instances, CECT can provide additional information.

Based on the present findings, the unique features of CEUS are useful in evaluating SRMs with a higher level of accuracy than CUS. CEUS may serve as a promising modality in the differential diagnosis of small RCCs and AMLs.

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