Original Article

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A comparative study of contrast enhanced ultrasound and contrast enhanced magnetic resonance imaging for the detection and characterization of hepatic hemangiomas

Liang Fang[1,*], Zheng Zhu[2,*], Beijian Huang[1], Hong Ding[1], Feng Mao[1], Chaolun Li[1], Mengsu Zeng[3], Jianjun Zhou[3], Ling Wang[4], Wenping Wang[1,], Yue Chen[5,**]**

[1] *Department of Ultrasound, Zhongshan Hospital, Fudan University, Shanghai, China;*
[2] *Department of Ultrasound, Taichang First People's Hospital, Jiangsu, China;*
[3] *Department of Radiology, Zhongshan Hospital, Fudan University, Shanghai, China;*
[4] *Department of Reproductive immunology, Obstetrics and Gynecology Hospital, Fudan University, Shanghai, China;*
[5] *Department of Ultrasound, Huadong Hospital, Fudan University, Shanghai, China.*

Summary **This study aims to compare contrast enhanced ultrasound (CEUS) and contrast enhanced magnetic resonance imaging (CEMRI) for the detection and characterization of hepatic hemangiomas. Included in this retrospective study were 83 histopathologically confirmed lesions of hemangioma in 66 hospitalized patients who underwent both CEUS and CEMRI and received surgery. The enhancement patterns on CEUS and CEMRI in each lesion were compared and analyzed. In addition, data obtained by the two modalities were then compared with the pathological findings to determine their value in differential diagnosis of hepatic hemangiomas. CEUS diagnosed 78 lesions of hemangioma against 80 by CEMRI. There were no statistical significant differences in the diagnostic value between CEUS and CEMRI in terms of sensitivity (88.0% *vs*. 92.8%), specificity (99.0% *vs*. 99.4%), accuracy (97.3% *vs*. 98.4%), positive predictive value (93.6% *vs*. 96.3%), and negative predictive value (98.0% *vs*. 98.8%) ($p > 0.05$, all). In the arterial phase, the main enhancement pattern on both CEUS and CEMRI was peripheral nodular enhancement (73 *vs*. 76), but lesions with diffuse enhancement on CEUS outnumbered those on CEMRI (3 *vs*. 1) and lesions with circular enhancement on CEMRI outnumbered those on CEUS (3 *vs*. 2). In the portal venous phase and delayed phase, the main enhancement pattern was hyperechoic change on CEUS and hyperintense on CEMRI (66 *vs*. 65), some lesions presented isoechoic change (12 *vs*. 15). These results suggested CEUS, an equivalent to CEMRI, may have an added diagnostic value in hemangiomas.**

Keywords: Contrast enhanced ultrasound (CEUS), hepatic hemangiomas, contrast enhanced magnetic resonance imaging (CEMRI)

1. Introduction

Hepatic hemangioma, the most common benign hepatic tumor (*1*), accounts for 0.4-20% of all hepatic tumors (*2*). The vast majority of hemangioma cases present no specific clinical manifestations, and its diagnosis has depended mainly on such imaging tests as B-mode ultrasound scans (US), contrast enhanced ultrasound (CEUS), contrast enhanced computed tomography (CECT), and contrast enhanced magnetic resonance imaging (CEMRI).

B-mode US, noninvasive, economical, convenient and non-radioactive, has been found effective in detecting hepatic hemangiomas. On B-mode US, hemangiomas appear typically as a hyperechoic and

*Both contributed equally to this works.
**Address correspondence to:
Dr. Wenping Wang, Department of Ultrasound, Zhongshan Hospital, Fudan University, 180 Fenglin Road, Shanghai 200032, China.
E-mail: puguang61@126.com

Dr. Yue Chen, Department of Ultrasound, Huadong Hospital, Fudan University, 211 West Yan'an Rd, Shanghai 200040, China.
E-mail: ultrasound_chen@126.com

well-defined lesion with or without small central regions of decreased echogenicity (*3*). However, the diagnostic accuracy of B-mode US in detecting hepatic hemangioma is low, usually only 46-60% (*3-7*), either because of its limitations in distinguishing different types of organization (*3,8*) or because of easy misdiagnosis of hypoechoic or mixed hyperechoic hepatic hemangioma as hepatic cancer (*5*) or because of the significantly increased difficulty of the ultrasound in detecting hepatic focal lesions in fatty liver (*9,10*). Color Doppler US can visualize intratumoral and peritumoral blood flow in 10-50% of hemangiomas (*4,11*). Since other focal liver lesions have the same characteristics as hemangioma, color Doppler does not improve the diagnostic sensitivity of the ultrasound. Its accuracy may also be limited by motion artifacts, inappropriate color scale settings, interference of heart beats in detecting lesions located in the left lobe, or inability to display gas-covered lesions in the right lobe. Therefore, B-mode US and color Doppler are limited in the characterization of hepatic hemangiomas (*4*).

CECT can accurately characterize most hemangiomas but has limitations in relation to the radiation exposure and its contraindications (*12*). Considered the gold standard in the diagnosis of hepatic hemangioma with a sensitivity of 90-100% and a specificity of 91-99% (*13,14*), CEMRI is also limited by extended scanning time. CEUS is a technically simple imaging modality that allows real-time acquisition without any of the drawbacks of contrast-enhanced MRI. CEUS with microbubble contrast agents and contrast-specific US modes have been introduced to overcome the limitations of B-mode and color Doppler US. Several studies compared the diagnostic value of CEUS and CEMRI in focal liver lesions (*15,16*), but reports about their use in specifying hepatic hemangiomas are yet to be found. In some other studies, CEMRI rather than pathological evaluation was used as the gold standard for the final diagnosis (*17,18*).

The objective of this study was to investigate, by comparing with pathological findings, the sensitivity and specificity of CEUS and CEMRI in hepatic hemangiomas.

2. Materials and Methods

2.1. *Subjects*

A retrospective review was performed on 763 focal liver lesions from 413 consecutive Chinese inpatients from January 2011 to July 2014. We identified a total of 83 histopathologically confirmed hemangioma lesions in 66 hospitalized patients (12 male and 54 female; aged 31-77 years old with an average of 51.3 ± 14.5 years) who underwent both CEUS and CEMRI and received surgical treatment. We excluded 3 lesions from 3 patients which were located at the subphrenic liver and could not be visualized with baseline US and CEUS. All patients included did not suffer from severe cardiovascular and/or cerebrovascular diseases and/or lung diseases. Among those patients, 31 had abdominal pain, 5 had acute abdominal pain resulting from bleeding within the tumor, and 22 had nausea, anorexia and early satiety. Eight patients were mistaken as malignant liver lesions. Of all the 66 patients, 55 had a single lesion, 7 had 2, 2 had 3, and 2 had 4, with their sizes ranging from 18.9 × 16.3 mm to 129.3 × 109.7 mm. As shown in Table 1, the characteristics of the size and location of 83 hemangiomas lesions were presented. After examination, the patients underwent sonographically guided core biopsies, regular or irregular hepatectomy or local lesion resection for all the target lesions for pathological diagnosis. Chronic liver diseases were observed in 4 patients, while liver tissues were found normal in all other patients.

The study was conducted under the approval and supervision of the ethics committee of Fudan University and the procedure followed was in accordance with the Declaration of Helsinki. After informed consent was obtained, CEUS followed by CEMRI were performed and all patients were monitored for adverse events for four hours after the procedure. The clinical status, blood pressure and heart rate were followed up.

2.2. *Ultrasound examinations*

Color Doppler ultrasound was performed using the Philips iU22 (Philips Ultrasound, Bothell, Washington, USA), ACUSON S2000 (Siemens Medical Solutions, Mountain View, CA, USA) and LOGIC E9 (GE, Healthcare, Milwaukee, WI, USA) ultrasound system, which is capable of real-time contrast-enhanced imaging. The 3.5 MHz transducer was used with a mechanical index (MI) of 0.06-0.09. The contrast agent used was SonoVue (Bracco, SpA, Milan, Italy), which was formulated into a suspension of sulphur

Table 1. Characteristics (location, number and size) of 83 hemangioma lesions

Lexicon	Lesion Number (*n*)
Anatomic site	
S II, S III	7
S IV	13
S I	3
S V, S VIII	21
S VI, S VII	25
S IV, S V, S VIII	4
S II, S III, S IV	2
S IV, S V, S VIII	4
S I, S IV	4
Size	
< 2 cm	3
2-5 cm	6
5-10 cm	20
> 10 cm	54

hexafluoride microbubbles (8 μL/mL) by adding 5 mL of physiological saline. A baseline ultrasound examination was performed to detect lesions and images were saved on a hard disk. For each lesion, we measured its size, position, border, shape, echogenicity, and blood flow. CEUS was performed with bolus administration, *via* cubital vein, with the contrast agent at a dose of 1.5-2.0 mL flushed with 5 mL saline. In patients with multiple lesions, an additional bolus of SonoVue (1.5-2.0 mL) was administered for each lesion at an interval of at least 15 min to allow for the clearance of the previous contrast injection. No contrast agent was appreciable either in the liver parenchyma or hemangiomas before starting a new examination. All the CEUS examinations were digitally recorded. The hemodynamic contrast enhancement was evaluated during three phases as defined by Guidelines and Good Clinical Practice Recommendations for Contrast Enhanced Ultrasound (CEUS) – Update 2008 (*19*): the arterial phase (within 40 sec), portal venous phase (40-120 sec) and delayed phase (120-300 sec).

2.3. *MRI examinations*

MRI was performed with a 1.5 T MR scanner (Siemens Magnetom Avanto, Germany) in combination with 8-channel phase array surface coils. Unenhanced fat-suppressed fast spin-echo (FS-FSE) T2WI was done with a slice thickness of 5.0 mm and a slice gap of 2.0 mm: one pre-contrast scan and three post-contrast scans. Gadobenate-dimeglumine (Gd-DTPA; MultiHance, Bracco, Milan, Italy) were administered through cubital vein at a dose of 0.2 mmol/kg at 3 mL/s. Multiple breath-hold contrast-enhanced imaging was performed at 20-25 s, 70-90 s and 120-180 s after the contrast injection.

2.4. *Image analysis and data evaluation*

All the conventional ultrasound images and CEUS video clips were reviewed independently by two experienced radiologists blinded to the final diagnosis and not involved in the scanning reviewed all cineloops off-line. They had respectively 6 and 9 years of experience in conventional liver US and more than 3 years of experience in liver CEUS interpretation. The other two experienced radiologists in CEMRI studies of the liver, blinded to the final diagnosis, recorded and analyzed changes in the dynamic enhanced images at different phases and made independent diagnoses and conclusions. In case of inconsistent conclusions, a mutually accepted final conclusion was made *via* consultation. Examiners engaged in CEUS and CEMRI were blind to each other's diagnosis. The echotexture or signal intensity from the lesion was identified as hyperechoic, isoechoic or hypoechoic in contrast with the surrounding hepatic parenchyma. Perfusion uniformity was observed to determine the homogeneity of the echoes. The filling defect referred to an area of non-perfusion in the lesion.

2.5. *CEUS criteria*

The characteristic findings of grayscale sonography in hepatic hemangioma included the regular shape, well-defined border, hyperechoic mass with/without the internal hypoechoic area, and presence/absence of posterior acoustic enhancement. Color Doppler US presented color flow inside or around the tumor lesions with RI < 0.6 (*20*). Based on the literature (*19,21*) and clinical experience, CEUS findings in hepatic hemangiomas were classified into three categories: *i*) nodular enhancement in arterial phase with gradual centripedal filling (Figure 1) and hyperechoic/isoechoic change in the portal venous phase and delayed phase; *ii*) peripheral circular enhancement in the arterial phase with continuous centripedal filling (Figure 2) and hyperechoic/isoechoic change in the portal venous phase and delayed phase; *iii*) diffuse enhancement in the arterial phase with hyperechoic change (Figure 3) in the portal venous phase and delayed phase. Diagnostic criteria for hepatic hemangioma were: A) focal liver lesion as indicated by the presence of CEUS features in categories *i* or *ii*; B) focal liver lesion as indicated by the presence of CEUS

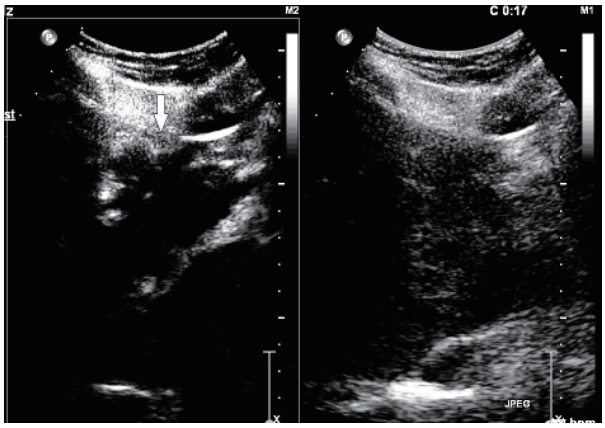

Figure 1. Category 1 of the enhancement pattern on CEUS: Peripheral nodular enhancement with continuous centripedal filling in arterial phase (arrow).

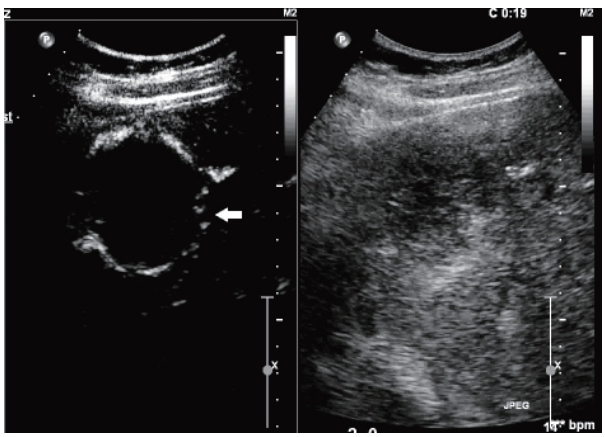

Figure 2. Category 2 of the enhancement pattern on CEUS: Peripheral circular enhancement with continuous centripedal filling in the arterial phase (arrow).

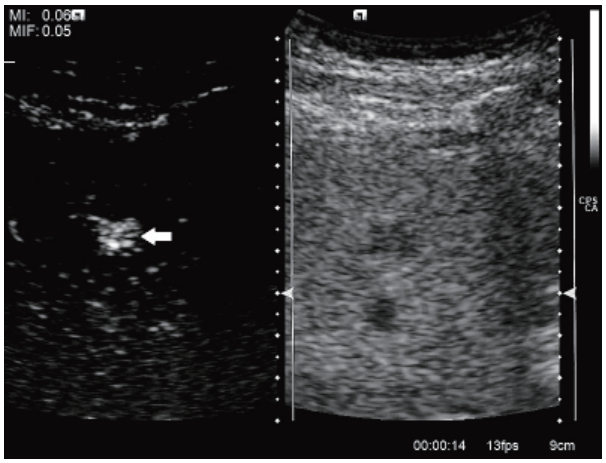

Figure 3. Category 3 of the enhancement pattern on CEUS: Diffuse enhancement with fast filling in the arterial phase (arrow).

features in categories *iii* and at least more than 5 features on conventional US.

2.6. *CEMRI criteria*

Unenhanced MRI features included regular shape, well-defined border, low signal intensity on T1WI and high signal intensity on T2WI. Characteristic CEMRI findings in hepatic hemangiomas were classified into three categories (*22,23*): *i*) nodular enhancement in the arterial phase with gradual cetripedal filling and hyperintense/isointense change in the portal venous phase and delayed phase; *ii*) peripheral circular enhancement in the arterial phase with continuous centripedal filling and hyperintense/isointense change in the portal venous phase and delayed phase; *iii*) diffuse enhancement in the arterial phase with hyperintense change in the portal venous phase and delayed phase. Diagnostic criteria for hepatic hemangioma were: A) focal liver lesion as indicated by the presence of CEMRI features in categories *i* or *ii*; B) focal liver lesion as indicated by the presence of CEUS features in category *iii* and at least more than 2 features on unenhanced MRI.

2.7. *Statistical analysis*

Chi-square tests were performed to analyze the sensitivity, specificity, accuracy, and the positive and negative predictive values of CEUS and CEMRI. The difference was considered statistically significant at a 2-tailed $p < 0.05$. The SPSS 13.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

3. Results

3.1. *CEUS and CEMRI findings*

CEUS showed peripheral nodular enhancement in the arterial phase in 73 confirmed lesions, among which 61 presented hyperechoic change and 12 presented isoechoic change in the portal venous phase and delayed phase. In 2 lesions, CEUS showed peripheral nodular enhancement in the arterial phase with continuous centripedal filling and hyperechoic change in the portal venous phase and delayed phase. In 3 lesions, CEUS showed diffuse enhancement in the arterial phase with hyperechoic change in the portal venous phase and delayed phase.

CEMRI showed nodular enhancement in the arterial phase with gradual cetripedal filling in 76 lesions, and 62 presented hyperechoic change and 15 isoechoic change in the portal venous phase and delayed phase. On CEMRI, 3 lesions showed peripheral circular enhancement in the arterial phase with continuous cetripedal filling and hyperechoic areas in the portal venous phase and delayed phase. One lesion presented diffuse enhancement in the arterial phase with hyperechoic change in the portal venous phase and delayed phase.

With CEUS, homogeneous perfusion was observed in 35 lesions, heterogeneous perfusion in 48, and filling defect in 46 against 42, 41, and 51, respectively, with CEMRI.

Table 2. Diagnostic performances of the CEUS and CEMRI as compared with histopathology

Modality	SE	SP	AC	PPV	NPV
CEUS	88.0% (73/83)	99.0% (475/480)	97.3% (548/563)	93.6% (73/78)	98.0% (475/485)
CEMRI	92.8% (77/83)	99.4% (477/480)	98.4% (554/563)	96.3% (77/80)	98.8% (477/483)
p	0.293	0.478	0.216	0.446	0.317

SE, sensitivity; SP, specificity; AC, accuracy; PPV, positive predictive value; NPV, negative predictive value.

3.2. *Diagnostic performance of CEUS and CEMRI against histopathology in hemangiomas*

Of all the 763 lesions recorded from January 2011 to July 2014, CEMRI identified 80 as hepatic hemangiomas and CEUS identified 78 as hepatic hemangiomas. The performance of CEUS in hepatic hemangiomas was close to that of CEMRI in terms of sensitivity (88.0% *vs*. 92.8%), specificity (99.0% *vs*. 99.4%), accuracy (97.3% *vs*. 98.4%), positive predictive value (93.6% *vs*. 96.3%), and negative predictive value (98.0% *vs*. 98.8%). There was no statistically significant difference between the two modalities ($p > 0.05$ for all) (Table 2).

4. Discussion

Imaging such as US, CT, and MRI are currently the most often used diagnostic modalities for hepatic hemangioma. In recent years, CEUS has been increasingly used in clinical medicine. The European Guidelines state that typical features of hepatic hemangiomas on CEUS include continuous centripetal filling in arterial phase

and hyperechoic change in the portal venous phase and delayed phase, a pattern which can be summed as "fast in slow out". In our current study, CEUS showed continuous centripetal filling with peripheral nodular and circular enhancement in 81 lesions of which 75 were pathologically confirmed as hemangiomas, showing a strong agreement with the European Guidelines. Of 81 lesions in question, 61 presented hyperechoic change in the portal venous phase and delayed phase, an observation attributable to the histological similarity between the benign tumor and normal liver parenchyma: presence of the blood sinus in both. However, isoechoic change in the portal venous phase and delayed phase was observed in 12 lesions, which differed from the European Guidelines. This might be accounted for by the rupture of the microbubbles caused by the prolonged exposure to sound waves of the lesions and their vicinity in particular. In addition, a small number (n = 3) of lesions presented diffuse enhancement in the arterial phase on CEUS, which is an atypical perfusion pattern. Some authors thought that diffuse enhancement in the arterial phase was associated with tumor size (usually < 3 cm) (*24*), while others thought that dynamic contrast enhancement patterns were associated with size of the blood vessels rather than tumor size (*25*). E. Quaia suggested that diffuse enhancement on CEUS occurs more easily in cirrhotic patients (*21*). The small number of the lesions with diffuse enhancement warrants further investigation using bigger samples. Filling defect was observed in 46 lesions on CEUS and 51 on CEMRI. Filling defect may be due to tumor sizes (all > 4 cm) and presence of thrombosis or fibrosis.

Similar enhancement patterns, featuring mainly peripheral nodular enhancement, were observed in 83 lesions on CEUS (88.0%, 73/83) and on CEMRI (92.8%, 77/83). There was no significant difference between the two modalities. More lesions, however, presented circular enhancement on CEMRI rather than CEUS (3 *vs*. 2). This may be due to the nature of the contrast agent used. SonoVue, a blood pool contrast agent, does not extravasate into the extravascular space and is, therefore, capable of reflecting the blood supply to and hemodynamics of the tumor lesion. Varied blood supply to different types of tumor results in different patterns of enhancement.

Gd-DTPA used in dynamic CEMRI is a non-tissue-specific extracellular contrast agent whose distribution in a tissue depends on the blood supply to the tissue and microvascular permeability. The principles of the two imaging modalities are different and the distribution and metabolism of the contrast agents in body tissues are also different. CEUS enjoys an edge over CEMRI for its real-time operation where the sonographer is able to observe the whole process of the contrast agent entering and leaving the lesion, while enhancement information on CEMRI may be missed by the radiologist as it is collected dynamically at the different phases. However, CEUS is limited in that observation of the enhancement and decline can be made only on one plane of the lesion after a single injection of the contrast agent, a disadvantage for CEMRI.

CEMRI, with a sensitivity of more than 90% and a specificity as high as 91-99%, is now considered the most accurate noninvasive imaging modality in diagnosing hepatic hemangioma (*13*). The characteristic manifestations of the hepatic hemangioma on CEMRI slices include low signal intensity on T1WI and high signal intensity on T2WI, peripheral nodular enhancement in the arterial phase with gradual centripedal filling, which is in agreement with the findings in this current study. Recently, CEUS has been playing an increasingly important role in the diagnosis of focal liver lesions. CECT or CEMRI or liver biopsy was taken as the gold standard in a multicenter study by Tranquart F. *etc*., in which CEUS was performed in 874 patients with 1,034 liver focal lesions (*26*). The study found that CEUS showed a sensitivity of 85.4% and a specificity of 93.7% against a sensitivity of 94.0% and a specificity of 96.4% respectively in this study, ours being obviously higher. This may be accounted for by the fact that, in the French study, pathological findings were not used as the gold standard in all patients, and using findings on CECT or CEMRI as the gold standard decreased sensitivity and specificity. In a comparative study of CEUS and CEMRI, Kristina Žvinienė (*18*) reported that CEUS as a diagnostic imaging modality for hepatic hemangioma was comparable to CEMRI in terms of specificity and positive predictive value but obviously underperformed the latter in terms of sensitivity and negative predictive value. However, the study in question was limited because evaluation of the two modalities could not be objective when pathological findings were not employed for the final assessment. This current study, employing pathological findings as the gold standard, compared CEUS and CEMRI in terms of sensitivity (88.0% *vs*. 92.8%), specificity (99.0% *vs*. 99.4%), accuracy (97.3% *vs*. 98.4%), positive predictive value (93.6% *vs*. 96.3%), and negative predictive value (98.0% *vs*. 98.8%). There were no statistical differences among the five value pairs. Therefore, CEUS is very likely to become an independent diagnostic imaging modality for hepatic hemangioma. However, lesions located deep at the subphrenic liver can still present a diagnostic dilemma even for CEUS. We excluded 3 lesions from 3 patients because of their location. Also, the typical characteristics of liver hemangiomas on CEUS were lost when cirrhosis was present, especially in small lesions (*24*). In our study, 2 lesions presented diffuse enhancement in the arterial phase with hypoechoic change in the portal venous phase and delayed phase on CEUS (Figures 4A-4D). This was explained by the presence of fibrosclerosis and vascular wall structure in the lesion on histologic analysis.

Two limitations are mentionable. First, our study was

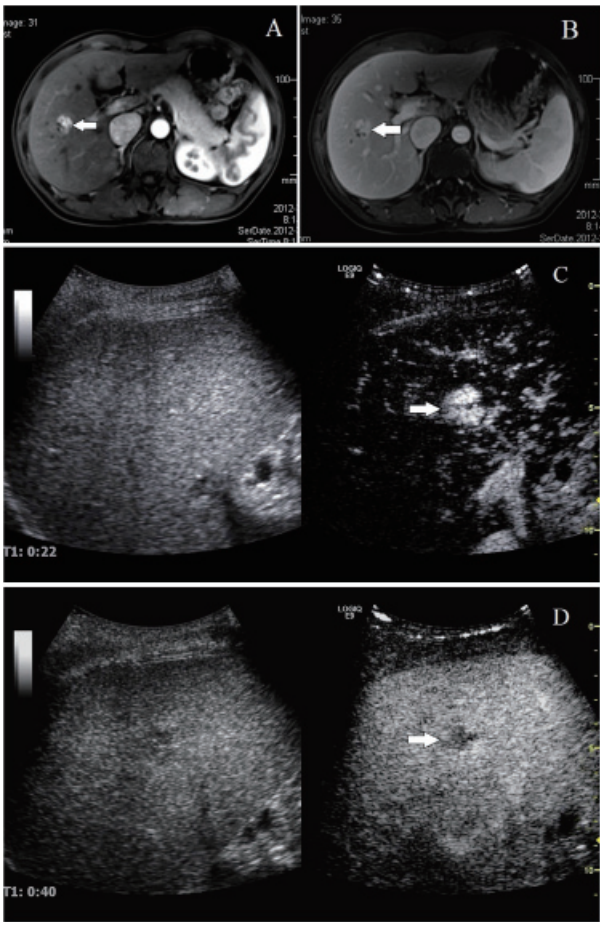

Figure 4. Liver hemangiomas on CEMRI, but malignant tumor on CEUS. (A) MRI: Peripheral enhancement with centripedal filling in the arterial phase (arrow). **(B)** MRI: High signal intensity with low-intensity signals from vascular structure in the portal venous phase (arrow). **(C)** CEUS: Diffuse enhancement in the arterial phase with fast filling (arrow). **(D)** CEUS: Hypoechoic change in the arterial phase (arrow).

retrospective in nature, and we will proceed with a future prospective analysis for the same purpose. Second, we did not explore the relationship between the determined sizes and contrast-enhancement patterns, which warrants further investigation.

In conclusion, CEUS and CEMRI play an equally important diagnostic role for hepatic hemangioma. CEUS serves as a substitute for CEMRI when the latter is impossible in claustrophobic patients or in patients with a pacemaker or metal foreign bodies or metal implants in the body. A small number of cases of atypical hepatic hemangioma require employment of the two imaging modalities as justified by the patient's medical history, clinical manifestations and findings in laboratory tests. Such comprehensive judgment by the radiologist, sonographer, and clinician improves the diagnosis of hepatic hemangioma.

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