Objective. The purpose of this study was to investigate the characteristics of focal hypoechoic tumors of fatty liver using conventional ultrasonography and contrast-enhanced ultrasonography (CEUS). 

Methods. Sixty-four hypoechoic tumors of fatty liver in 52 patients were examined by both conventional ultrasonography and CEUS. Contrast pulse sequencing and a sulfur hexafluoride contrast agent were used for CEUS. The enhancement patterns were evaluated in real time. Results. Hypoechoic tumors of fatty liver showed posterior echo enhancement, including 71.4% (25 of 35) of hemangiomas, 73.3% (11 of 15) of metastases, and 50.0% (3 of 6) of hepatocellular carcinomas (HCCs) on conventional ultrasonography. During the early arterial phase, 62.5% (5 of 8) of focal nodular hyperplasia lesions showed a central spoked wheel enhancement pattern, whereas the remaining 37.5% (3 of 8) showed eccentric spoked wheel enhancement. During the arterial phase, 97.1% (34 of 35) of hemangiomas showed peripheral enhancement and centripetal fill-in, including ringlike peripheral enhancement (12 of 35), small nodular peripheral enhancement (19 of 35), and massive irregular peripheral enhancement (3 of 35). In total, 76.5% (26 of 34) of hemangiomas were completely filled in. All HCCs showed complete enhancement from 9 to 24 seconds during the arterial phase and began to wash out from 21 to 114 seconds. During the arterial phase, 40.0% (6 of 15) of metastases showed ringlike enhancement; 26.7% (4 of 15) showed slight hyperenhancement; 13.3% (2 of 15) showed hyperenhancement quickly; and the remaining 20.0% (3 of 15) showed heterogeneous hyperenhancement. All metastatic tumors began to wash out from 25 to 40 seconds. In total, 92.2% (59 of 64) of focal hypoechoic tumors of fatty liver were diagnosed as the correct pathologic type with CEUS. Conclusions. With CEUS, characterization of hypoechoic tumors of fatty liver is greatly improved. Key words: contrast agent; fatty liver; hypoechoic liver tumor; ultrasonography.
Further adding to the diagnostic challenge, there is a marked paucity of ultrasonographic findings for tumors of fatty liver. For example, when a typical hemangioma is present in the liver, if fatty infiltration of the liver has occurred, its ultrasonographic appearance will be altered. Fatty infiltration of the liver may also cause obscuration of the echogenic border around the tumor. Chemotherapy for a patient with a malignant tumor can lead to fatty liver, further confounding the imaging challenge. Ultrasonographic interpretation of tumors of fatty liver is difficult, and diagnosis of hypoechoic tumors is especially challenging. As a result, there has been a tendency for clinicians to prefer contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) over conventional ultrasonography in evaluating hypoechoic tumors of fatty liver.

Low–mechanical index (MI) real-time contrast-enhanced ultrasonography (CEUS) is a recently developed ultrasonographic technique that minimizes microbubble destruction and thus improves the differentiation and diagnosis of focal liver lesions. The sulfur hexafluoride contrast agent SonoVue (Bracco SpA, Milan, Italy) is widely available in Europe and China. Therefore, we analyzed and described the characteristics of hypoechoic tumors of fatty liver using conventional ultrasonography and CEUS.

Materials and Methods

Patients

During a 1-year period, 52 consecutive patients with 64 hypoechoic tumors of fatty liver having a final diagnosis were examined by unenhanced ultrasonography and CEUS and were included in this prospective study. The ultrasonographic diagnosis of fatty liver was established on the basis of these typical ultrasonographic findings: (1) a markedly fine echogenic liver compared with the right kidney and (2) absence of ultrasonographic findings suggestive of chronic hepatic diseases, such as an irregular hepatic surface, a coarse echo texture, and an enlarged caudate or left lobe. In our study, the diagnosis of fatty liver was confirmed by histologic analysis of perilesional hepatic tissue, CT attenuation values, or a difference between the MRI signal intensity on in- and out-of-phase sequences. We excluded all patients with liver fibrosis or cirrhosis and those without a definitive final diagnosis established by means of the reference standards outlined above.

There were 39 men and 13 women with a mean age ± SD of 45 ± 9 years (range, 25–67 years). The mean diameter of the lesions was 2.5 ± 1.4 cm (range, 0.9–7.6 cm). The tumors and peripheral fatty livers in 25 patients were confirmed by histologic analysis of biopsy and surgical specimens, including 10 hemangiomas in 8 patients, 8 focal nodular hyperplasia (FNH) lesions in 8 patients, 6 HCCs in 4 patients, and 5 metastases in 5 patients. The tumors and peripheral fatty livers in the other patients were confirmed by CT or MRI as well as follow-up, including 25 hemangiomas in 23 patients and 10 metastases in 4 patients. Written informed consent was obtained from each patient, and the study was approved by the Ethical Committee of our institution.

Conventional Ultrasonography

Ultrasonographic examinations were performed with an Acuson Sequoia 512 scanner (Siemens Medical Solutions, Mountain View, CA) equipped with contrast pulse sequencing (CPS) software, which permits real-time depiction of lesion blood perfusion under a low MI. A 4V1 vector transducer with a frequency range of 1 to 4 MHz was used. The entire liver was thoroughly scanned with conventional gray scale ultrasonography, and the focal hypoechoic liver lesion was identified. The location, size, shape, margin regularity, and posterior enhancement of the lesion were recorded. The pulse repetition frequency was set at the lowest value that was free of motion artifacts to show the color signal of low-velocity blood flow to the greatest extent possible. The color gain was set just before noise was displayed in color. The waveform of the blood flow signals was evaluated via spectral Doppler analysis.

Contrast-Enhanced Ultrasonography

The contrast agent used in this study was SonoVue, which was supplied as a lyophilized powder and reconstituted with 5 mL of saline to form a homogeneous microbubble suspension that contained sulfur hexafluoride at a concentration of 8 µL/mL stabilized by a phospholipid shell. All patients involved in this study gave their
full informed consent for SonoVue administration. Contrast-enhanced ultrasonographic studies were performed after the administration of 2.4 mL of SonoVue as a bolus through a 20-gauge cannula placed in the antecubital vein. Every injection was followed by a 5-mL saline flush. Contrast pulse sequencing was activated after contrast agent injection. The range of MI values shown on the screen was 0.13 to 0.17. A dual-image real-time display was used to help locate the target lesion during the examination. Digital cine clips of typical baseline ultrasonographic images and the whole CEUS process were stored on the hard disk and transferred to a high-performance personal computer for subsequent analysis.

**Imaging Analysis**
Dynamic CEUS images were analyzed by 2 radiologists (L.-P.L. and X.-L.Y.), who were experienced in CEUS studies of the liver. Enhancement characteristics and the time to enhancement were recorded for each lesion. Compared with the peripheral liver enhancement pattern, the lesions were classified as showing hyperenhancement, isoenhancement, or hypoenhancement.

The CEUS diagnostic criteria were as follows: (1) for hemangiomas, peripheral enhancement with gradual fill-in during the arterial phase; (2) for FNH, spoked wheel contrast enhancement during the arterial phase; (3) for HCCs, homogeneous hyperenhancement during the arterial phase and hypoenhancement during the portal and late phases; and (4) for metastases, peripheral rimlike hyperenhancement, variable intraluminal enhancement during the arterial phase, and hypoenhancement or marked hypoenhancement during the portal and late phases.

**Results**

**Characteristics of 64 Hypoechoic Tumors of Fatty Liver on Conventional Ultrasonography**
Thirty-five hemangiomas (0.9–7.0 cm in diameter; mean, 2.4 ± 1.2 cm) were found in 23 men and 8 women. Eight FNH lesions (1.2–4.3 cm in diameter; mean, 2.4 ± 1.1 cm) were found in 7 men and 1 woman. Six HCCs (1.2–4.2 cm in diameter; mean, 2.0 ± 1.2 cm) were found in 3 men and 1 woman. Fifteen metastases (1.1–7.6 cm in diameter; mean, 2.9 ± 1.9 cm) were found in 6 men and 3 women.

Tumor margins, arterial vessel detection, and posterior echo enhancement are shown in Table 1. Twenty-five hemangiomas showed posterior echo enhancement, 8 of which showed obvious enhancement. Three HCCs showed posterior echo enhancement, 1 of which showed obvious enhancement. Six FNH lesions had no posterior enhancement, and estimation was difficult in 2. In total, posterior echo enhancement broke down as follows: metastases, 73.3% (11 of 15); hemangiomas, 71.4% (25 of 35); HCCs, 50.0% (3 of 6); and FNH lesions, 0.0% (0 of 6). Tumor arterial vessel detection rates on color Doppler ultrasonography were as follows: FNH lesions, 37.5% (3 of 8); metastases, 33.3% (5 of 15); HCCs, 33.3% (2 of 6); and hemangiomas, 25.7% (9 of 35).

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<th>Table 1. Characteristics of 64 Hypoechoic Tumors of Fatty Liver on Conventional Ultrasonography</th>
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*Because of the location, determination of posterior echo enhancement was difficult.
Characteristics of 64 Hypoechoic Tumors of Fatty Liver on CEUS

Hemangiomas
Thirty-four lesions showed a peripheral enhancement process with gradual centripetal fill-in (Figure 1), and only 1 small tumor showed complete enhancement during the arterial phase. Twelve tumors showed ringlike peripheral enhancement during the arterial phase (Figure 1); 19 showed small nodular peripheral enhancement; and 3 showed massive irregular peripheral enhancement. In total, 76.5% (26 of 34) of hemangiomas were completely filled in, although the time required for filling varied widely from 4 to 145 seconds. At the end of the arterial phase, 14 of 34 hemangiomas showed complete fill-in. From 41 to 120 seconds during the portal phase, 7 were completely filled in. The remaining 5 showed complete fill-in during the late phase. In total, 97.1% (34) of the hemangiomas were correctly diagnosed by CEUS. One small lesion showed...
overall enhancement during the arterial phase; thus, the correct diagnosis was not established. Hemangiomas with complete fill-in showed hyperenhancement or isoenhancement during the late phase.

**Focal Nodular Hyperplasia**

During the early arterial phase, from 8 to 17 seconds, 62.5% (5 of 8) of FNH lesions showed central spiked wheel contrast enhancement (Figure 2), whereas the remaining 37.5% (3 of 8) showed eccentric spiked wheel enhancement and then complete enhancement from 15 to 27 seconds. During the portal phase, 5 showed hyperenhancement, and 3 showed isoenhancement. In the late phase, 2 showed hyperenhancement, and 6 showed isoenhancement. Central scars were shown in 4 of these during the late phase (Figure 2). Only 2 of these were correctly diagnosed by conventional ultrasonography. All of them were correctly diagnosed by CEUS.

**Hepatocellular Carcinoma**

All of these tumors showed homogeneous enhancement (wash-in) from 9 to 24 seconds during the arterial phase and wash-out from 21 to 114 seconds (Figure 3). All of them were correctly diagnosed by CEUS.

**Metastasis**

During the arterial phase, 40.0% (6 of 15) of these tumors showed ringlike enhancement; 26.7% (4 of 15) showed slight enhancement; and 13.3% (2 of 15) showed hyperenhancement quickly (Figure 4). The remaining 20.0% (3 of 15) showed heterogeneous hyperenhancement. Metastasis lesions began to wash out from 25 to 40 seconds; therefore, all of them showed hypoenhancement during the portal phase. Eleven of them showed marked hypoenhancement during the late phase. In total, 73.3% of metastases were correctly diagnosed by CEUS.

**All Tumors**

Overall, 92.2% (59 of 64) of focal hypoechoic tumors of fatty liver were diagnosed as the correct pathologic type with CEUS. The CEUS characteristics of the tumors are shown in Table 2.

**Discussion**

Obesity-related cirrhosis should now be recognized as a distinct entity that can cause HCC. If a malignant tumor of fatty liver is detected and diagnosed early, it can be effectively treated to improve the patient's prognosis. Furthermore, NAFLD may predispose patients to HCC in the absence of cirrhosis. The incidence of chemotherapy-induced fatty liver is increasing, and early diagnosis of liver metastases in this clinical context is critical for further treatment. In addition, the high prevalence of benign hepatic lesions in the general population reinforces the need for accurate characterization of focal fatty liver lesions. We have reported some characteristics of focal fat sparing in liver. If conventional ultrasonography is unable to exclude a malignant hypoechoic fatty liver lesion, there may be a role for CEUS for further evaluation.

Hypoechoic tumors of fatty liver had no distinctive characteristics when we analyzed posterior echo enhancement, internal echoes, and arterial vessels with conventional ultrasonography. The tumor posterior echo enhancement rates in fatty liver were 73.3% (11 of 15) for metastases, 71.4% (25 of 35) for hemangiomas, and 50.0% (3 of 6) for HCCs. Eight hemangiomas and 1 HCC showed obvious enhancement. Because of the posterior echo enhancement, some hypoechoic fatty liver lesions can be easily misdiagnosed as liver cysts by inexperienced radiologists. Some of the tumors were seen to contain arterial vessels; the most common types in these instances were FNH lesions, metastases, and HCCs. This observation fits with our understanding of the pathogenesis of FNH. One metastasis was of particular interest because it showed a spoked wheel appearance and looked like FNH on color Doppler flow imaging. However, CEUS did not reveal a spiked wheel enhancement pattern but rather showed wash-out; therefore, FNH was excluded. According to internal echoes, the most heterogeneous tumors in this study were FNH, followed by metastases. The echo nonuniformity of FNH may be attributable to scars and large vessels.

Hemangiomas are the most common benign tumors of the liver. In this study, they made up 79.5% of the benign hepatic tumors and 59.6% of the liver tumors overall. They were much more common in men, with a ratio of 2.9:1. In our
Focal Hypoechoic Tumors of Fatty Liver

study, 97.1% (34 of 35) of hypoechoic fatty liver hemangiomas showed peripheral enhancement and gradual fill-in, whereas only 1 small lesion showed complete enhancement during the arterial phase. Enhancement patterns varied widely and included what may be classified as ringlike

Figure 2. Focal hypoechoic tumor of fatty liver (FNH) and a gallbladder polypus in a 41-year-old woman. A, Sonogram showing the focal hypoechoic lesion (arrows) in the diffusely hyperechoic fatty liver. B, Power Doppler image showing a spoked wheel appearance in the tumor. C and D, Contrast-enhanced CPS images showing a central spoked wheel contrast enhancement pattern during the arterial phase (15, 16, 17, and 21 seconds). E, Hyperenhancement (left arrows) of the tumor during the portal phase (50 seconds), corresponding to the hypoechoic area (right arrows) in the fatty liver on the baseline sonogram. F, Hyperenhancement (left arrows) and scar during the late phase (205 seconds), corresponding to the hypoechoic area (right arrows) in the fatty liver on the baseline sonogram. G, Surgical specimen confirming FNH (hematoxylin-eosin, original magnification ×80).
peripheral, small nodular peripheral, massive irregular peripheral, and whole enhancement. Liver hemangiomas show prevalent persistent bubble uptake during the late phase with an isoenhanced or hyperenhanced appearance.\textsuperscript{14} Small hemangiomas showing complete enhancement during the arterial phase can usually be easily distinguished from malignant lesions because they do not show hypoenhancement during the portal and late phases. When it is difficult to determine the type of a tumor, biopsy is needed. In general, a wide range of contrast enhancement patterns have been described for liver hemangiomas, even though the most typical pattern has been peripheral enhancement with centripetal fill-in.\textsuperscript{14} In this study, the typical centripetal fill-in was the most prevalent pattern, and its appearance allowed a definitive diagnosis.

Focal nodular hyperplasia lesions are the second most common benign hepatic tumors after hemangiomas.\textsuperscript{15,16} In our study, an arterial vessel was observed in 37.5\% of them, but only 1 FNH lesion showed a spoked wheel appearance on color Doppler flow imaging. Therefore, conven-

\textbf{Figure 3.} Focal hypoechoic tumor of fatty liver (HCC) in a 48-year-old woman who had hepatitis B for the past 10 years. \textbf{A,} Sonogram showing the focal hypoechoic lesion (arrows) with slight posterior echo enhancement in the fatty liver. \textbf{B,} Pulsed Doppler image showing an arterial vessel in the tumor. \textbf{C,} Contrast-enhanced CPS image showing hyperenhancement (left arrows) of the HCC during the early arterial phase (11 seconds), corresponding to the hypoechoic area (right arrows) in the fatty liver on the baseline sonogram. \textbf{D,} The tumor is washed out, with hypoenhancement (left arrows) during the late phase (164 seconds), corresponding to the hypoechoic area (right arrows) in the fatty liver on the baseline sonogram. \textbf{E,} Biopsy specimen confirming HCC (hematoxylin-eosin, original magnification \times200).
Focal Hypoechoic Tumors of Fatty Liver

tional ultrasonography has certain limitations in the diagnosis of FNH. Quaia et al\(^{17}\) described FNH as having central spoked wheel contrast enhancement during the arterial phase and a hyperechoic or isoechoic appearance after microbubble injection during the late phase. Lin et al\(^{18}\) and Liu et al\(^{19}\) reported that FNH typically showed central spoked wheel and eccentric spoked wheel enhancement patterns during the early arterial phase. In this study, all of the lesions showed a spoked wheel enhancement pattern during the early arterial phase on CEUS. During the portal and late phases, FNH showed isoenhancement or hyperenhancement compared with the surrounding liver parenchyma. Central scars in FNH showed a hypoechoic area in the isoenhanced or hyperenhanced lesion. The scars were shown in 50% (4 of 8) of the FNH lesions in our study.

Liver metastases have enhancement patterns that are quite complex as a result of pathologic and vascular differences from their primary tumors.\(^{20}\) Most investigators have classified the enhancement patterns during the arterial phase

Figure 4. Focal hypoechoic tumor of fatty liver (metastasis) in a 56-year-old woman with ovarian cancer who underwent surgery and chemotherapy. A, Sonogram showing the focal hypoechoic lesion (arrows) with posterior echo enhancement in the fatty liver. B, Contrast-enhanced CPS image showing hyperenhancement (left arrows) of the tumor during the early arterial phase (16 seconds), corresponding to the hypoechoic area (right arrows) in the fatty liver on the baseline sonogram. C, The tumor is washed out (left arrows) during the portal phase (30 seconds), corresponding to the hypoechoic area (right arrows) on the baseline sonogram. D, Hypoenhancement (left arrows) during the late phase (144 seconds), corresponding to the hypoechoic area (right arrows) in the fatty liver on the baseline sonogram. E, Biopsy specimen confirming well-differentiated adenocarcinoma from ovarian cancer (hematoxylin-eosin, original magnification ×40).
as 2 kinds. In tumors that metastasize from the gastrointestinal tract, poor blood supplies promote the development of peripheral ringlike enhancement, whereas the organization of the tumor’s interior may lead to mild punctual enhancement, with subsequent contrast medium wash-out; on the other hand, metastases from primary tumors with rich blood vessels, such as malignant melanomas, can have multiple appearances during the arterial phase, which sometimes makes them difficult to distinguish from HCCs. In our study, metastatic tumors from ovarian cancer showed obvious enhancement during the arterial phase and subsequent wash-out. Liver metastases from lung cancer showed slight ringlike or complete enhancement during the arterial phase. However, all of them showed hypoenhancement during the portal phase, and some of them showed especially marked hypoenhancement during the late phase. Xu et al reported that 76.2% of liver metastases showed marked hypoenhancement (ie, nearly nonenhanced) during the late phase, which was validated by our own findings and may be used to differentiate a metastasis from an HCC.

In this study, some patients had a history of hepatitis B; their tumors were observed to have arterial vessels, and 2 lesions in 2 patients were considered likely to be HCCs on conventional ultrasonography. The other lesions could not be distinguished as benign or malignant on conventional ultrasonography. Contrast-enhanced ultrasonography provided the correct diagnosis. Diagnosis of HCCs was much more accurate with CEUS. Typically, with CEUS we can characterize the wash-in and wash-out periods. Fan et al reported that the characteristic manifestation of moderately to poorly differentiated HCCs on CEUS was quick enhancement during the arterial phase and fast wash-out during the portal phase, whereas half of the well-differentiated HCCs washed out slowly during the late phase.

In general, characterization of hypoechoic tumors of fatty liver on conventional ultrasonography is challenging, with a limited ability to differentiate between malignant and benign tumors and to judge tumor types. Contrast-enhanced ultrasonography allows us to observe the vascular characteristics of the tumors and is far superior to conventional ultrasonography in characterizing hypoechoic tumors of fatty liver. Analysis of enhancement patterns during the arterial phase allows correct diagnoses of FNH and hemangioma. Furthermore, late-phase imaging is important for differentiation between benign and malignant lesions. Thus, CEUS has an important role in the diagnosis of hypoechoic tumors of fatty liver.
References


