Role of contrast enhanced ultrasound in characterization of focal liver lesions

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Received 29 April 2013; accepted 3 November 2013
Available online 5 December 2013

KEYWORDS
Conventional baseline sonography; Contrast enhanced sonography; Focal liver lesions; Microbubble contrast agent

Abstract  Aim: The purpose of the study was to describe the enhancement patterns of focal liver lesions (FLLs) on contrast enhanced sonography (CEUS), assessing the potential of this technique for characterizing the lesions and to compare its diagnostic accuracy with conventional baseline sonography including color Doppler.

Materials and methods: Between August 2009 and July 2010, 50 patients with FLLs underwent gray scale sonography, color Doppler and CEUS. The enhancement patterns of these FLL’s were analyzed throughout the arterial phase, the portal venous phase and the extended portal venous phase (the late parenchymal phase). The final diagnosis was established on the basis of histopathologic examination or CT/MRI imaging.

Results: Out of these 50 FLLs, 33 were malignant (4 hepatocellular carcinoma and 29 metastasis) and 17 were benign (5 hemangioma, 5 abscess, 2 cyst and 1 each of FNH, focal fat sparing area, focal fatty infiltration, adenoma and benign/granulomatous lesion). The enhancement patterns after injecting microbubble contrast agent allowed characterization of FLLs. The malignant lesions...
showed intratumoral and/or peritumoral vascularity during the arterial phase and perfusion defect during the late parenchymal phase. Contrast enhanced sonography improved sensitivity in detecting malignancy (CEUS vs. baseline sonography, 100% vs. 81.8%).

**Conclusion:** CEUS improves detection and characterization of FLLs. It should be used as problem solving tool in cases where conventional gray scale and color Doppler sonography are non-diagnostic.

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1. Introduction

Liver is a home for variety of focal lesions. Once identified, it becomes necessary to characterize these lesions as it has important therapeutic consequences. Conventional gray scale sonography lacks specificity and sensitivity; however it is the most common imaging modality for screening purposes. When augmented with color Doppler, it gives better results in characterization of lesions. It was further strengthened by introduction of microbubble contrast agents for sonography in the mid 1990s (1). Contrast enhanced ultrasound (CEUS) uses contrast agents that constitute of microbubbles of gas, stabilized with coating of a biocompatible surfactant or polymer like phospholipid or protein (2). These microbubble contrast agents are purely intravascular, safe, well-tolerated and are easy to administer, hence do not harm the patient (3). These contrast agents are not excreted by the kidneys, so, deranged renal function is not a contraindication for contrast enhanced sonography, which is an advantage over CT and MRI (4). CEUS allows accurate characterization of very small lesions where even CT and MRI may fail (5). CEUS has evolved as a problem solving tool for the characterization of focal liver lesions (FLLs). It depicts rapid dynamic changes, largely attributed to its real time dynamic scans and high temporal resolution.

The objective of this study was to describe the characteristic enhancement patterns of various FLLs on CEUS, assessing the potential of this technique for characterizing these lesions and to compare its diagnostic accuracy with conventional baseline sonography including color Doppler.

2. Materials and methods

Between August 2009 and July 2010, a prospective study was conducted and included fifty patients (29 males and 21 females) with a mean age of 52 years (age range from 22 to 79 years). The inclusion criteria were (1) patients of cirrhosis being evaluated for hepatocellular carcinoma (HCC), (2) suspected liver metastasis and (3) incidental detection of focal liver lesions (FLLs) on sonography. The exclusion criteria were (1) history of allergy to drugs or other contrast agents, (2) critically ill or medically unstable patients, (3) portal vein thrombosis because of possibility of impaired hemodynamics, and (4) pregnant patients. Written informed consent was taken from all patients.

<table>
<thead>
<tr>
<th>Focal liver lesion</th>
<th>Baseline gray scale and color Doppler criteria</th>
<th>CEUS criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC</td>
<td>Heterogeneous echogenicity, satellite nodules, peripheral arterial vessels with intratumoral branches</td>
<td>Diffuse enhancement during arterial phase with washout during portal venous and late phases, giving hypoechoic appearance</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Heterogeneous echogenicity, but with no or few vascular signals, and peripheral hypoechoic halo</td>
<td>Enhancing peripheral rim, variable intralesional enhancement during arterial phase that decreases during portal venous and late phases, giving hypoechoic appearance</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>Homogeneously hyperechoic, no or few peripheral or intranodular vessels (arterial or venous)</td>
<td>Nodular peripheral enhancement during arterial phase, with centripetal progression during portal venous and late phases</td>
</tr>
<tr>
<td>Focal nodular hyperplasia</td>
<td>Homogeneous, variable echogenicity, central arterial vessel with spoke wheel appearance</td>
<td>Central spoke wheel–shaped enhancement during early arterial phase that becomes homogeneous during late arterial phase, homogeneous enhancement similar to that of the liver parenchyma during portal venous and late phases, hypoechoic central region corresponding to scar during late phase</td>
</tr>
<tr>
<td>Hepatocellular adenoma</td>
<td>Variable echogenicity, intralesional venous signals, peritumoral venous and arterial signals, absence of central artery</td>
<td>Diffuse homogeneous or heterogeneous enhancement during arterial phase, enhancement similar to that of the liver parenchyma during portal venous and late phases, homogeneous or heterogeneous</td>
</tr>
<tr>
<td>Focal fatty sparing</td>
<td>Hypoechoic, triangular shape, segmental distribution, no vessels</td>
<td>Homogeneous enhancement similar to that of the surrounding liver parenchyma during all phases</td>
</tr>
<tr>
<td>Focal fatty change</td>
<td>Homogeneously hyperechoic, no vessels</td>
<td>Homogeneous enhancement similar to that of the surrounding liver parenchyma during all phases</td>
</tr>
</tbody>
</table>
Baseline sonography which included gray scale and color Doppler ultrasound was performed in all patients. Blood flow was classified subjectively as absent or no vascularity, peripheral, peripheral and intralosomal and intralosomal only depending on the blood vessels seen within or around the tumor.

Contrast enhanced sonography was performed on a Xario XG (Toshiba) machine using SonoVue (Braco, Milan, Italy) as the contrast agent. Contrast was reconstituted by adding 5 ml of saline to a vial containing sterile lyophilized powder to form a microbubble suspension. 2.4 ml of contrast agent was injected intravenously through 18/20G cannula in a bolus fashion, followed by 5 ml flush of normal saline. Each patient received only one injection.

The ultrasound machine was enabled with a contrast specific mode, using technical settings like frame rate and focal zone optimized to obtain images of best quality. The mechanical index (MI) was kept low (<0.2). Zero time was recorded at the completion of the saline flush. Real time imaging of microbubble contrast agent was done throughout the arterial phase (15–25 s), the portal venous phase (25–100 s) and the extended portal venous phase (100–300 s) in both the liver vessels and the parenchyma. If multiple lesions were present, the largest lesion was observed.

The contrast enhancement pattern was classified (6) as Absent/No vascularity: no difference in enhancement between the lesion before and after contrast injection, Dotted: tiny separate spots of enhancement distributed throughout the lesion, Rim-like/Peripheral: a continuous rim of peripheral contrast enhancement, Nodular/Peripheral nodular: discontinuous or continuous peripheral enhancement and a nodular appearance, Central/intratumoral: enhancement of the central portion of the lesion, Diffuse/peripheral and intratumoral: homogeneous or heterogeneous enhancement of the entire lesion, Perfusion defect: washout of contrast from the lesion with appearance of hypoechoic area in the background of normally enhancing liver parenchyma, Residual enhancement: persistence of contrast enhancement in the lesion on late parenchymal phase.

3. Image analysis

Both gray scale/Doppler and contrast enhanced images were retrospectively analyzed by a radiologist who was blinded to each patient’s identification, clinical history, histopathologic and other imaging results. The lesions were categorized as benign and malignant and further subclassified according to the histopathologic criteria wherever possible. The comparison of the results was made on the observation of the blinded observer. The criteria for characterizing the lesions as benign or malignant are given in Table 1.

Histopathologic examination (HPE) was used as the gold standard, and wherever HPE was not possible, final diagnosis was obtained on the basis of CT/MRI findings.

4. Statistical analysis

The sensitivity, specificity, positive predictive value and negative predictive value of conventional sonography as well as contrast enhanced ultrasound were calculated and the values expressed in percentages.

5. Results

Out of a total of fifty FLLs, 33 proved to be malignant and 17 benign on HPE or CT/MRI as shown in Table 2. Of the 33 malignant lesions 4 were HCC and 29 were metastasis.

On conventional (baseline) sonography 27 lesions were diagnosed as malignant (n = 27%, 54%), 14 as benign (n = 14%, 28%) and rest 9 were indeterminate (n = 9%, 18%) in which no single diagnosis was possible.

<table>
<thead>
<tr>
<th>Characterization of FLLs</th>
<th>Baseline sonography</th>
<th>CEUS</th>
<th>FNAC/CT/MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>True positive</td>
<td>False positive</td>
<td>Total</td>
</tr>
<tr>
<td>HCC</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Metastases</td>
<td>22</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>5</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Abscess</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Cyst</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>FNH</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Focal fat sparing (FFS)</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Focal fatty infiltration (FFI)</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Adenoma</td>
<td>–</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Benign/granulomatous lesion</td>
<td>–</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>9</td>
<td>–</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arterial phase</th>
<th>Portal venous phase</th>
<th>Late parenchymal phase</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intratumoral/central vessels</td>
<td>Perfusion defect</td>
<td>Perfusion defect</td>
<td>5</td>
</tr>
<tr>
<td>Intratumoral/central vessels</td>
<td>Homogeneous or heterogeneous/diffuse enhancement</td>
<td>Perfusion defect</td>
<td>1</td>
</tr>
</tbody>
</table>

3. Image analysis

Both gray scale/Doppler and contrast enhanced images were retrospectively analyzed by a radiologist who was blinded to each patient’s identification, clinical history, histopathologic and other imaging results. The lesions were categorized as benign and malignant and further subclassified according to the histopathologic criteria wherever possible. The comparison of the results was made on the observation of the blinded observer. The criteria for characterizing the lesions as benign or malignant are given in Table 1.

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On conventional (baseline) sonography 27 lesions were diagnosed as malignant (n = 27%, 54%), 14 as benign (n = 14%, 28%) and rest 9 were indeterminate (n = 9%, 18%) in which no single diagnosis was possible.
Table 4  Enhancement patterns of metastases on contrast enhancement.

<table>
<thead>
<tr>
<th>Arterial phase</th>
<th>Portal venous phase</th>
<th>Late parenchymal phase</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peritumoral vessels</td>
<td>Perfusion defect</td>
<td>Perfusion defect</td>
<td>10</td>
</tr>
<tr>
<td>Perfusion defect</td>
<td>Perfusion defect</td>
<td>Perfusion defect</td>
<td>9</td>
</tr>
<tr>
<td>Intratumoral vessels</td>
<td>Homogeneous or heterogeneous enhancement</td>
<td>Perfusion defect</td>
<td>4</td>
</tr>
<tr>
<td>Peritumoral vessels</td>
<td>Homogeneous or heterogeneous enhancement</td>
<td>Perfusion defect</td>
<td>2</td>
</tr>
<tr>
<td>Intratumoral vessels</td>
<td>Peripheral nodular enhancement</td>
<td>Perfusion defect</td>
<td>1</td>
</tr>
<tr>
<td>Intratumoral vessels</td>
<td>Ring enhancement</td>
<td>Perfusion defect</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>27</td>
</tr>
</tbody>
</table>

Fig. 1  HCC in a 60-year-old man. (A) Color Doppler shows peritumoral vascularity. (B) CEUS-arterial phase shows intratumoral enhancement. (C) Portal venous phase shows diffuse enhancement and (D) late parenchymal phase shows wash out of contrast with perfusion defect (E) CECT-shows heterogeneous enhancement of the FLL.
On contrast enhanced sonography, 33 lesions were diagnosed as malignant and 17 lesions as benign. Six lesions were diagnosed as HCC of which 4 were true positive and 2 were false positive. CEUS enhancement pattern of HCC is given in Table 3. The 2 false positive lesions proved to be metastases on FNAC. So, the sensitivity of CEUS in diagnosing HCC was 100%. However, the specificity, positive predictive value and negative predictive value were 95.6%, 66.7% and 100%, respectively.

Fig. 2 Metastatic malignant melanoma in a 70-year-old man. (A) Gray scale sonography shows ill defined heterogeneously hyperechoic lesions. (B) Color Doppler shows absent vascularity. (C) CEUS-arterial phase shows no enhancement. (D) CEUS-portal venous phase (E) CEUS-late parenchymal phase shows perfusion defect. The lesions are more conspicuous on CEUS.
Fig. 3  Hemangioma in a 39-year-old man. (A) Gray scale sonography shows heterogeneously hyperechoic lesion. (B) Color Doppler shows peripheral vascularity. (C) CEUS-arterial phase shows rim enhancement. (D) CEUS-portal venous phase shows peripheral nodular enhancement. (E) CEUS-late parenchymal phase shows residual enhancement with isoechogenecity to normal liver parenchyma. (F) and (G) CECT shows peripheral nodular enhancement with central fill in.
Out of 29 metastatic lesions, 27 were correctly diagnosed as hepatic metastasis on CEUS. The 2 false negative cases were diagnosed as HCC on CEUS. All the metastatic lesions showed perfusion defect on late parenchymal phase. CEUS enhancement pattern of metastasis is shown in Table 4.

So, the sensitivity, specificity, positive predictive value and negative predictive value of CEUS in diagnosing metastases were 93.1%, 100%, 100% and 91.3%, respectively.

Of the 5 hemangiomas, all 4 diagnosed on CEUS showed perilesional enhancement on arterial phase, perinodular enhancement on portal venous phase and were homogeneous to liver on late parenchymal phase. One hemangioma which was missed showed no vascularity on any of the phases and was diagnosed as focal fatty infiltration on CEUS. Therefore, the sensitivity, specificity, positive predictive value and negative predictive value of CEUS in diagnosing hemangioma were 80%, 100%, 100% and 97.8%, respectively.

Hepatic abscesses were diagnosed in 5 cases on CEUS which were all positive on CT/serology. They showed perilesional vascularity on arterial phase, ring enhancement on portal venous phase and retained their enhancement pattern on late parenchymal phase. All the abscesses in our study showed dense rim of opacification with a persistent hypoechoic center. Also, both the external and internal margins became sharper after contrast administration (Fig. 5).

Two lesions showed no vascularity in any phase and were diagnosed as cysts. One lesion which showed intratumoral vascularity with central feeding vessel on arterial phase, diffuse enhancement on portal venous phase and residual enhancement on late parenchymal phase, was diagnosed as FNH.

Fig. 4 Hemangioma in a 54-year-old woman. (A) Gray scale sonography shows homogeneous hyperechoic lesion. (B) Color Doppler image shows no vascularity. (C) CEUS-arterial phase (D) portal venous phase (E) late parenchymal phase show no enhancement, hence, misdiagnosed as focal fatty sparing. (F) CECT show peripheral nodular enhancement.
(Fig. 6). The lesion diagnosed as adenoma \( n = 1 \) showed peritumoral enhancement on arterial phase, diffuse enhancement on portal venous phase and residual enhancement on late parenchymal phase (Fig. 7). Focal fat sparing and focal fatty infiltration had enhancement pattern similar to that of normal liver parenchyma.

6. Discussion

Hepatic lesions may be detected on surveillance scans in symptomatic patients or may be incidentally seen on sonography. On conventional gray scale sonography, there is considerable overlap in the appearances of focal liver lesions. Today, however, contrast-enhanced ultrasound (CEUS) is excellent in characterization and detection of most focal liver lesions.

SH U 508 (Leovist) is a first generation, air filled microbubble contrast agent. The studies using Levovist showed that it improved the detection and characterization of FLLs (7). However, it required imaging at high mechanical index to obtain a strong harmonic response from destruction of Levovist microbubbles to visualize the contrast enhancement. It produced nonlinear emission signals from the destroyed bubbles. Therefore, its capability for proper real time imaging was limited as the investigator had to reduce the scanning frame rate significantly to permit the reaccumulation of microbubbles into the area of interest. So it was substantially incompatible with real-time scanning, a fundamental aspect of modern ultrasound imaging.

This incompatibility was overcome by the development of the second generation microbubble contrast agents such as SonoVue (Bracco), Definity (Bristol–Myers Squibb) and Sonazoid (Amersham Health). SonoVue is a sulfur hexafluoride filled microbubble contrast agent stabilized by phospholipids. The nonlinear vibration properties of these microbubbles enable the use of a low mechanical index (MI < 0.2), which prevents microbubble destruction thereby preserving the microbubbles throughout their half-life in microvessels and allowing real-time examination of liver vasculature (7). It allows continuous assessment of the vessel as contrast agent traverses the imaging field, yielding the distribution and morphology of the vessels, providing information that is only occasionally seen on CT and MRI. With careful analysis of characteristic enhancement patterns, CEUS can provide accurate diagnosis of hepatic malignancy. Apart from its diagnostic potential, it may be a useful alternative to CT and MRI for the assessment of treated liver lesions by percutaneous ablation, intra-arterial transcatheter chemoembolization or systemic chemotherapy (8).

Fig. 5  Hepatic abscess in a 22-year-old man. (A) Gray scale shows a well defined heterogeneous hypoechoic lesion in right lobe. (B) Color Doppler shows no vascularity. (C) CEUS-arterial phase shows intense peritumoral enhancement. (D) CEUS-portal venous phase shows persisting rim enhancement.
In our study, out of 33 malignant lesions, 27 were correctly diagnosed on baseline sonography. In these, 4 were HCC, out of which 2 were true positive and 2 were false positive. 23 were metastases, out of which 22 were true positive and one was false positive. Therefore, the sensitivity, specificity, positive predictive value and negative predictive value of this modality in diagnosing malignant lesions were 81.8%, 100%, 100% and 73.9%, respectively. Chami et al. (9) conducted a study in which they found the sensitivity and specificity of gray scale sonography in detecting malignant lesions to be 58.8% and 50.7%. The increased sensitivity and specificity in our study were because of augmentation of gray scale ultrasound with color Doppler.

In our study 6 lesions were diagnosed as HCC on CEUS, out of which 2 were false positive. Out of the 4 correctly diagnosed HCC, 3 showed intratumoral vascularity on arterial phase with perfusion defect on portal venous and late parenchymal phases (3/4 = 75%). One HCC although had intratumoral vascularity on arterial phase, showed diffuse enhancement on portal venous phase and finally perfusion defect on late parenchymal phase (1/4 = 25%, Fig. 1). This feature was also seen in a study conducted by Jang, et al. (10) who observed broad variations in enhancement features of HCC depending upon their histologic grade. 9% of all the hypervascular HCC including 50% of well differentiated HCC in their study did not show washout. In moderately differentiated HCC which accounted for majority of their cases, classic enhancement features of arterial phase hypervascularity (96%) and portal venous phase washout (97%) were seen.

Similar findings were reported by Liu et al. (11) who found that well differentiated HCCs showed contrast wash out more slowly than poorly differentiated ones. In their study, the echogenicity of lesions in late phase correlated with tumor cellular differentiation, hyperechoic lesions were likely to be well differentiated whereas hypoechoic lesions were more likely to be poorly differentiated.

![Fig. 6](FNH in a 22 year female. (A) On gray scale sonogram a hyperechoic lesion is seen in liver. (B) CEUS-arterial phase shows atypical spoke wheel pattern of enhancement and on porto venous phase (C) it is isoechoic to liver.)
In the 33 metastatic lesions studied by Kim et al. (12) the arterial contrast enhancement pattern was as follows: rim like in 16 (48%), diffuse in 9 (27%) i.e. homogeneous in seven (21%), and stippled in two (6%); in the remaining eight metastases (24%), no enhancement was seen. Similarly in our study, out of 29 lesions, 12 showed peritumoral/rim-like vessels (12/29 = 41.4%), 8 showed intratumoral vessels (8/29 = 27.6%) and no tumor vessel was found in 9 lesions (9/29 = 31.0%) on arterial phase. All the metastatic lesions showed perfusion defect on late parenchymal phase.

In one lesion seen on baseline sonography no diagnosis was possible; however, it was diagnosed as metastasis on CEUS with increased conspicuity of the lesions. Another case although diagnosed as metastasis on both baseline and contrast enhanced sonographies, showed that CEUS increased the visibility of the lesions, with more clearly defined margins, size and also showed more number of lesions in postcontrast scanning (Fig. 2). This certainly has bearing on treatment options and results if percutaneous ablation, intra-arterial transcatheter chemoembolization, systemic chemotherapy or partial hepatectomy is contemplated.

Out of total of 5 hemangiomas 4 showed typical enhancement pattern of hemangiomas (Fig. 3). The hemangioma which was not diagnosed on CEUS showed no vascularity on any of the three phases of enhancement (Fig. 4). A possible explanation for such an enhancement pattern was given by Michele Bertolotto et al. (8) who proposed that it might be due to extensive thrombosis or fibrotic changes in hemangioma causing absent or minimal contrast enhancement not adequate for its diagnosis. Similarly, presence of central scar in giant hemangiomas causes their partial fill in with no enhancement seen in the central scar tissue (13). On gray scale, this lesion was oval, homogeneously hyperechoic with well defined margins and showed no vascularity on color Doppler, so, diagnosed as hemangioma. Therefore, in this case conventional baseline sonography proved to be superior to CEUS.

One lesion in our study was diagnosed as benign lesion and its further characterization was not possible on CEUS. It showed intratumoral enhancement on arterial phase, diffuse enhancement on portal venous phase and residual enhancement even on late parenchymal phase. Based on these enhancement features, as there was no washout of contrast, the diagnosis of benign lesion was given. On FNAC, it was diagnosed as granulomatous lesion, thereby, confirming its benignity.

7. Conclusion

Contrast enhanced sonography due to its non–invasive, non–irradiating and real time imaging capability has significantly improved the diagnostic efficacy in focal liver lesions. The present study shows that CEUS can diagnose malignant
lesions with a sensitivity and specificity reaching 100%. However, the cost of generalized use of contrast enhanced sonography to exclude liver metastases in all patients with extrahepatic cancer is excessive. Therefore it is necessary to identify subpopulations of patients who may benefit from this approach and in such patients; a real capillary spread is still required. Hence, it is concluded that CEUS should be used as a problem solving tool in cases where conventional gray scale and color Doppler sonography are non-diagnostic.

**Author contributions**

1. Guarantor of integrity of the entire study–Shruti Thakur.
2. Study concepts and design–Shruti Thakur, D.S. Dhiman, Anupam Jhobta.
3. Literature research–Charu S. Thakur, Arun Chauhan.

**Conflict of interest**

There is no conflict of interest to disclose.

**References**