

Original Article

Comparison of contrast-enhanced ultrasonography and contrast-enhanced computed tomography in the diagnosis of cystic renal cell carcinoma

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Abstract: Objective: To analyze the imaging features of contrast-enhanced ultrasonography (CEUS) on the cystic renal cell carcinoma (CRCC), and to assess the application value and clinical significance of CEUS in evaluating CRCC compared with conventional ultrasonography (US) and contrast-enhanced computed tomography (CECT). Methods: From April 2013 and July 2016, Thirty-two patients with 32 cystic lesions including 26 cases of CRCC and 6 cases of renal cysts who had undergone CEUS were retrospectively studied. All of the lesions were histopathologically proved. Evaluate diagnostic value of the conventional ultrasonography (US), CEUS and contrast-enhanced computed tomography (CECT) for CRCC. The conventional US was mainly used to observe the position, size, shape, border, echogenicity and blood supply of tumor. The CEUS mainly observes the enhancement performance of wall, septa and solid component of cystic lesions. The parameters include enhancement patterns, enhancement degree and pseudocapsule. The imaging findings and histopathological results were contrasted for statistically comparing capability of diagnosis on CRCC. Results: Among these 32 cystic lesions, 14 multilocular cystic renal cell carcinomas, 12 clear cell carcinomas and 6 renal cysts were confirmed through postoperative histopathologically. The accuracy rate, visualization rate of blood flow and visualization rate of pseudocapsule display rate of CRCC by the conventional US and CEUS are 62.3% (20/32), 31.2% (10/32), 12.5% (4/32) and 90.6% (29/32), 93.7% (30/32), 71.8% (23/32), respectively. CEUS can effectively reflect the blood supply of the lesions compared with the conventional US, so has higher diagnostic accuracy. The differences between them were statistically significant ($P < 0.01$). By Receiver Operating Characteristic (ROC) curve analysis, this CECT (Area under the Curve (AUC)=0.776, $P=0.038$) and CECT (AUC=0.878, $P=0.004$), but not US (AUC=0.577, $P=0.562$) signature showed high accuracy in discriminating malignant from benign cystic lesions. The difference in diagnosis on CRCC by CEUS and CECT has no statistic significance ($P > 0.05$). Conclusion: The CEUS can sensitively and effectively show the blood supply situation within CRCC. It is helpful to the diagnosis of CRCC, and has a certain clinical value. The Contrast-enhanced ultrasonography may play a similar role to contrast-enhanced computed tomography in the diagnosis of cystic renal cell carcinoma.

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

Introduction

Cystic renal cell carcinoma (CRCC) refers to a renal carcinoma featured as cystic or cystic-solid change in imaging examination. It is a subtype of renal cell carcinoma that rarely seen, which accounts for 10%-15% [1] and the prognosis is good. It is hard to be differentiated from renal carcinoma since the image featuring as complex cysts, which including hemorrhagic cysts, infectious cysts and simple separate cysts. The diagnosis of these complex cysts is based on enhanced CT and MRI [2].

Contrast-enhanced ultrasonography is a new technology developing rapidly in recent years. It

can sensitively display the situation of microvessels in tumor tissues. In our study, we retrospectively analyzed the imaging features of CEUS for 32 cases of renal cystic lesions, and compares the examination results of conventional US and CECT. The purpose of this paper is to evaluate the clinical value of CEUS in diagnosing CRCC.

Materials and methods

Patients

Between April 2013 and July 2016, a total of 32 consecutive patients underwent CEUS after being diagnosed with Cystic Renal lesion first

CEUS vs CECT in the diagnosis of CRCC

Table 1. Baseline characteristics of study patients

Characteristics	Number of patients
M/F ratio	20/12
Age (yrs)	40.2 ± 10.3
Tumor size (cm)	3.01 ± 2.15
Clinical manifestation	
Painless hematuria	6
Hematuria and lumbago	3
Asymptom	23

M, male; F, female.

detected by conventional US and histopathologically proved. In this study, the included 32 patients were 20 men and 12 women with a mean age ± SD of 40.2 ± 10.3 years (range, 25-68 years). The tumor size ranged from 1.1 to 11.0 cm in diameter (mean ± SD, 3.01 ± 2.15 cm). The clinical manifestation of 6 cases of painless gross hematuria, 3 cases of hematuria and lumbago and 23 cases without symptom that confirmed in conventional physical examination (**Table 1**). This study was approved by the ethics committee, which is equivalent to an institutional review board, at our institution and patient informed consent was obtained after the procedure had been fully explained.

Contrast-enhanced ultrasonography examinations

Conventional US and CEUS were performed using the same ultrasound scanner (IU22; Philips Medical Systems, The Netherlands, C5-1, 1-5 MHz). A contrast-specific software operating at low acoustic power-contrast pulse sequencing (CPS; Philips Medical Solutions)-was installed in the scanner, low-acoustic power modes were used with a mechanical index (MI) of 0.10-0.20. The Ultrasonographic contrast agents (UCA) used in this study was SonoVue (Bracco, Milan, Italy), a sulfur hexafluoride (SF₆)-filled microbubble UCA that is stabilized by phospholipids.

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 lesion. Taking the cross section displaying lesion and adjacent nephridial tissue as the best face for contrast observation, then switched to mode of CEUS. A total of

2.0 mL of SonoVue was shook 5 s then injected into the antecubital vein in a bolus fashion followed by a 5-mL saline flush. The timer was activated simultaneously at the beginning of contrast agent 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 mean scan time used for CEUS was about 3 min. 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). All of the scanned images were automatically stored in the picture archiving communication systems. All the examinations described above were performed by an ultrasonography physician (Xin-Chun Yuan) with rich experience in US (15 years) and in CEUS (4 years with Levovist and then 8 years with SonoVue).

Contrast-enhanced CT examinations

The CT examinations were performed using one of two CT scanners: Lightspeed 64 (GE Medical Systems, Milwaukee, USA) and Somatom definition 64 (Siemens Medical System, Erlangen, Germany). The section thickness ranged 2.5-5 mm slice and 2.5-5 mm slice interval, All patient received 120-140 mL (300 mg I/mL) of non-ionic iodinated contrast material (Omnipaque, Nycomed, Zurich, Switzerland) at a rate of 2-3 mL/s followed by 50 mL of saline flush. Contrast-enhanced images were obtained in the corticomedullary (25-30 s) and nephrographic (80-90 s) phases.

Image interpretation

All conventional US, CECT and CEUS images were retrospectively analyzed in consensus by 2 radiologists who both had at least 4 years of experience in renal CEUS. The radiologists were unaware of clinical information and histological findings and images were assessed based on the imaging features of renal cystic lesions. CT images for each patient were first interpreted and then CEUS images in the same patient were reviewed.

To observe the enhancement performance of cyst wall, septa and solid components. The parameters described below were evaluated and recorded: enhancement patterns, enhance-

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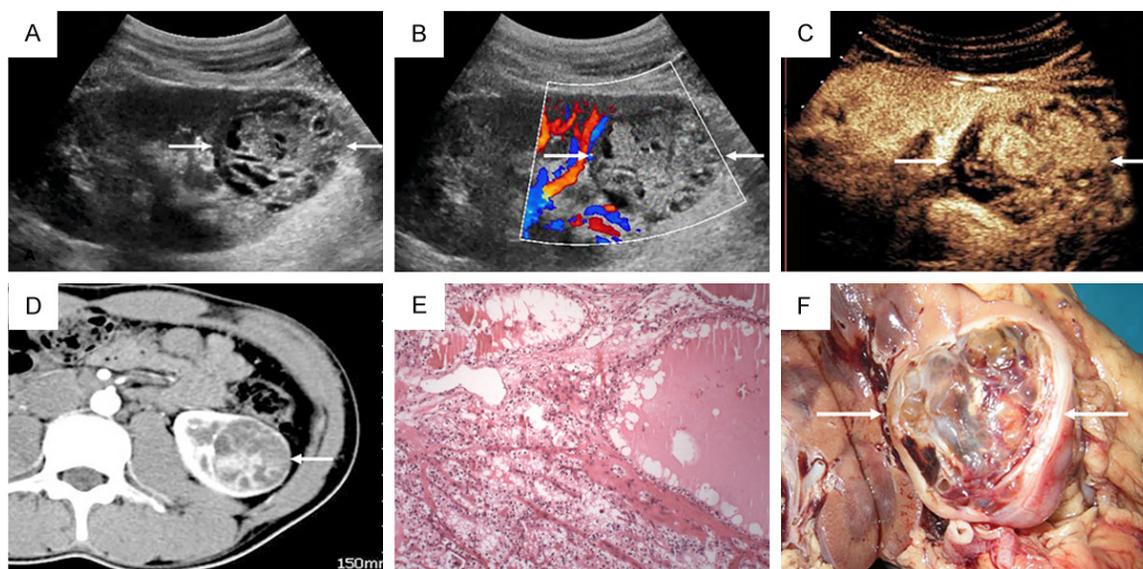


Figure 1. Conventional ultrasonography and CT and CEUS in a 65-year-old woman with CRCC. A. Two-dimensional ultrasound showed well-defined, 3-cm multiloculated cystic mass (arrows) with several thin septa. B. CDFI showed no blood flow signal in internal tumor and septa (arrows). C. CEUS showed hyperenhancement in internal tumor and septa, heterogeneous enhancement and the peritumoral rim enhancement (arrows). D. CECT showed heterogeneous enhancement (arrows). E. Pathology showed multilocular cystic renal cell carcinoma, MCRCC (HE staining, $\times 400$). F. Specimen showed large septa, cyst fluid and the formation of Peritumoral pseudocapsule (arrows).

ment degree and pseudocapsule on CEUS. The enhancement patterns 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”, (5) “equal-in and equal-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 enhancement degree of the tumor was classified as hyperenhancement, iso-enhancement, hypoenhancement, and non-enhancement. 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].

The imaging diagnostic criteria for cystic renal cell carcinoma is: on the color Doppler flow imaging (CDFI), the cyst wall, septa and solid component display color blood signal; on the CEUS image, the cyst wall, septa and solid component have contrast agent perfusion; while in CECT scanning, the CT value of cyst wall, septa and solid component increased by 15HU above comparing with routine CT scan [5]. The imaging results and postoperative and histopatho-

logical results were contrasted for statistically comparing capability of diagnosis on CRCC.

Statistical analysis

All statistical analyses were performed with the SPSS 16.0 (SPSS Inc., Chicago, IL, USA) software package. Continuous variables were expressed as mean \pm standard deviation (SD). The Pearson χ^2 or Fisher exact test was applied to compare the diagnostic accuracy rate, blood flow visualization and rate of pseudocapsule of lesions for CRCC 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. A *P* value of less than 0.05 was considered to indicate a statistically significant difference.

Results

Surgical results

The diagnoses of 32 renal cystic lesions in the study were confirmed by means of surgery. The histopathological examination showed there were 14 multilocular cystic renal cell carcinomas, 12 clear cell carcinomas, 6 renal cysts, and cystic degeneration, 6 renal cysts.

CEUS vs CECT in the diagnosis of CRCC

Table 2. Conventional US and CEUS on the accuracy rate, visualization rate of blood flow, visualization rate of pseudocapsule for CRCC

Method	Accuracy rate	Visualization rate of blood flow	Visualization rate of pseudocapsule
Conventional US	62.3 (20/32)	31.2 (10/32)	12.5 (4/32)
CEUS	90.6 (29/32)	93.7 (30/32)	71.8 (23/32)
χ^2	7.053	26.667	23.127
P-value	0.008	0.000	0.000

CEUS, contrast-enhanced ultrasonography; US, ultrasonography.

Table 3. Benign and malignant lesion of diagnosis on CRCC by CEUS and CECT

Examining method	Pathological Result		Total	P-value
	Malignant (n)	Benign (n)		
CEUS				
Malignant (n)	24	1	25	1.000
Benign (n)	2	5	7	
CECT				
Malignant (n)	23	2	25	1.000
Benign (n)	3	4	7	

CECT, contrast-enhanced computed tomography; CEUS, contrast-enhanced ultrasonography. P values were calculated using the chi-square test.

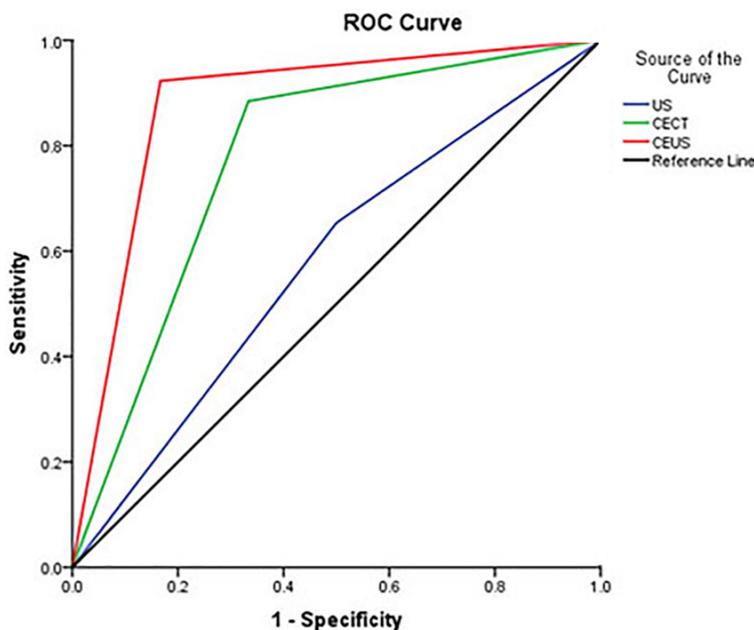


Figure 2. Receiver Operating Characteristic (ROC) curve shows the difference of diagnosis among US, CECT and CEUS by regression analysis. The value of area under curve (AUC) was showed following each method.

Conventional ultrasonography

32 lesions are solitary, 22 cases were cystic solid lesions indicated by two-dimensional US,

8 multilocular and septa cystic lesions, 2 lesions without septa and solid component; CDFI showed 10 cyst wall, septa and solid components featuring as dotted, short-rod and spherical blood flow signal, and 22 tumors did not displayed blood flow signals.

Contrast-enhanced ultrasonography performance

30 lesions showed enhancement of contrast agents in cyst wall, septa and solid components (**Figure 1**), 2 lesions showed no enhancement; on the enhancement patterns, 19 lesions showed “fast-in and slow-out”, 7 lesions showed “fast-in and fast-out” and 6 lesions showed “equal-in and equal-out”; on the enhancement degree, 18 lesions showed hyperenhancement, 8 lesions showed isoenhancement, 4 lesions showed hypoenhancement and 2 lesions showed nonenhancement; On the peritumoral rim enhancement, 23 lesions showed pseudocapsule and 9 lesions showed non-pseudocapsule.

Diagnostic performance

The detection rate of blood flow of CRCC's cyst wall, septa and solid component in CDFI was 31.2% (10/32), in the CECT was 65.6% (21/32) and in CEUS was 93.7% (30/32). The CEUS is sensitive to the blood flow of the tumor. CEUS significantly increased the accuracy rate, visualization rate of blood flow and visualization rate of pseudocapsule of lesions for CRCC compared with conventional US ($P < 0.01$) (**Table 2**). There was no statistical

difference between CEUS and CECT for diagnosing benign or malignant cystic lesions ($P > 0.05$) (**Table 3**). By Receiver Operating Characteristic (ROC) curve analysis (**Figure 2**),

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Table 4. The diagnosis value of US, CECT and CEUS for Benign and malignant lesion of CRCC by Receiver Operating Characteristic (ROC) curve analysis

Method	Sensitivity	Specificity	AUC \pm S.E.	P value
US	0.654	0.50	0.58 \pm 0.13	0.562
CECT	0.885	0.667	0.78 \pm 0.12	0.038
CEUS	0.923	0.833	0.88 \pm 0.10	0.004

CECT, contrast-enhanced computed tomography; CEUS, contrast-enhanced ultrasonography; AUC, Area under the Curve of ROC; S.E., Stand Error.

this CECT (Area under the Curve (AUC)=0.776, P=0.038) and CEUS (AUC=0.878, P=0.004), but not US (AUC=0.577, P=0.562) signature showed high accuracy in discriminating malignant from benign cystic lesions (Table 4). The difference in diagnosis on CRCC by CEUS and CECT has no statistic significance (P>0.05). Therefore, CEUS and CECT exhibited equivalent performance in diagnosing CRCC.

Discussion

CRCC refers to a renal carcinoma that is special and rarely seen [6, 7]. It is featured as cystic or cystic-solid change in imaging examination. The characteristic of CRCC in pathology is that the cyst wall and septa surface lining has one or more clear cell [8]. The cell grading and TNM is low and the prognosis is good. It is hard to be differentiated from renal carcinoma since the image featuring as complex cyst, which including hemorrhagic cysts, infectious cysts and simple separate cysts [9, 10]. Hence, it has importance significance for the early diagnosis and treatment on CRCC.

Along with the development and upgrade in ultrasonic and related equipments, there is a new method in diagnosis on CRCC. The ultrasonic contrast agent is a real blood pool imaging agent [11]. The acoustic impedance difference of vessel and tissues is increased by imaging agent. Through increasing the reflectivity of the interface, it can sensitively display the micrangium in tumor tissues and the rate of low-speed blood flow signal. Among 32 CRCC cases, 10 tumors did not display flood flow signal in CDFI and 20 tumors did not display flood flow signal. The detection rate of blood flow was 31.2% (10/32). The reason is that the CDFI is easily to display big blood flow signal but limited in display of small and low-speed blood flow

signal, particularly the blood flow signal of cyst wall, septa and solid component of cystic lesions. However, the display rate of blood flow in lesion by CEUS reached 93.7% (30/32), which is the highest compared with 31.2% (10/32) and 65.6% (21/32) of CDFI and CECT, respectively. The high sensitivity of displaying blood flow of tumor by CEUS makes diagnostic accuracy of CRCC increase from 62.3% to 90.6%, even higher than CECT (84.4%). The result is same as the previous study on CEUS in diagnosis on CRCC. Ascenti et al. [12] analyzed the evaluation of blood supply for 44 cases of renal focus live gray-scale CEUS imaging and CECT, and discovered 14 lesions enhanced in CEUS, 4 cases did not display enhancement in CECT. Then, they believed that CEUS is more sensitive than CECT in displaying blood supply in tumor.

However, in other aspect, since its high sensitivity in display of blood flow in lesion, it is hard to differentiate the CRCC from renal cyst with bleeding or inflammation, the irregular thickness of cyst septa, the solid component or its inner layer have less enhancement, which may result in false positive diagnosis, misdiagnosis [13]. In the data, one case of benign lesion was misdiagnosed for such circumstance. In the previous study, there were circumstances that the septa or solid component displayed enhancement in CEUS or CECT but confirmed as the benign lesion after surgery [14]. Hence, it does not indicate that it is the CRCC even CEUS displayed enhancement in septa. It shall combine with other characteristics of lesion and other imaging examination to confirm the result.

CEUS is helpful to display the wall, septa and solid component of lesion [15, 16]. Influenced by the obesity, bowel gas and depth of tumor of the patients, the inner structure of tumor did not display clearly in conventional US, and the specificity of cyst lesion is also low. However, CEUS can display inner septa and solid component, and can measure the septa thickness and wall thickness, describe the scale and size of liquefaction, necrosis and cyst change of tumor [17, 18].

In the aspect of CEUS enhancement patterns, enhancement degree and pseudocapsules, among 32 lesions, 19 lesions showed "fast-in and slow-out", 7 lesions showed "fast-in and

fast-out”, 6 lesions showed “equal-in and equal-out”; on the enhancement degree, 18 lesions showed hyperenhancement, 8 lesions showed iso-enhancement, 4 lesions showed hypoenhancement and 2 lesions showed non-enhancement; it indicates rich blood supply and big diameter of vessel in lesion. CEUS perfusion showed fast in and hyperenhancement, which is basically same as the enhancement pattern of malignant renal tumor. It has certain value in differential diagnosis on CRCC. In this group, 23 lesions showed pseudocapsules and 2 lesions showed non-pseudocapsules. The characteristic of pseudocapsules in CEUS is ring hyperecho around the tumor and that is the typical pathological feature of renal clear cell carcinoma [19]. It has referential value in differentiating clear cell carcinomas and same as the study report in the past.

In addition, the CRCC also needs to be differentiated from renal abscess and nephrotuberculosis [20]. The characteristic of them showed in conventional US are all anechoic in renal, aniso-thickness of wall. The difference in CEUS is (1) on nephropostasis, border irregular enhancement, “slow-in and slow-out” and hypoenhancement; (2) on renal abscess formed by nephrophthisis, heterogeneous enhancement in renal, honeycombing and septa enhancement.

CEUS also has some disadvantages over CT [21-23]. First, CEUS can be influenced by lesion location. A poor sonic window due to bowel gas or ribs prevents good quality image. Second, CEUS is an operator-dependent imaging modality and requires sufficient experience. Third, the US contrast agent used in our study has a high mechanical index and is unsuitable for continuous scan. A higher mechanical index leads to increase in the likelihood of microbubble because this index determines the level of interaction between bubbles and ultrasound. Therefore, second harmonic contrast agent requiring low mechanical index can be suitable for performing continuous scan and evaluating cystic renal masses.

In conclusion, CEUS can sensitively display the situation of low-speed blood flow and microcirculation blood supply and reflect the complex internal renal structure and blood supply of CRCC. It is helpful to the diagnosis of CRCC and

has certain clinical application value. The CEUS may play a similar role to CECT in the diagnosis of CRCC.

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Disclosure of conflict of interest

None.

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