



Original Article

High Frame Rate Contrast-enhanced Ultrasound Helps Differentiate Malignant and Benign Focal Liver Lesions

Xiang Fei¹, Peng Han¹, Bo Jiang¹, Lianhua Zhu¹, Wenshuo Tian², Maodong Sang³, Xirui Zhang³, Yaqiong Zhu¹ and Yukun Luo^{1*}

¹Department of Ultrasound, The First Medical Centre, Chinese PLA General Hospital, Beijing, China; ²Clinical Research Division of Ultrasound Imaging System, Shenzhen Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, Guangdong, China; ³R&D Division of Ultrasound Imaging System, Shenzhen Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, Guangdong, China

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Abstract

Background and Aims: This study aimed to evaluate the diagnostic performance of high frame rate contrast-enhanced ultrasound (H-CEUS) of focal liver lesions (FLLs). **Methods:** From July 2017 to June 2019, conventional contrast-enhanced ultrasound (C-CEUS) and H-CEUS were performed in 78 patients with 78 nodules. The characteristics of C-CEUS and H-CEUS in malignant and benign groups and the differences between different lesion sizes (1–3 cm, 3–5 cm, or >5 cm) of C-CEUS and H-CEUS were examined. The diagnostic performance of C-CEUS and H-CEUS was analyzed. The chi-square test or Fisher's exact test was used to assess inter-group differences. The receiver operating characteristic curve was plotted to determine the diagnostic performance of C-CEUS and H-CEUS. **Results:** There were significant differences in the enhancement area, fill-in direction and vascular architecture between C-CEUS and H-CEUS for both benign and malignant lesions (all $p=0.000-0.008$), but there were no significant differences in washout results ($p=0.566$ and $p=0.684$, respectively). For lesions 1–3 cm in size, the enhancement area, fill-in direction, and vascular architecture on C-CEUS and H-CEUS were significantly different (all $p=0.000$), unlike for lesions 3–5 cm or >5 cm in size. For differentiation of malignant from benign FLLs in the 1–3 cm group, H-CEUS showed sensitivity, specificity, accuracy, and positive and negative predictive values of 92.86%, 95.0%, 96.3%, 90.48% and 93.75%, respectively, which were higher than those for C-CEUS (75.0%, 70.0%, 77.78%, 66.67% and 72.91%, respectively). **Conclusions:** H-CEUS provided more vascular information which could help differentiate malignant from benign FLLs, especially for lesions 1–3 cm in size.

Keywords: Contrast-enhanced ultrasound; Focal liver lesion; High frame rate; Hepatocellular carcinoma.

Abbreviations: AM, amplitude modulation; AUC, area under the curve; C-CEUS, conventional contrast-enhanced ultrasound; CDFI, color Doppler flow imaging; CEMRI, contrast-enhanced magnetic resonance imaging; CEUS, contrast-enhanced ultrasound; FLL, focal liver lesion; FOV, field of view; FR, frame rate; H-CEUS, high frame rate contrast-enhanced ultrasound; HEM, hemangioma; NPV, negative prediction value; PPV, positive prediction value; ROC, receiver operating characteristic; ZST⁺, Zone Sonography Technology plus.

*Correspondence to: Yukun Luo, Department of Ultrasound, The First Medical Centre, Chinese PLA General Hospital, NO. 28 Fu Xing Road, Beijing 100853, China. Tel: +86-10-66936848, E-mail: lyk301@163.com

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Introduction

The second generation of ultrasound (US) contrast agents involves the real blood-pool agent and contrast-enhanced ultrasound (CEUS) can dynamically display the microcirculatory perfusion of organs in real-time, which has widely been used for both liver and non-liver applications due to its high temporal resolution, convenience, and low allergy incidence rate.¹ In the past decade, CEUS was mainly applied in the differentiation of focal liver lesions (FLLs), and a large number of studies demonstrated that CEUS can improve the detection rate and characterization of FLLs.² Therefore, CEUS was recommended for the diagnosis of FLLs, monitoring of therapy, and aiding in surgical management.^{1,3–6}

To characterize FLLs, the arterial phase, portal venous phase, and late phase need to be recorded and analyzed. For the arterial phase, the stored cine loop is recommended to be replayed such that the degree and pattern of the arterial vascular supply can be observed frame by frame. For the late phase, the lesion is recommended to be observed for at least 5 min since wash-out may be delayed for some hepatocellular carcinomas.¹ Hence, frame rate (FR) is an important equipment-setting parameter in CEUS. A low FR will reduce the temporal resolution, negatively affecting the real-time display of FLLs. However, an FR that is too high will increase the disruption of the microbubble due to the launch of the US pulse, which will reduce the imaging time.⁷

Currently, most US equipment offers CEUS with a FR mainly ranging from 8 to 20 fps for the convex transducer, which depends on the scanning depth and width of the examination window. However, in some FLLs with hypervascularity in the arterial phase, wash-in occurs very rapidly and the progress lasts only for a few seconds.⁸ The current FR may not be sufficient to capture the wash-in pattern and vascular architecture, which is crucial for diagnosis

Table 1. Characteristics of the studied population

	Age in years, mean±SD	Sex		Diameter in cm, median (range)	Number of nodules		Hepatitis		
		Male	Female		Single	Multiple	HBV	HCV	None
Malignant, n=53	55.8±12.6	40	13	3.39±0.24 (1.0–8.1)	38	15	41	2	10
HCC, n=46		36	10	3.30±0.25 (1.0–8.1)	32	14	41	2	3
ICC, n=7		4	3	3.6 (1.7–6.3)	6	1	0	0	7
Benign, n=25	45.5±11.6*	16 [#]	9	2.24±0.24 (1.0–5.7)	20	5	0	0	25
FNH, n=8		5	3	1.8 (1.0–3.2)	8	0	0	0	8
HEM, n=17		11	6	2.43±0.32 (1.0–5.7)	12	5	0	0	17

*Compared to malignant group, $p=0.01$, $^{\#}p=0.293$. FNH, focal nodular hyperplasia; HCC, hepatocellular carcinoma; HEM, hemangioma; ICC, intrahepatic cholangiocarcinoma; SD, standard deviation.

because malignant and benign FLLs have different microcirculations.⁹ Hence, increasing the FR of CEUS in the arterial phase and avoiding destruction of contrast agents is an important issue. However, due to the conventional line-by-line scanning mode, the FR of the current CEUS is restricted to a lower value, reducing the ability to capture the rapid enhancement progress of FLLs with hypervascularity in the arterial phase in clinical practice.

Therefore, we designed a novel technique called high FR CEUS (H-CEUS) to improve the FR of CEUS in the arterial phase based on a new zone scanning mode. This study aimed to evaluate the diagnostic performance of H-CEUS in FLLs.

Methods

Study population

The study and corresponding informed consent were approved by the Ethics Committees of our hospital (No. S2019-211-01), and written informed consent was obtained from each patient before enrollment. From July 2017 to June 2019, a total of 143 consecutive patients with an FLL underwent CEUS examination in our department. The inclusion criteria were as follows: (a) presence of a local liver lesion detected using conventional US; (b) lesion diameter more than 1 cm; and (c) patient age of older than 18 years. The exclusion criteria were as follows: (a) patient having received any treatment of the FLL (such as chemotherapy or transarterial chemoembolization) ($n=35$); (b) lesion having showed non-enhancement in the arterial phase ($n=27$); and (c) final pathological findings proven to be liver metastasis or inability to obtain a definitive diagnosis ($n=3$). For the malignant group, the histopathology results obtained following biopsy or surgery were used as the standard reference. For the benign group, the contrast-enhanced magnetic resonance imaging (CEMRI) and a 6-month follow-up were used as the standard reference. In total, 78 patients (56 males, 22 females; mean age of 49.8 ± 10.4 years, range of 23–82 years) and 78 nodules (mean size of 3.34 ± 0.25 cm, range of 1.0–8.1 cm) were ultimately included in the study based on the inclusion and exclusion criteria. The characteristics of the malignant and benign groups are summarized in Table 1.

Examination technique

Both conventional US and CEUS were acquired with a Resona7 US system (Mindray, Shenzhen, China) equipped with the SC5-1U convex transducer probe. The CEUS software

was ultra-wide nonlinear and used an FR ≥ 50 fps (we defined this kind of CEUS as H-CEUS). A low mechanical index, ranging from 0.05 to 0.08, was used for real-time imaging for both C-CEUS and H-CEUS. The contrast agent was SonoVue (Bracco, Milan, Italy), a suspension of stabilized sulfur hexafluoride microbubbles in saline.

All examinations were performed by a single radiologist with 8 years of experience in abdominal CEUS. Each patient was scanned as follows. First, grayscale US was used to scan the whole liver and locate the lesion. The blood flow of the target lesion was evaluated using color Doppler flow imaging (CDFI). For patients with multiple lesions, only the largest lesion was selected. Second, C-CEUS scanning was performed. Third, H-CEUS was performed after no less than 10 min, when the microbubbles from the previous injection had disappeared. The field of view (FOV) was set depending on the maximum diameter of lesion. Both C-CEUS and H-CEUS used the same scanning protocol. After the section that showed the maximum size of lesion was located, the C-CEUS or H-CEUS imaging mode was initialized. A bolus of 2.0 mL of contrast agent was injected intravenously followed by 5 mL of saline flush as per the manufacturer's instruction. For the arterial and portal venous phase, scanning of the FLL was continuous, while late phase scanning of the FLL was intermittent to avoid the destruction of contrast agents. Both the C-CEUS and H-CEUS scanning lasted for at least 5 min after the injection of contrast agent. All imaging data were recorded.

Implementation of H-CEUS

C-CEUS adopted the focused transmission and line-by-line receiving mode. With the advent of parallel multibeam technology, multiple receiving lines can be simultaneously formed under each transmission to increase the FR for C-CEUS. The amplitude modulation (AM) technology in which pulses are emitted three times is adopted to separate microbubbles from background tissue signal. The time for transmission/receiving initialization and receive-end processing are ignored. We can observe that, even in such an ideal scenario, the upper limit of the FR for four-beam C-CEUS is only 32 fps and is even lower in practice.

All in all, reducing the number of transmissions for obtaining a single frame without sacrificing image quality is critical in the implementation of H-CEUS. In this study, we applied Zone Sonography Technology plus (ZST+) in Mindray to achieve this purpose. ZST+ is a two-stage beam-forming scheme. In its first stage, weakly focused transmissions are emitted to illuminate the region-of-interest in a subject; due to its wider transmission beam patterns as compared to those of the traditional focused transmissions, more receiving lines can be formed corresponding to

Table 2. Characteristics of conventional US in malignant and benign groups*

Characteristics	Malignant, n=53	Benign, n=25	χ^2	p
B-mode			1.118	0.572
Hyper-	18	8		
Iso-	6	1		
Hypo-	31	16		
CDFI			4.146	0.042
Present	38	12		
Absent	15	13		

*Data represent number of nodules.

every single transmission. Consequently, the transmissions needed to cover the whole region-of-interest are reduced to raise the FR while avoiding the spatial under-sampling problem. As a drawback, the lateral resolution, as well as penetration, are reduced because of the weakly focused transmission. In the second stage of ZST⁺ a phase alignment scheme is utilized to make all received echo data in the same phase for every overlapping point (the same point appearing in different sets of received echo data) in order to achieve better focusing performance (improved lateral resolution). For an enhanced signal-to-noise ratio (enhanced penetration), a coherent synthesis is then performed, synthesizing each pixel at overlapping points with both amplitude and phase.

In addition to using the above-mentioned novel beam-forming technique, we still performed some straightforward adjustments to the preset configuration to achieve a higher CEUS FR. In particular, the FOV is appropriately controlled to a smaller range in which the targeted lesion and normal tissue are both shown on the screen. US transmissions were only emitted to illuminate the area within the FOV. In other words, a smaller FOV would correspond to a reduced number of transmissions. Thus, we can further raise the CEUS FR.

In summary, by exploiting a novel beam-forming technique and making practical adjustments to the machine presets, the H-CEUS was implemented as an effective tool in our clinical study.

US and CEUS images features

All US, C-CEUS, and H-CEUS images and cine-loops were reviewed respectively by two radiologists (who both had more than 8 years of experience in abdominal CEUS). Neither clinical nor pathological information was available to them. The diagnosis of a malignant or benign lesion was made by each radiologist according to the CEUS guideline.¹ In case of discordance, a third investigator (with 15 years of experience in CEUS) reviewed the data to make the final decision.

The following features on conventional US were recorded: (1) maximum diameter of lesion; (2) echogenicity level of lesion: hypo-echoic, iso-echoic, or hyper-echoic relative to the adjacent liver parenchyma; (3) number of lesions: solitary or multiple lesions; and (4) blood flow within the lesion on CDFI: present or absent. The following features on CEUS were recorded: (1) start time of enhancement: earlier enhancement was defined as enhancement of the lesion that started earlier than that of the adjacent liver parenchyma; (2) enhancement intensity: hyperenhancement was defined as the level of enhancement of the lesion being higher than that of the adjacent liver parenchyma; (3) homogeneity: homogeneous and heterogeneous enhancement were clas-

sified according to the enhancement intensity distribution within the lesion; (4) enhancement area: peripheral, central, and entirety of the lesion based on the area within the lesion where the enhancement was first seen in the early arterial phase; (5) fill-in direction: centripetal, centrifugal, and entirety; (6) vascular architecture: regular branch/irregular, spoke-wheel, diffusion nodular, and unidentified; and (7) wash-out: presence was defined as the reduction of enhancement relative to adjacent liver parenchyma after peak enhancement.¹

Statistical analysis

Statistical analysis was performed using SPSS for Windows (version 21.0; IBM Corp., Armonk, NY, USA). All quantitative parameters were expressed as mean±standard deviation. The Student's *t* test was used to compare the differences of continuous variables between the two groups for age and lesion size. Comparisons of categorical data were performed using the χ^2 test or Fisher's exact test. Receiver operating characteristic (ROC) curves were plotted to evaluate the diagnostic performance of C-CEUS and H-CEUS for the differential diagnosis of malignant FLL. A *p*-value of less than 0.05 was considered to indicate a statistically significant result.

Results

Characteristics on conventional US

Characteristics on B-mode and CDFI in the malignant and benign lesions are summarized in Table 2. For echogenicity level, no significant difference was found between benign and malignant lesions. CDFI showed more blood flow for malignant lesions than for benign lesions (*p*=0.042).

Comparison of features on C-CEUS and H-CEUS for malignant and benign lesions

For all FLLs, both malignant and benign, the features on C-CEUS (FR fixed at 12 fps) and H-CEUS (mean FR of 52.5 fps; range of 50–57 fps), including start time of enhancement, enhancement intensity, homogeneity, enhancement area, fill-in direction, vascular architecture and wash-out, are summarized in Table 3. Significant differences were found in the enhancement area, fill-in direction, and vascular architecture between C-CEUS and H-CEUS for FLLs in the malignant and benign groups. No significant difference was found in wash-out between C-CEUS and H-CEUS for FLLs in

Table 3. Comparison of features on conventional and high FR CEUS in malignant and benign groups*

	FLL, n=78			Malignant, n=53			Benign, n=25					
	C-CEUS	H-CEUS	χ^2	P	C-CEUS	H-CEUS	χ^2	P	C-CEUS	H-CEUS	χ^2	P
Start time of enhancement			1.567	0.211			2.650	0.104			0.000	1.000
Earlier	61	67			42	48			19	19		
Non-earlier	17	11			11	5			6	6		
Enhancement intensity			0.788	0.375			0.986	0.321			0.000	1.000
Hyper	64	68			41	45			23	23		
Non-hyper	14	10			12	8			2	2		
Homogeneity			0.691	0.406			1.383	0.240			0.117	0.733
Homogeneous	47	52			27	33			20	19		
Heterogeneous	31	26			26	20			5	6		
Region			60.832	0.000			57.111	0.000			10.630	0.005
Peripheral	29	67			13	50			16	17		
Central	2	9			0	1			2	8		
Entirety	47	2			40	2			7	0		
Fill-in direction			60.832	0.000			57.111	0.000			10.630	0.005
Centripetal	29	67			13	50			16	17		
Centrifugal	2	9			0	1			2	8		
Entirety	47	2			40	2			7	0		
Vascular architecture			24.695	0.000			15.725	0.000			9.600	0.008
Branch/irregular	30	48			30	48			0	0		
Spoke-wheel	2	8			0	0			2	8		
Diffuse nodular	17	17			0	0			17	17		
Unidentified	29	5			23	5			6	0		
Wash-out			0.495	0.482			0.329	0.566			0.166	0.684
Present	69	66			47	45			22	21		
Absent	9	12			6	8			3	4		

*Data represent number of nodules.

Table 4. Features on conventional and high FR CEUS for FLLs of different sizes*

	1–3 cm, n=48				3–5 cm, n=22				>5 cm, n=8			
	C-CEUS	H-CEUS	χ^2	<i>p</i>	C-CEUS	H-CEUS	χ^2	<i>p</i>	C-CEUS	H-CEUS	χ^2	<i>p</i>
Region			44.514	0.000			11.460	0.003			0.008	0.929
Peripheral	14	39			10	20			7	7		
Central	2	8			0	1			0	0		
Entirety	32	1			12	1			1	1		
Fill-in direction			44.514	0.000			11.460	0.003			0.008	0.929
Centripetal	14	39			10	20			7	7		
Centrifugal	2	8			0	1			0	0		
Entirety	32	1			12	1			1	1		
Vascular architecture			43.913	0.000			0.366	0.947			0.000	1.000
Branch/irregular	6	28			15	16			8	8		
Spoke-wheel	1	7			1	1			0	0		
Diffuse nodular	13	12			4	4			0	0		
Unidentified	28	1			2	1			0	0		

*Data represent number of nodules.

the malignant and benign groups ($p=0.482$, $p=0.566$, and $p=0.684$, respectively).

Comparison of features on C-CEUS and H-CEUS for FLLs of different sizes

The enhancement area, fill-in direction, and vascular architecture on C-CEUS and H-CEUS for FLLs that were 1–3 cm, 3–5 cm and >5 cm in size are shown in Table 4. For the 1–3 cm group, enhancement area, fill-in direction, and vascular architecture on C-CEUS and H-CEUS were significantly different (all $p=0.000$) (Fig. 1). For the 3–5 cm group, only the enhancement area and fill-in direction on C-CEUS and H-CEUS were significantly different ($p=0.003$ and $p=0.003$, respectively).

Diagnostic performance of C-CEUS and H-CEUS for FLLs

The diagnostic performance of C-CEUS and H-CEUS for malignant FLLs was determined using ROC analysis (Fig. 2A). The area under the curve (AUC) for H-CEUS in diagnosing malignant FLL was significantly greater than that for C-CEUS ($p=0.003$). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of H-CEUS were higher than those of C-CEUS in differentiating malignant from benign lesions (Table 5). For the 1–3 cm group, the AUC for H-CEUS in diagnosing malignant FLL was also significantly higher than that for C-CEUS ($p=0.003$) (Fig. 2B). The sensitivity, specificity, PPV, NPV, and accuracy of C-CEUS and H-CEUS for differentiating malignant from benign lesions are shown in Table 6. All H-CEUS related variables were greater than those for C-CEUS.

Discussion

CEUS allows continuous recording and evaluation of the complete wash-in and wash-out of the contrast agent over

several minutes. Due to the special blood supply of the liver, CEUS could provide unique and accurate diagnostic information for the characterization of FLLs, in many cases, this is comparable and sometimes superior to the performance of computed tomography and MRI.^{2,10} Setting parameters such as mechanical index(MI), gain, dynamic range, transmission frequency, equipment software, and FR could affect the quality of the contrast image, which may influence the decision of the radiologist.⁷ FR is one of the important parameters for optimizing images, especially for FLLs with quick wash-in patterns. In our study, we reported a new technique that could increase the FR of the contrast image without increasing the destruction of the microbubble, improving the characterization of the FLL in the enhancement area, fill-in direction, and vascular architecture of the contrasted image.

In the present study, we found some features of C-CEUS need to be reconsidered after using H-CEUS. The enhancement area, fill-in direction, and vascular architecture were significantly different between C-CEUS and H-CEUS. Dietrich *et al.*^{7,11} recommend an FR of significantly more than 10 images/s as necessary to adequately visualize flow direction and vascular architecture. We found that only more than 10 images/s may not be enough to capture the whole process of microbubble movement in the wash-in phase. Previous reports discussed the destruction of the microbubble after increasing FR.⁷ However, H-CEUS did not lead to a higher destruction of microbubbles compared to that with C-CEUS in our study. Specifically, the number of transmissions of H-CEUS is less than that of C-CEUS for every single frame. Although the FR is increased, the overall excitation of microbubbles is the same as for C-CEUS during the same scanning period. Intermittent scans in later phases are recommended in CEUS guidelines.¹ Our result showed neither C-CEUS nor H-CEUS had a significant influence on wash-out, which demonstrated that H-CEUS had not increased the destruction of contrast agents.

More malignant lesions showed centripetal and peripheral enhancement on H-CEUS than that on C-CEUS (51 vs. 13). Although most malignant lesions demonstrated entire enhancement on C-CEUS, when the FR was increased, it could be clearly shown that the contrast-enhanced area appeared

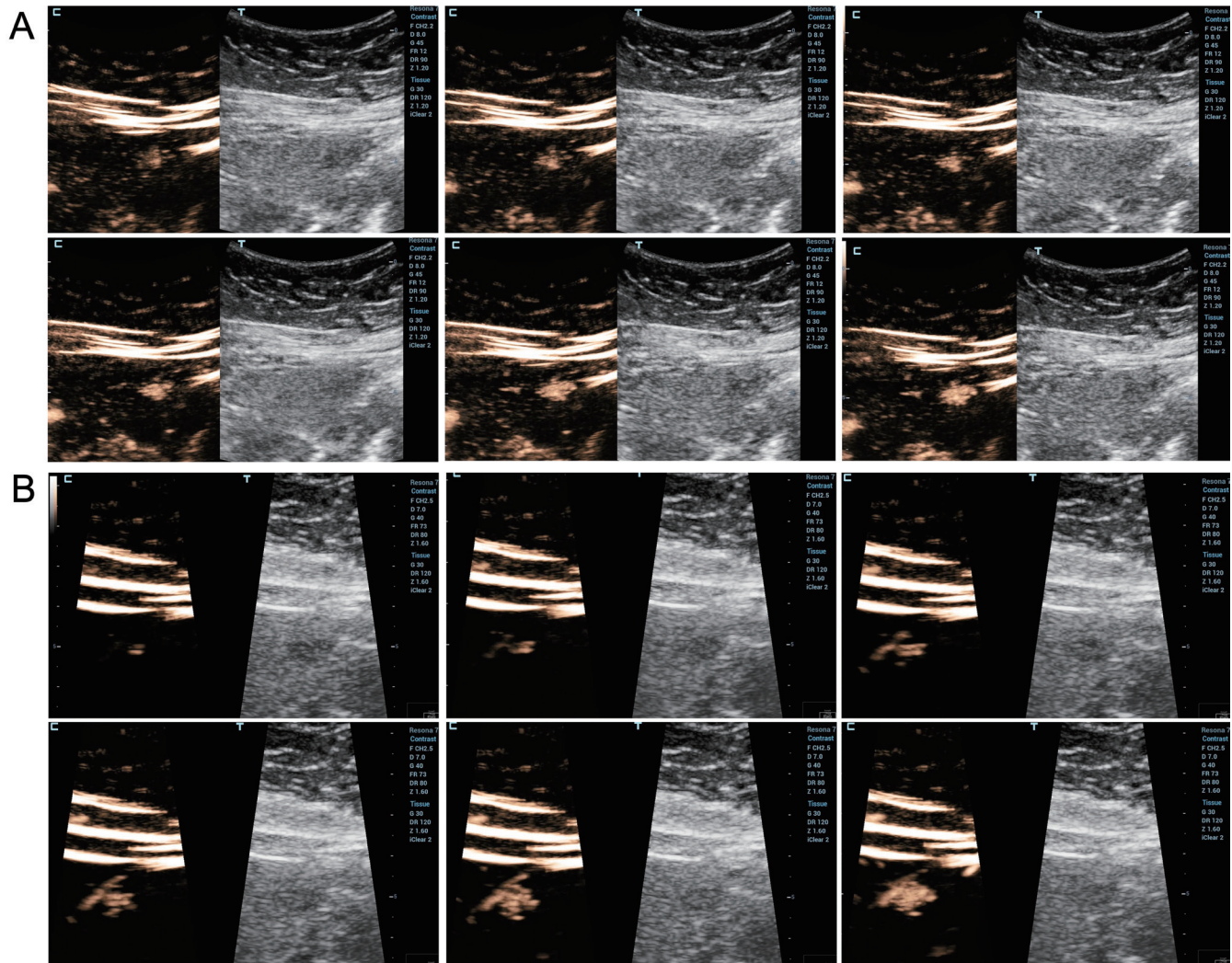


Fig. 1. FNH on C-CEUS and H-CEUS. (A) The small lesion (1 cm in diameter) was recognized as an entire and unidentified enhancement on C-CEUS. (B) The lesion shows central, centrifugal, and spoke-wheel enhancement.

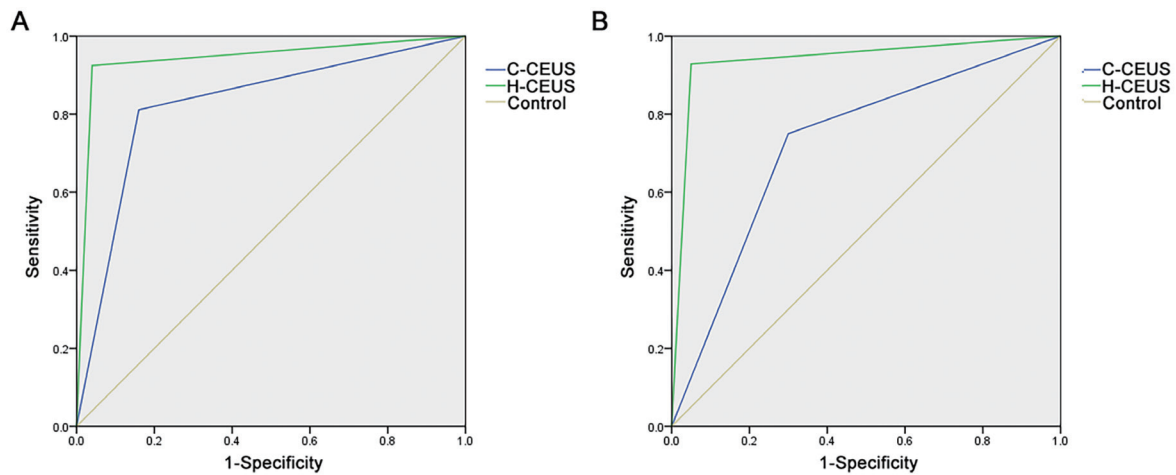


Fig. 2. ROC analysis of C-CEUS and H-CEUS for the diagnosis of malignant FLL. (A) ROC analysis of C-CEUS and H-CEUS for the diagnosis of all malignant FLLs. (B) ROC analysis of C-CEUS and H-CEUS for the diagnosis of malignant FLLs 1–3 cm in diameter.

Table 5. Comparison of the diagnostic performance of conventional and high FR CEUS for FLLs

Criteria	Sensitivity	Specificity	PPV	NPV	Accuracy
C-CEUS, <i>n</i> =78	81.13%	84.00%	91.49%	67.74%	82.05%
H-CEUS, <i>n</i> =78	92.45%	96.00%	98.00%	85.71%	93.59%

first in the periphery of the lesion and then enlarged over time. That is to say, after the FR increased, the fill-in direction of the lesion was reconsidered. For benign lesions, after we increased the FR of CEUS, eight cases of focal nodular hyperplasia showed centrifugal enhancement rather than two cases of focal nodular hyperplasia on C-CEUS.

Out of a total of 78 lesions, 43.4% (23/53) of malignant lesions demonstrated an unidentified architecture pattern; however, when using H-CEUS, only 6.4% (5/48) of malignant lesions remained unidentified. For malignant lesions, we found 14 showed branch/irregular vascular architecture on H-CEUS that were classified as unidentified enhancement on C-CEUS. For benign lesions, six showed branch/irregular vascular architecture on H-CEUS that were classified as unidentified enhancement on C-CEUS. The arterial phase is an important period for observing the morphology of FLL blood vessels, but the rapid flow of arterial blood causes the contrast agent to move fast. Therefore, the vascular morphology depicted by contrast agent movement can be clearly reflected only when the FR of contrast imaging reaches a certain threshold. Compared to conventional CEUS technology, high FR technology is more suitable for accurately capturing the movement of contrast agents in vessels.

The minimum size of lesions in our study was 1 cm. When the lesion is smaller than 1 cm, the diagnostic criteria are controversial.¹² According to our results, a significant difference was found between C-CEUS and H-CEUS in the 1–3 cm group. Smaller lesions with quick hyperenhancement in the arterial phase make it harder to record and recognize the direction and area of enhancement.⁸ For this circumstance, the H-CEUS showed its advantage in differentiating malignant lesions from benign. Although H-CEUS has a smaller FOV than C-CEUS, it is still adequate for covering FLLs smaller than 3 cm at a depth of 10 cm. Reducing the FOV for C-CEUS could increase the FR as well; however, the US equipment has a limited maximum FR on C-CEUS mode considering the destruction of the contrast agent. In any situation, the FR of C-CEUS cannot be increased to as high as that of H-CEUS. Our study showed in the >5 cm group, there was no difference between C-CEUS and H-CEUS for the enhancement area, fill-in direction, or vascular architecture features. That is to say, if the lesion was larger than 5 cm, C-CEUS is sufficient to visualize the lesion and there is no need to perform H-CEUS. Furthermore, for FLL of 3 to 5 cm in diameter, although we have made technical optimization in engineering, high FR CEUS will affect the lateral resolution and penetration of the image to a certain extent, thus affecting the evaluation of FLL vascular morphology. In addition, the time of perfusion is relatively long when the lesion volume increases, and the conventional FR CEUS can capture the process of blood perfusion and reflect the vascular morphology. Therefore, compared with conventional FR CEUS, high FR CEUS has no significant advantage in judging the nature of larger lesions.

Prospective and retrospective studies reported the sensitivity and specificity of CEUS for differentiating malignant FLL from benign FLL were 81–97.3% and 83–95%, respectively,^{2,13–16} which were consistent with those of C-CEUS in our study. However, the sensitivity and specificity of C-CEUS was lower in the 1–3 cm group. Meta-analyses showed the sensitivity in studies of lesions lower than 2 cm in size was less than that in other studies of lesions of any size.^{2,9,17,18} Another study also reported it was difficult to diagnose lesions with 1–3 cm in size.³ Our results showed the sensitivity, specificity, PPV, NPV, and accuracy for differentiating malignant lesions from benign was better for H-CEUS than for C-CEUS in the 1–3 cm group. When the FR of the CEUS is insufficient, it is difficult to clearly view the perfusion process in a small lesion. Therefore, increasing the FR of CEUS is helpful to show the perfusion process of such FLLs.

This study has several limitations. First, we only enrolled 78 patients with 78 nodules, which included limited types of FLL. The clinical value of H-CEUS in the diagnosis of FLL requires prospective studies with larger samples for further evaluation. In our study, all benign FLLs were diagnosed using CEMRI and follow-up instead of pathological findings, since some previous studies indicated that CEMRI plays a dominant role and it is widely regarded as the most reliable imaging technique in the classification and characterization of FLLs,¹⁹ precluding comments on CT or combining these two modalities. We also excluded liver metastasis in this study. Because the advantage of H-CEUS is to depict the detail of the perfusion pattern in the arterial phase, most liver metastases show heterogeneous enhancement or rim hyperenhancement in the arterial phase followed by rapid wash-out in the late arterial phase or early portal phase. It is not difficult to recognize liver metastasis from other FLLs on CEUS.^{20,21} Second, deeply situated FLLs and those near the diaphragm are not easily accessible with C-CEUS. Third, many factors influence the diagnostic performance of H-CEUS, such as the dose of the contrast agent, FOV size and depth, which were not discussed in this preliminary study. In addition, in this study, our examination sequence was first grayscale US and CDFI, then C-CEUS, and finally H-CEUS, which was in line with the diagnosis and treatment process during regular clinical work. Therefore, it was inevitable that H-CEUS obtained better CEUS technical conditions than C-CEUS (e.g., timing of holding a breath and subtle differences in the insonation angle of the US from the probe), which leads to a certain bias. Further studies considering all possible confounding factors with H-CEUS are necessary.

Conclusions

In conclusion, H-CEUS could provide more information regarding the enhancement area, fill-in direction, and vascular architecture of FLLs, which could be used for the visualization and recording of the wash-in patterns of small FLLs

Table 6. Comparison of the diagnostic performance of conventional and high FR CEUS for FLLs 1–3 cm in diameter

Criteria		Sensitivity	Specificity	PPV	NPV	Accuracy
1–3 cm, <i>n</i> =48	C-CEUS	75.00%	70.00%	77.78%	66.67%	72.92%
	H-CEUS	92.86%	95.00%	96.30%	90.48%	93.75%

Fei X. *et al*: H-CEUS identifies malignant and benign FLL

in the arterial phase. Especially for FLLs 1–3 cm in size, H-CEUS could help differentiate malignant and benign lesions.

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None to declare.

Conflict of interest

The US machine used in this study was the Resona7 US system (Mindray, Shenzhen, China). The authors belong to Shenzhen Mindray Bio-Medical Electronics Co., Ltd. and have no conflict of interests related to this publication.

Author contributions

Guarantor of integrity of entire study (XF, LZ, YZ, YL), study design, data acquisition or data interpretation (all authors), manuscript drafting for important intellectual content (all authors), approval of the final version (all authors), agreement to ensure any questions related to the work are appropriately resolved (all authors), literature research (XF, YL), statistical analysis (XF, LZ), and manuscript editing (XF).

Data sharing statement

All data are available upon reasonable request.

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