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Original Article

Comparison of contrast-enhanced ultrasound and contrast-enhanced helical CT in the diagnosis of high echo-level small focal liver lesions

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Abstract: Objective: To compare the diagnosis accurate rate of contrast-enhanced ultrasound (CEUS) and contrast enhanced helical CT (CECT) in high echo-level small focal liver lesions (HSFLLs) (diameter ≤3 cm), and to explore the application value of CEUS in the diagnosis and differential diagnosis of the benign and malignant liver hyperechoic lesions. Methods: The institutional review board of Tumor Hospital of Guangxi Medical University approved the study protocol. The CEUS Time intensity curves (TICs) results of 75 cases (107 lesions) with HSFLLs detected by two-dimensional ultrasound (2DUS) were reviewed and analyzed. And the results were compared with CECT. Results: The area under the curve of CEUS and CECT were 0.941 and 0.936 respectively. The cut off value of CEUS diagnosis for malignant lesions was 2.5. The sensitivity, specificity and the accuracy of CEUS for diagnosing malignant hepatic tumors were respectively 90.0%, 89.4% and 89.71%, versus 90.0%, 87.2% and 88.79% in CECT. The positive predictive value of CEUS and CECT were 0.895 and 0.875. The negative predictive value of CEUS and CECT were 0.101 and 0.103. In the diagnosis and differential diagnosis of cirrhotic nodules lesions and small hepatocellular carcinoma (SHCC) lesions, the accurate rate of CEUS was 92.86%, and CECT was 90.48%. Conclusion: CEUS could effectively and dynamically evaluate the hemodynamics of liver tumors, and provide qualitative and quantitative diagnosis to HSFLLs. In the diagnosis of HSFLLs and SHCC, CEUS was equal to CECT.

Keywords: Contrast enhanced ultrasound, contrast enhanced CT, high echo-level small focal liver lesions, time-intensity curves

Introduction

With the application and development of second-generation ultrasound contrast agent (SonoVue®) and contrast-enhanced ultrasound (CEUS) imaging technology, there are more applications of CEUS in liver detection [1-3]. But for the researches of high echo-level small focal liver lesions (HSFLLs) by 2DUS, the reports are rare. So in this study, we underwent CEUS and CECT in HSFLLs (diameter ≤3 cm), and analyzed the results of the time-intensity curves (TICs), and compared the diagnosis rate of CEUS and CECT. This study was aim to explore the value of CEUS in the diagnosis of HSFLLs.

Materials and methods

Clinical data

A total of 75 cases (107 lesions) were collected in Tumor Hospital of Guangxi Medical University from March 2011 to November 2014. All cases showed slightly hyperechoic or hyperechoic lesions in 2DUS. Among them, 58 cases were male and 17 cases were female, aged between 21 to 87 years old, mean age was 51.2±13.6 years old. The diameters of lesions were between 0.7 cm and 3 cm, average diameter was 1.97 cm.

Inspection instrument

Ultrasonic examination: GE LogiqE9 color Doppler ultrasonography equipped with time-intensity curve (TIC) software was applied in this study. Abdominal convex array probe with frequency between 3.5~5 MHz was used. All facilities were equipped with low mechanical index CEUS technique (M = 0.11). Contrast agent was SonoVue® (Bracco company, Italy), 5 ml 0.9% NaCl was compatible with SonoVue into 5 mg/ml of sulfur hexafluoride microbub-

Table 1. Analyzed 107 HSFLLs ultrasound contrast patterns

Pathological type	Lesion (n)	Typical enhancement mode	Enhanced level		
			Arterial phase	Portal phase	Delay phase
HCC	28	Fast-in, fast-out	H	L	L
	15	Fast-in, slow-out	H	E	E
	3	Slow-in, fast-out	E	E	L
Metastases	6	Fast-in, fast-out	H	L	L
Cirrhotic nodules	33	Equal-in, equal-out	E	E	E
	3	Equal-in, equal-out	E	E	SL
	2	Fast-in, slow-out	SH	E	E
Hemangioma	5	Slow-in, slow-out	L	H	E
	4	Fast-in, slow-out	H	H	H or E
Adenoma	3	Fast-in, fast-out	H	E	L
FNH	2	Fast-in, slow-out	H	H	E
Inflammatory lesion	1	Fast-in, fast-out	H	L	L
Liver fat maldistribution	1	Equal-in, equal-out	E	E	E
HAML	1	Fast-in, slow-out	H	H	H

Notes: H = high enhancement, E = equal enhancement, L = low enhancement, SH = slightly higher enhancement, SL = slightly lower enhancement.

Table 2. TIC results of benign and malignant HSFLLs ($\bar{X}\pm s$)

	Benign	Malignant	P
TTP (s)	45.17±17.37	23.37±10.7	0.007*
WT (s)	183.7±66.61	77.9±46.0	0.02
AUC	1509.7±380.48	1471.7±446.37	0.08

Note: *P<0.05.

bles suspensions, and then bolus injected through elbow intravenous, 1.5 ml each time, then 5 ml 0.9% NaCl solution was used for pipe washing.

Enhanced CT examination: SIEMENS 64 CT scanner was applied in this study, including plain and contrast enhanced scan. In enhanced scan, Iohexol was injected with a rate of 4.5 ml/s via ulnar vein by high-pressure injector.

Two professional diagnostic physicians with more than 10 years experience made the diagnosis results of CEUS and CECT double-blinded.

Inspection methods

Firstly, we scanned the liver with 2DUS. After the detection of lesions, we compared the echo with the surrounding liver tissue. Slightly hyperechoic or hyperechoic lesions were selected to record lesion location, number, size, shape, boundaries, etc. Then we switched to CEUS imaging mode when the lesions showed the best section. Arterial phase (contrast agent injection of 0~30 s), portal phase (30~120 s) and delayed phase (after 120 s) perfusion enhanced performances were recorded for at least 5 mins. Then we started the TIC software to analyze the lesions. In this process, the necrosis of the lesion should be avoided. The fixed sampling frame was placed in the lesion region of interest, and selected equal area or 1/2 area of the surrounding liver tissue as control. The software automatically drew the TIC curve; the following quantitative parameters were obtained from the TIC curve: time to peak (TTP), washout time (WT), and area under the curve (AUC).

Image analysis

Two professional diagnostic physicians with more than 10 years experience made the diagnosis results of CEUS and CECT double-blinded. All lesions were divided into four levels according to the results of CEUS and CECT: (1) Benign; (2) Probably benign; (3) Probably malignant; (4) Malignant.

Statistical methods

SPSS 16.0 statistical software was used for statistical analysis. Mean ± Standard deviation was applied for measurement data. The sensitivity, specificity and the accuracy of CEUS and CECT for diagnosing malignant hepatic tumors were calculated, and ROC curve was constructed. Fourfold table of chi-square test was applied for comparison between CEUS and CECT results. P<0.05 was considered as statistically significance.

Results

Pathology, CECT, MRI and 6-12-month follow-up findings

Within the 107 hyperechoic lesions, there were 46 small hepatocellular carcinoma (SHCC) lesions, 6 metastases lesions, 38 cirrhotic nod-

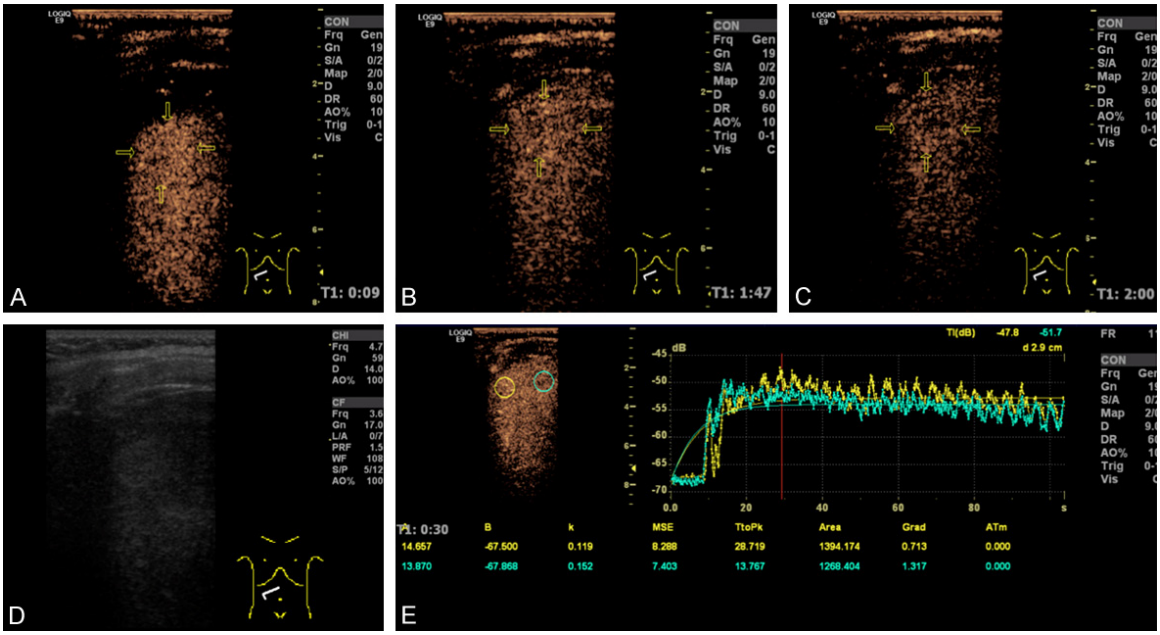

Figure 1. CEUS and TIC analysis for FNH. A: CEUS image shows high enhancement on 9 s in the arterial phase; B: CEUS image shows high enhancement on 107 s in the portal phase; C: CEUS image shows equal enhancement on 125 s in the late phase; D: Gray-scale ultrasound shows a hyperechoic mass within the right lobe of the liver; E: FNH time-intensity curve is "flat".

ules lesions, 9 hemangioma lesions, 3 adenoma, 2 hepatic focal nodular hyperplasia (FNH) lesions, 1 inflammatory lesion, 1 liver fat maldistribution lesions and 1 hepatic angiomyolipoma (HAML) lesion. Among them, 81 lesions were confirmed after surgery or biopsy pathology; 9 hemangioma lesions were confirmed by magnetic resonance imaging (MRI), 17 cirrhotic nodules lesions were confirmed by 6-12 months follow-up.

CEUS performance

Within the 107 hyperechoic lesions, there were 52 malignant lesions and 55 benign lesions. 94.2% (49/52) malignant lesions showed a rapid high enhancement in the arterial phase, 71.15% (37/52) showed low enhancement and 28.85% (15/52) malignant lesions showed equal enhancement in the delay period; 67.27% (37/55) benign lesions showed equal enhancement and 23.64% (13/55) showed high enhancement in the arterial phase, 87.27% (48/55) benign lesions showed equal or high enhancement, and 12.73% (7/55) showed low enhancement in the delay period (**Table 1**).

TIC results of benign and malignant HSFLLs

The TTP of benign lesions (45.17±17.37) was longer than that of the malignant lesions (23.37±10.7) ($P<0.05$). The WT of the malignant lesions (77.9±46.0) was shorter than that of the benign lesions (183.7±66.61) ($P<0.05$). The difference of AUC between benign (1509.7±380.48) and malignant (1471.7±446.37) TICs curves was not significant ($P>0.05$). Detailed in **Table 2**; **Figures 1** and **2**.

CEUS and CECT diagnostic results of 107 HSFLLs

The AUC of CEUS and CECT were 0.941 and 0.936 respectively. Selected positive likelihood ratio and Youden index reached a maximum as the optimal operating point, The cut off value of the malignant lesions of CEUS diagnosis was 2.5, of which 48 lesions were between 1 to 2 points (42 were benign, and 6 were malignant), 59 lesions were between 3 to 5 points (5 were benign, and 54 were malignant). The cut off value of CECT diagnosis for malignant lesions was 2.5, of which 47 lesions were between 1 to 2 points (41 were benign, and 6 were malignant), 60 lesions were between 3 to 5 points (6 were benign, and 54 were malignant). The sensitivity, specificity and the accuracy of CEUS for diagnosing malignant hepatic tumors were 90.0%, 89.4% and 89.71% respectively, versus 90.0%, 87.2% and 88.79% in CECT. The positive predictive value (PPV) of CEUS and CECT were 0.895 and 0.875. The negative predictive

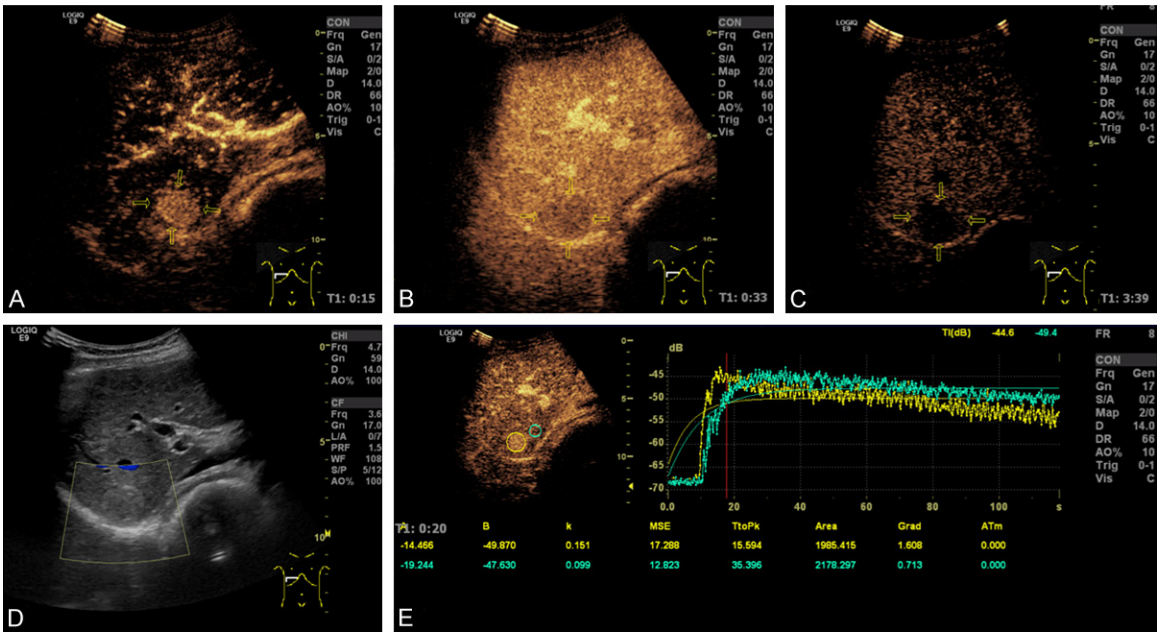

Figure 2. CEUS and TIC analysis for SHCC. A: CEUS image shows high enhancement on 15 s in the arterial phase; B: CEUS image shows low enhancement on 33 s in the portal phase; C: CEUS image shows low enhancement on 219 s in the late phase; D: Gray-scale ultrasound shows a hyperechoic mass within the right lobe of the liver; E: SHCC time-intensity curve is "high and sharp".

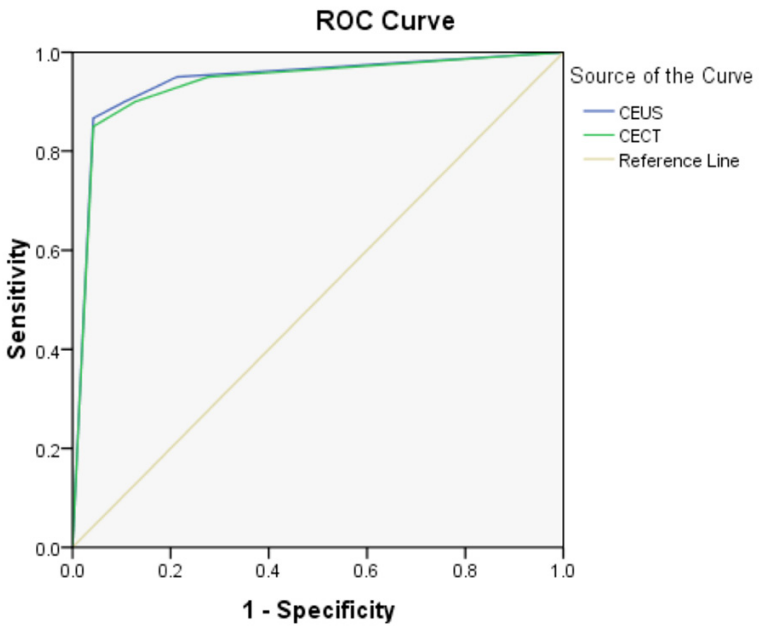

Figure 3. ROC curves for CEUS and CECT diagnosis of benign and malignant liver tumors.

value (NPV) of CEUS and CECT were 0.101 and 0.103. Detailed in **Figure 3**. The difference of diagnosis rate between CECT and CEUS was not significant (x^2 = 0.049, P>0.05). Detailed in **Table 3**.

Differential diagnose rate of CEUS and CECT for cirrhotic nodules and SHCC

In 107 HSFLLs, there were 46 SHCC and 38 cirrhotic nodules lesions. There were 78 cases accurately diagnosed by CEUS (confirmed by pathology and clinical findings), and 6 cases were misdiagnosed by CEUS. The diagnosis rate of CEUS was 89.71% (96/107). There were 76 cases accurately diagnosed by CECT (confirmed by pathology and clinical findings), and 8 cases were misdiagnosed by CECT. The diagnosis rate of CECT was 88.79% (95/107). The difference of diagnosis rate between CECT and CEUS was not significant (x^2 = 0.3, P>0.05). Detailed in **Table 4**.

Discussion

The focal lesions of the liver can be divided into two categories: benign and malignant. CEUS combined with second-generation blood pool

Table 3. CEUS and CECT diagnostic results of 107 HSFLLs

	CEUS	CECT	P
Accurate diagnosis (n)	96	95	
Misdiagnosis (n)	11	12	
Accuracy diagnosis rate (%)	89.71%	88.79%	0.199

Table 4. Differential diagnose rate of CEUS and CECT for cirrhotic nodules and SHCC

	CEUS	CECT	P
Accurate diagnosis (n)	79	76	
Misdiagnosis (n)	5	8	
Accuracy diagnosis rate (%)	92.86%	90.48%	0.157

contrast agent is one of the most effective methods for determining tumor vascularization patterns [4]. This method provides a real-time demonstration of continuous hemodynamic changes of liver tumors.

In this study, during arterial phase, 94.2% (49/52) malignant lesions showed a fast and high enhancement, 67.27% (37/55) benign lesions showed equal enhancement and 23.64% (13/55) showed high enhancement. During delay period, 71.15% (37/52) malignant lesions showed low enhancement and 28.85% (15/52) malignant lesions showed equal enhancement, 87.27% (48/55) benign lesions showed equal or high enhancement, and 12.73% (7/55) showed low enhancement. According to the European Imaging Guide [5], most malignant lesions showed low enhancement in the delay period, and most benign lesions showed equal enhancement or high enhancement in the delay period. This is consistent with the results of our study. Due to the differences in blood supply, some benign and malignant liver lesions showed different CEUS patterns. Most malignant lesions obtain blood supply through hepatic artery, which gives a rich supplement, and are often accompanied by a large number of abnormal proliferations of nourishing blood vessels. This vascular structure performs fast and high enhancement in arterial phase. Moreover, because of the arteriovenous fistulas in malignant lesions are relative increasing, a more rapid clearance will perform in portal phases. Due to the echo of liver parenchyma is still in the enhancement state, the echo intensity is significantly higher than the tumor [6]. And for benign FLLs, like cirrhotic nodules, the blood supply mainly depends on portal vein, which leads to a performance of "equal enhancement in the three phase". But when the cirrhotic nodules show a change of precancerous lesions, the CEUS patterns can also show as "fast-in and slow-out" [7]. Another benign FLLs, adenomas, according to the European Imaging Guide and literatures [8-10], the typical adenoma CEUS pattern were "high enhancement in arterial phase, equal enhancement or slightly high enhancement in portal and delayed phases". For some adenoma, low enhancement could be seen in delay period, which is easy to be misdiagnosed as malignant tumor, In this study, 1 cases of adenoma (3 lesions) was misdiagnosed as malignant lesions (metastatic liver cancer) because of its low enhanced performance in CEUS delay period.

TIC is a real-time imaging technology based on ultrasound contrast, which can represent every moment of ultrasound contrast by graphs [8], and can show the velocity and flow of contrast agent inside the tumors dynamically. According to domestic and foreign researchers [11, 12], TICs showed high sensitivity (94.1-97.2%), high specificity (90%-90.7%), and high diagnostic coincidence rate (95.11%-95.7%) in the diagnosis of HCC. It is a promising and reliable technology for clinical diagnosis. In this study, we found that the TTP of most benign lesions (45.17±17.37 s) was longer than that of the malignant lesions (23.37±10.7 s) ($P<0.05$). The WT of the malignant lesions (77.9±46.0) was shorter than that of the benign lesions (183.7±66.61) ($P<0.05$). The difference of AUC between benign (1509.7±380.48) and malignant (1471.7±446.37) TICs curves was not significant ($P>0.05$). The results are consistent with domestic and foreign researches [13, 14]. The TTP reflects the speed of the blood perfusion; the slope of rising and descending curve reflects the velocity and flow of contrast agents inside tumor. The results in this study indicated that the perfusion rate of malignant lesions was faster, and the perfusion flows were larger. Moreover, for the malignant lesions, the curve of was high and sharp, but perfusion time was shorter. Because the perfusion time of benign lesions was longer, but the curve was flat, therefore the AUC of benign and malignant was with no significant difference.

In addition, the sensitivity, specificity and the accuracy of CEUS for diagnosing malignant hepatic tumors were 90.0%, 89.4% and 89.71%

respectively, versus 90.0%, 87.2% and 88.79% of CECT. The PPV of CEUS and CECT were 0.895 and 0.875. The differential diagnose rate of CEUS and CECT for cirrhotic nodules and SHCC were 92.86% (78/84) and 90.48% (76/84) respectively. According to Westwood M et al [15], CEUS may be a better method in excluding 11-30 mm SHCC (except for lesions <10 mm). In this study, there was not enough evidence to support this conclusion. CECT and CEUS had their advantages and limitations in the diagnosis of HSFLLs. We found that there was 4 lesions were not displayed on CECT. Mainly due to the lesions were small in size, and with respiratory movement, the small lesions were possible for missed diagnosis. And for the limitations of CEUS, when the lesions are located under the diaphragm, especially in S8 section, the diagnosis will be hard to made by the block of the lung. There was 1 case of SHCC located in S8 section in this study, the lesion showed "fast-in and slow-out" in CEUS, and it was misdiagnosed as hemangioma.

In conclusion, CEUS could effectively and dynamically evaluate the hemodynamics of liver tumors, and provide qualitative and quantitative diagnosis to HSFLLs. In the diagnosis of HSFLLs and SHCC, CEUS was equal to CECT.

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Disclosure of conflict of interest

None.

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