

Original Article

Diagnostic efficacy of contrast-enhanced ultrasonography for small renal cell carcinoma

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Abstract: Objective: To analyze the characteristics of contrast-enhanced ultrasonography (CEUS) on the small renal cell carcinoma (SRCC), and to discuss the application and clinical significance of CEUS in the diagnosis of SRCC. Methods: From April 2011 to February 2015, Eighty-nine patients with 89 renal lesions who had undergone CEUS were retrospectively studied. All of the lesions were histopathologically proved. Contrast-enhanced ultrasonography was performed using low-acoustic power modes and a sulfur hexafluoride-filled microbubble contrast agent. The conventional ultrasonography (US), contrast-enhanced computed tomography (CECT) and CEUS images were analyzed respectively. The conventional US was mainly used to observe the position, size, shape, border, echogenicity and blood supply of tumor. The dynamic change of the enhancement from the cortical phase to the late phase, the enhancement patterns, degree of enhancement and pseudocapsule at different phases were evaluated by CEUS. The accuracy rate, visualization rate of blood flow, visualization rate of pseudocapsule and focal necrosis area were compared between the conventional US and CEUS. Study on comparison with the results between CEUS and CECT. Results: Among these 72 renal lesions, 55 clear cell carcinomas, 3 chromophobe cell carcinomas, 3 papillary carcinomas, 1 acidophilic cell adenoma (malignant potentially) and 10 angiomyolipomas (AML) were confirmed through postoperative histopathologically. The accuracy rate, visualization rate of blood flow, visualization rate of pseudocapsule and focal necrosis area of lesions display rate of SRCC by the conventional US and CEUS are 76.3% (55/72), 65.2% (47/72), 13.9% (10/72), 11.1% (8/72) and 90.2% (65/72), 100.0% (72/72), 75.0% (54/72), 62.5% (45/72), respectively. CEUS had the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for SRCC diagnostic efficacy of 95.1% (59/62), 60.0% (6/10), 93.6% (59/63), 66.6%(6/9), and 90.2% (65/72), respectively. The lesions of small renal cell carcinoma mostly were manifested as abundant blood-supply, and showed CEUS pattern of "fast-in and slow-out, hyperenhancement, heterogeneous enhancement and perilesional rim-like enhancement". The detection rate of blood flow in CEUS was 100%. CEUS can effectively reflect the blood supply of the lesions compared with baseline sonograms, and can sensitively display pseudocapsule and necrotic area of lesions, so has higher diagnostic sensitivity. The differences between them were statistically significant ($P<0.001$). The difference in diagnosis on SRCC by CEUS and CECT has no statistic significance ($P>0.05$). Conclusion: The CEUS has higher sensitivity in showing low-speed blood flow and microcirculation blood supply situation within SRCC compared with conventional US. It is helpful to the diagnosis of SRCC, and has a certain clinical value. CEUS and CECT complement each other in the diagnosis of SRCC.

Keywords: Contrast-enhanced ultrasonography, renal neoplasms, renal cell carcinoma, ultrasonography

Introduction

Small renal cell carcinoma (SRCC) refers to renal carcinoma of tumor diameter ≤ 3 cm. incidence of SRCC nearly accounts for 8.7%-25.4% of renal carcinoma [1]. The symptoms of SRCC rarely appeared in its early stage, and mostly were discovered accidentally. Once the clinical symptoms such as lumbodynia, hematuria, abdominal lump occurred, it developed to mid-to-late stage, and had worse prognosis. Th-

erefore, early diagnosis of SRCC had important significance to the selection of clinical treatment and prognosis of patients. The conventional Ultrasound (US) is are liable imaging technique for the early diagnosis of renal cell carcinoma (RCC). It is a readily accessible, cost-effective, noninvasive imaging modality that provides real-time features. However, it may not provide differentiation in special cases of RCC and renal angiomyolipoma (AML). The usefulness of US is limited because of its lower accu-

racy in the characterization of such small renal masses. RCC is a malignant neoplasm, which requires total or partial nephrectomy, and thus definite distinction between RCC and AML is essential. Patients with uncharacterized small renal masses have to be examined by further imaging study such as CECT and contrast-enhanced magnetic resonance imaging (MRI) for confirmation. CECT remains the most appropriate imaging modality for differentiating benign from malignant lesions; the sensitivity and specificity of CECT for the differentiation of RCC from other subtypes of renal tumors have been reported as 74% and 100%, and 84% and 91%, respectively [2].

Recently, the development of new contrast media and imaging techniques has enabled contrast-enhanced ultrasound (CEUS), which is already being actively used in organs such as the liver.

CEUS can be used to observe the continuous micro- and macrocirculation of a renal mass, which may also be useful in the diagnosis of a renal mass. In view of these, we conducted a retrospective analysis for the CEUS characteristics of 72 SRCC patients hospitalized in this study, and compared its results with that of conventional US and CECT to probe the application value in diagnosing SRCC. The reports were as following.

Materials and methods

Patients

Between April 2011 to February 2015, a total of 89 consecutive patients underwent CEUS after being diagnosed with renal masses first detected by baseline US. In this study, the 72 included patients were 42 men and 30 women with a mean age $\pm$ SD of 35.9 ± 11.7 years (range, 25-68 years). The tumor size ranged from 0.9 to 3.0 cm, and mean diameter was 2.01 ± 1.15 cm. The remaining 17 patients were excluded because of the following reasons: (1) no definite final diagnoses ($n = 10$); and (2) other final diagnoses in 7 patients, including renal metastasis in 2, complex cysts in 5. Specimens were obtained from surgical resections, which were all performed by a single. The final diagnosis was confirmed by histopathological examination as RCC ($n = 62$) or AML ($n = 10$). Informed consent was obtained from all patients, and the study was approved by the Ethical Committee of the hospital.

Equipments and contrast agents

CEUS: Conventional US and CEUS were performed using the same ultrasound scanner (IU22; Philips Medical Solutions) and C5-2 vector transducer with frequency range of 3.0-5.0 MHz. A contrast-specific software operating at low acoustic power-contrast pulse sequencing (CPS; Philips Medical Solutions)-was installed in the scanner, low mechanical index (MI) values were used (0.07-0.20 for CPS). The ultrasonographic contrast agents (UCA) used in this study was SonoVue (Bracco SpA, Milan, Italy), a sulfur hexafluoride (SF₆)-filled microbubble UCA that is stabilized by phospholipids. Each bottle contains 59 mg SF₆ gas and 25 mg white freeze drying powder. A total of 2.4 mL of SonoVue was injected into the antecubital vein in a bolus fashion through a 20-gauge intravenous cannula, followed by a flush of 5 mL of a 0.9% sodium chloride solution.

Contrast-enhanced ultrasonography

The patient accepted examination of conventional ultrasonography in the supine or lateral position. The observation contents included the position, size, shape, border, echogenicity and blood supply of tumor. Taking the cross section displaying lesion and adjacent nephridial tissue as the best face for contrast observation, then switched to mode of CEUS. The timer was activated simultaneously at the beginning of SonoVue administration. The patient was told to hold or slow down the respiratory frequency as far as possibly. The transducer was kept in a stable position, and the real-time imaging feature of inside of tumor was continuously observed for 3-4 minutes. A timer was started immediately after the injection of the ultrasound contrast agent. The vascular phases of CEUS were classified into cortical (8-15 to 30-35 seconds after UCA injection), corticomedullary (36-41 to 120 seconds), and late (>120 seconds to the disappearance of bubbles). Digital video clips of characteristic conventional US and CEUS images were stored for off-line analysis.

Image analysis

The conventional ultrasonography and CEUS images were retrospectively analyzed in consensus by 2 radiologists who both had at least 4 years of experience in renal CEUS. The image

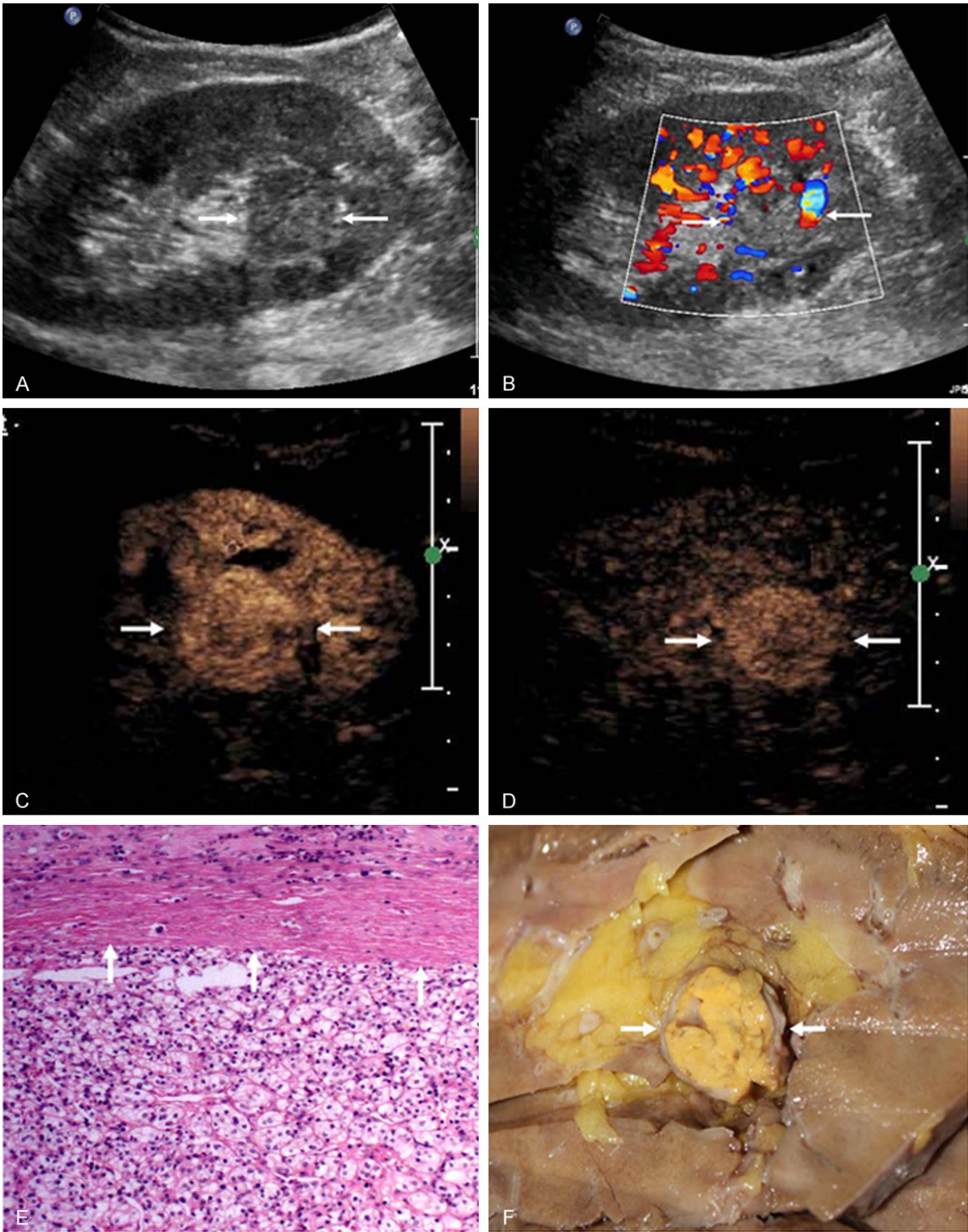


Figure 1. Conventional ultrasonography and CEUS in a 57-year-old woman with SRCC. A. Baseline ultrasonography shows a well defined mass (arrows) with slightly hyperechogenicity relative to adjacent renal parenchyma in the left kidney. B. CDFI showed pointed blood flow signal in the internal tumor (arrows). C, D. In the cortical and late phases of CEUS, the tumor (arrows) shows “fast-in and slow out” and heterogeneous enhancement and the peritumoral rim enhancement (arrows). E. Pathology showed left renal clear cell carcinoma and the pseudocapsule is composed of fibrous tissue (arrows), Nucelus level:II (HE staining, ×400). F. Specimen showed the formation of Peritumoral pseudocapsule (arrows).

data in the stored instrument was replayed. The parameters described below were evaluat-

ed and recorded: the initial enhancement time of the tumor and renal cortex, the dynamic

Table 1. Contrast-Enhanced ultrasonographic Findings of SRCC

Tumor types	Dynamic change of the enhancement			Enhancement mode		Enhancement degree			Pseudo-capsule	
	Fast-in and Slow-out (44)	Fast-in and fast-out (14)	Slow-in and fast-out (4)	Homogeneous (30)	Heterogeneous (32)	Hyperenhancement (39)	Isoenhancement (19)	Hypoenhancement (4)	Yes (47)	No (15)
Clear cell carcinoma	41	14	0	28	31	36	19	0	44	11
Chromophobe cell carcinoma	1	0	2	1	0	1	0	2	1	2
Papillary carcinoma	1	0	2	0	1	0	0	2	1	2
Acidophilic cell adenoma	1	0	0	1	0	1	0	0	1	0

CEUS significantly increased the accuracy rate, visualization rate of blood flow, visualization rate of pseudocapsule and focal necrosis area of lesions for SRCC compared with conventional US (Table 2).

Table 2. Comparison of conventional US and CEUS on the accuracy rate, visualization rate of blood flow, visualization rate of pseudocapsule and focal necrosis area for SRCC

Examining method	Accuracy rate	Visualization rate of blood flow	Visualization rate of pseudocapsule	Visualization rate of focal necrosis area
Conventional us	76.3 (55/72)	65.2 (47/72)	13.9 (10/72)	11.1 (8/72)
CEUS	90.2 (65/72)	100.0 (72/72)	75.0 (54/72)	62.5 (45/72)
χ^2	5.000	30.252	55.879	40.874
P-value	0.043	0.000	0.000	0.000

With respect to CECT, the differential diagnosis on renal carcinoma (lesion diameter <3 cm) in perspective of benign and malignant has no statistical significance (Table 3).

change of the enhancement from the cortical phase to the late phase, enhancement patterns, degree of enhancement and pseudocapsule on CEUS. The initial enhancement time of the tumor and the dynamic change of the enhancement from the cortical phase to the late phase were classified as follows: (1) fast-in and fast-out, (2) “fast-in and slow-out”, (3) “slow-in and fast-out”, (4) “slow-in and slow-out”. Fast-in referred to initial enhancement time of the tumor was earlier than renal cortex. Fast-out referred to time of contrast agents exiting tumor was earlier than renal cortex [3]. And vice versa. The contrast enhancement patterns were classified as follows: (1) no enhancement, i.e, no appearance of microbubble signals in the lesion; (2) homogeneous enhancement, i.e, uniform enhancement; (3) heterogeneous enhancement, i.e, different enhancement extents within the lesion, the enhancement degree of the tumor was classified as hyperenhancement, isoenhancement, hypoenhancement, and nonenhancement. Perilesional rim enhancement (i.e, the so-called pseudocapsule) was recorded, which was defined as an enhanced rim of peritumoral tissue that appeared in the cortical phase and became distinct in the late phase [4, 5].

Statistical analysis

All statistical analyses were performed by using SPSS Statistics ver.16.0. All data are presented as mean $\pm$ standard deviation (SD). The χ^2 -test was applied for the comparison of perfusion characteristic of CEUS. The Pearson χ^2 or Fisher exact test was applied to compare the diagnostic accuracy rate, blood flow visualization, rate of pseudocapsule and focal necrosis area of lesions for SRCC by US and CEUS. Statistical examination was performed by matched McNemar χ^2 test to comparison of benign and malignant lesion results of diagnosis on renal carcinoma by CEUS and CECT. The significant level is set at 0.05. $P < 0.05$ was considered to indicate a statistically difference, $P < 0.01$ was considered to indicate a statistically significant difference, and $P > 0.05$ was considered to indicate no statistically difference.

Results

Surgical results

The diagnoses of 72 renal lesions in the study were confirmed by means of surgery. The histopathological examination showed there were

Table 3. Comparison of benign and malignant lesion results of diagnosis on renal carcinoma by CEUS and CECT

Consecutive				
Examining Method	Pathological Result			
	Malignant	Benign	Total	P-value
CEUS				
Malignant	59	4	63	1.000
Benign	3	6	9	
CECT				
Malignant	56	3	59	0.508
Benign	6	7	13	

The difference in diagnosis on SRCC by CEUS and CECT has no statistic significance ($P>0.05$). CEUS had the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for SRCC diagnostic efficacy of 95.1% (59/62), 60.0% (6/10), 93.6% (59/63), 66.6% (6/9), and 90.2% (65/72), respectively. (Table 4).

55 clear cell carcinomas, 3 chromophobe cell carcinomas, 3 papillary carcinomas, 1 acidophilic cell adenoma (malignant potentially) and 10 AMLs.

Conventional ultrasonography

62 SRCCs all showed quasi-round tumors with sharply margined. Among them, 40 renal tumors were up to the kidney surface or completely on the surface of kidney, 22 renal tumors were located in renal parenchyma. 26 renal tumors showed hyperechoic or slightly hyperechoic, 20 renal tumors showed hypoechoic, 9 renal tumors showed isoechoic, and 7 renal tumors showed mixechoic. CDFI showed that 27 renal tumors displayed spherical rich blood flow signals with interior extension, 19 renal tumors displayed pointed or strip blood flow signal, and 16 renal tumors did not displayed blood flow signals. 10 AMLs all showed quasi-round tumors with clear boundary. 10 AMLs were located in renal parenchyma, and showed hyperechoic, homogeneous, and sharply margined. CDFI showed that 3 renal tumors displayed pointed or strip blood flow signal, and 7 renal tumors did not displayed blood flow signals.

Contrast-enhanced ultrasonography performance

62 SRCCs showed enhancement of contrast agents (62/62, 100%), the detecting rate of

blood flow in CEUS was 100%. Among 62 SRCC cases, 44 renal tumors showed “fast-in and slow-out” (Figure 1), 14 renal tumors showed “fast-in and fast-out”, 4 renal tumors showed “slow-in and fast-out”. On the enhancement patterns, 30 renal tumors showed homogeneous enhancement, 32 renal tumors showed heterogeneous enhancement, on the enhancement degree, 39 renal tumors showed hyperenhancement, 19 renal tumors showed isoenhancement, 4 renal tumors showed hypoenhancement. On the peritumoral rim enhancement, 47 renal tumors showed pseudocapsule, 15 renal tumors showed non-pseudocapsule (Table 1). 10 AMLs showed isoenhancement of contrast agents. 8 AMLs showed homogeneous enhancement, 2 AMLs showed heterogeneous enhancement. Sustained hyperenhancement was observed in most (9/10).

Discussion

Renal cell carcinoma (RCC) is the most common primary kidney tumor and accounts for 80%-90% of primary kidney malignant tumor. When diagnosed, it often developed to mid-to-late stage, and had worse prognosis. SRCC refers to renal carcinoma of tumor diameter ≤ 3 cm and incidence of SRCC nearly accounts for 8.7%-25.4% of renal carcinoma [1]. The symptoms of SRCC rarely appeared in its early stage, and mostly were discovered incidentally. Research showed SRCC with diameter less than 3 cm had big differences in the biological characteristics, clinical manifestations, treatment and prognosis compared with the renal cell carcinoma with diameter more than 3 cm [6]. SRCC with diameter less than 3 cm was well-differentiated, had no clinical manifestation, had pseudocapsule, and had rarely distant metastasis. The recurrence rate of this tumor was 0%-3% after operation of partial nephrectomy or enucleation of the tumor. However, renal cell carcinoma with diameter more than 3 cm was low-differentiated, had distant metastasis. The recurrence rate was 16% after implementation of radical excision operation [7]. Therefore, the early diagnose of SRCC has important significance for the selection of clinical treatment and prognosis of patients.

Since its introduction into clinical practice, the usefulness of conventional US for earlier diag-

Table 4. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of conventional CEUS and CECT

Examining Method	Sensitivity	Specificity	PPV	NPV	Accuracy
CEUS	95.1% (59/62)	60.0% (6/10)	93.6% (59/63)	66.6% (6/9)	90.2% (65/72)
CECT	90.3% (56/62)	70.0% (7/10)	94.9% (56/59)	53.8% (7/13)	87.5% (63/72)

CEUS, contrast-enhanced ultrasound. NPV, negative predictive value; PPV, positive predictive value.

nosis of renal masses has been well established. Although US has been widely used for evaluating the kidney, many reports have shown its limitations for tumor detection and characterization. About 77% of SRCCs were observed to have various echogenicity, and a minority showed hyperechogenicity (32%) such that these lesions could not be distinguished from renal AMLs [8, 9]. Therefore, conventional US has limited ability to characterize renal tumors, and further imaging examination such as CECT or MRI is currently required. Already, CEUS has been shown to have high diagnostic efficacy in characteristic images of liver tumors compared with conventional US [10]. Unlike the contrast agents used in CECT and MRI, CEUS contrast agents are present in microbubbles, which do not diffuse through the vascular endothelium into the interstitium [11]. These molecular features allow evaluation of both the micro- and macrocirculation of kidney and tumor tissues and can provide a better approach of vascular morphology and characteristic image enhancement. In addition, second-generation US contrast agents have been reported to increase the diagnostic confidence for renal tumors in terms of improved renal lesion conspicuity and effective delineation of tumor microvessels.

Among 62 SRCC cases, 16 renal tumors did not displayed blood flow signals in CDFI, and 46 renal tumors displayed blood flow signals with the detection rate of blood flow in CDFI being 74.1% (46/62). The main reason was that CDFI easily displayed the large blood flow signal, and had some limitation in displaying small and low-speed blood flow signal [12]. The detection rate of blood flow of internal structure of CEUS improved to 100% compared with 74.1% of CDFI, which was consistent with reference reports [13]. Conventional ultrasonography of some patients in this group showed hyperechoic and unobvious blood flow, and it was difficult to differentiate angiomyolipoma. Meanwhile, CEUS could better show low-speed blood flow

signal, and diagnosing rate improved greatly compared with conventional ultrasonography.

In the aspect of CEUS dynamic change of the enhancement, enhancement degree and pseudocapsules, 44 renal tumors showed “fast-in and slow-out”, 14 renal tumors showed “fast-in and fast-out”, 4 renal tumors showed “slow-in and fast-out”; 39 renal tumors showed hyperenhancement, 19 renal tumors showed isoenhancement, 4 renal tumors showed hypoenhancement; 47 renal tumors showed pseudocapsule, 15 renal tumors showed non-pseudocapsule. It revealed that SRCC mostly were rich blood supply and had tumor vessels with large internal diameter [14]. Blood vessel distorted and a large number of cancer embolus formed, which caused contrast agents stay at the vascular bed, and made radiography enhanced time prolong within tumor vessels. Its CEUS features showed mode of “fast-in and slow-out” and hyperenhancement, which truly reflected the characteristics of rich blood supply in small renal cell carcinoma. Peritumoral rim enhancement may be a special manifestation for RCC on CEUS. The thin rim enhancement might represent the tumoral pseudocapsule, which results from tumor growth, producing compression, ischemia, and necrosis to adjacent normal parenchyma, with subsequent deposition of fibrous tissue and is usually associated with a low histologic grade RCC. The presence of a pseudocapsule is considered a sign for discriminating RCC and may be a useful criterion for nephron-sparing surgery [15]. Ascenti et al. [16] found that detection rate of pseudocapsules in renal cell carcinoma increased from 19% of conventional ultrasonography to 87.5% of CEUS. Yang Bin et al. [17] found 59% of renal cell carcinoma showed pseudocapsules. Our data showed that detection rate of pseudocapsules of CEUS was 75.0% (54/72), which was consistent to previous studies. Pseudocapsule was the specific pathological features of clear cell carcinoma [18, 19], and had a certain reference value in the differential diagnosis.

In the present study, “fast-in and slow-out”, hyperenhancement, heterogeneous enhancement and perilesional rim-like enhancement were the most common findings for SRCCs. These were characteristic patterns in SRCCs with sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 95.1%, 60.0%, 93.6%, 66.6%, and 90.2%, respectively.

As for the lesion necrosis areas, because small hemorrhagic necrosis area within tumor mass was influenced by partial volume effect of ultrasound, conventional ultrasonography often showed isoechoi or mixechoi [20]. However, CEUS usually showed no enhancement, and formed contrast with the surrounding enhanced tumor area to provide a strong basis for the diagnosis. Most RCC nodules showed hypervascular heterogeneous enhancement, which indicated intratumoral necrosis or hemorrhage in the tumors. In our study, 45 renal tumors CEUS showed heterogeneous enhancement.

Within 62 renal tumors in this group, 4 renal tumors were misdiagnosed by CEUS, all of them were slightly hyperechoic masses. CEUS showed scarce blood supply such as slow-in and fast-out, hypoenhancement and non-pseudocapsules so as to be misdiagnosed as angiomyolipoma. Finally, postoperative pathology confirmed they were chromophobe cell carcinoma and papillary carcinoma. Li Fan et al. [21], the domestic scholar, found in the study of CEUS perfusion characteristics in renal carcinoma that 90% of clear cell carcinomas showed hyperenhancement and rich blood supply, however, chromophobe cell carcinoma and papillary carcinoma showed hypoenhancement and lacking blood supply. CEUS of angiomyolipoma often showed slow-in and slow-out and slow centripetal enhanced, which was helpful to identify.

With respect to SRCC, the CECT has high diagnostic value. According to references [22], the accuracy is 75% and it can make clear diagnosis on connected area metastasis and distant metastasis. By CT non contrast enhanced scan, it is showed as iso-intensity or little hypo-intensity, few of them will be manifested as hyper-intensity as a result of bleeding. In these cases, three of SRCCs were misdiagnosed by CECT. And all of them are ischemic with less and slow blood flow, which makes carcinoma be manifested as hypoenhancement.

In conclusion, our results suggest that CEUS features of “fast-in and slow-out”, hyperenhancement, heterogeneous enhancement and perilesional rim-like enhancement allow confirmation of SRCC. Compared with conventional US, CEUS can display more sensitively the microcirculation of blood supply of SRCC and low-speed blood flow conditions, and can better reflect the internal structure and blood supply of SRCC. CEUS improved the sensitivity and accuracy of the diagnosis of SRCC, and had certain clinical application value. CEUS and CECT complement each other in the diagnosis of SRCC.

Disclosure of conflict of interest

None.

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