Contrast-enhanced Ultrasonography in Small Liver Tumors (<3 cm)

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Ultrasonography is a safe, convenient, low cost and noninvasive diagnostic modality for liver tumors. Power Doppler sonography may demonstrate fine tumor vessels in small lesions and hypovascular lesions. However, it has limitations including motion artifacts, less sensitivity to slow vascular flow, poor demonstration of deep-seated lesions (>7 cm in depth), and high sensitivity to tissue motion (heart beat or aortic pulsation). Owing to improvements in contrast agents and new technologies such as harmonic and pulse inversion imaging, contrast-enhanced ultrasound (CEUS) has improved the detection rate compared with Doppler ultrasound in studies of liver lesions. The enhanced vascular patterns have been proved to correlate well with the findings from dynamic computed tomography or magnetic resonance imaging. CEUS provides the ability to detect small focal liver lesions and even metastatic liver tumors of less than 1 cm in diameter. This review attempts to determine ways to allow the diagnosis of small hepatocellular carcinomas (HCCs), especially in cirrhotic patients, using CEUS. Because HCCs are small, the feeding arteries are fine and the arterial blood flow to the tumor is slow, CEUS used in the diagnosis of nodules of 1–2 cm in cirrhotic patients is not satisfactory. The portal and late phases in pulse inversion imaging may provide more information to detect small lesions in the cirrhotic liver and improve the diagnostic sensitivity and specificity. Contrast-enhanced flash echo with subtraction mode is another way of detecting this type of small tumor. In the arterial phase, some tumors are hard to identify, owing to the isoechoic status of the tumors with respect to the surrounding liver parenchyma. However, these small lesions may be shown by flash echo subtraction imaging. Concurrent delayed phase imaging is useful in the diagnosis of small hypovascular HCCs. In conclusion, CEUS improves the diagnostic accuracy of focal liver lesions, even in tumors as small as 1–2 cm. This safe, convenient, low cost and noninvasive diagnostic modality should be promoted in routine clinical practice.

KEY WORDS — contrast-enhanced ultrasonography, focal liver lesion, hepatocellular carcinoma, liver, ultrasound contrast agent


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Introduction

Because real-time ultrasonography (US) demonstrates small liver tumors (<3 cm in diameter) [1], conventional US is used for the detection of focal liver lesions because of its efficiency, availability, non-invasiveness, and relatively low cost. On conventional US, it is sometimes difficult to differentiate benign lesions from malignant lesions, especially in smaller lesions. Anatomically, the blood supply of a malignant tumor is mainly from the hepatic artery, and Doppler ultrasound can demonstrate the vessels in and around the tumor [2]. Color Doppler US and power Doppler US have proved to be useful in demonstrating tumor vascularity [3–6]. However, color Doppler sonography failed to show the blood flow in a hypovascular lesion [2]. Although power Doppler sonography is superior to color Doppler sonography in demonstrating fine tumor vessels in small lesions (≤2 cm in diameter) and hypovascular lesions, power Doppler techniques have limitations such as motion artifacts, less sensitivity to slow vascular flow, poor demonstration of deep-seated lesions (>7 cm in depth), and high sensitivity to tissue motion (heart beat or aortic pulsation) [7]. The detection of increased arterial flow in a tumor by Doppler US is dependent on the size, depth, and blood flow of the lesion. However, Doppler US studies in patients at risk of developing hepatocellular carcinomas (HCCs) have not yet been proven to affect the sensitivity of detection of small HCCs. Sensitivity can be increased by improving contrast resolution and by new technologies involving harmonic frequencies (tissue harmonic imaging) [8]. Contrast-enhanced ultrasound (CEUS) improved the detection rate up to 90–97% compared with grayscale US in studies of liver metastatic lesions [9,10]. In a study by Solbiati et al, CEUS detected miliary metastases of 5–10 mm in diameter; the detection rate was as high as 82%, even better than that of helical computed tomography (CT) [8]. In an overview, Konopke et al stated that the use of CEUS in 100 patients increased the correct diagnosis of focal liver lesions from 64% to 87% compared with B-mode US, especially in the case of small metastases and following chemotherapy [11].

The enhancement pattern of CEUS in the vascular phase is based on the dynamic contrast behavior of different focal lesions in the liver. The enhanced vascular patterns were proved to correlate well with the findings from dynamic CT or magnetic resonance imaging (MRI) [12]. The enhancement patterns of liver HCC were also characteristic [11,12]. Furthermore, for the detection of focal liver lesions, CEUS was shown to improve accuracy in liver metastasis detection and was comparable to spiral CT [13]. Some studies have suggested that CEUS can detect lesions not visible on CT [5,13–18].

An initial report on the use of ultrasound contrast agents was published in 1969 [19]. The development of effective US contrast agents and of new sonographic techniques such as harmonic and pulse inversion imaging has considerably improved the possibilities of CEUS in the assessment of liver tumors [20,21]. Small focal liver lesions were correctly detected by CEUS [11,22–25], and even metastatic liver tumors of less than 1 cm in diameter as well as tumors located near the liver surface or situated around the ligamentum teres were also detected [25]. However, in small HCCs, especially in cirrhotic patients, current imaging techniques are still not accurate enough to establish a reliable diagnosis in nodular lesions of <2 cm [14,26] or in well-differentiated small HCCs [27]. The accurate and early diagnosis of HCC is essential for treatment planning in affected patients. This review attempts to find ways of using CEUS in the diagnosis of small HCCs.

Ultrasound Contrast Agents (UCAs)

Microbubbles with a diameter of <8 μm have been proved to pass through capillary vessels, and an ultrasound pulse with a frequency of 2 MHz and a negative pressure of about 700 kPa has the ability to disrupt the microbubbles and generate echo signals [28]. Thus, contrast agents with
transpulmonary stability, which are administered intravenously into peripheral veins, have become commercially available for use in sonographic enhancement studies.

Among the UCAs, which include SonoVue, Levovist, Sonazoid, Optison, Definity and Imagent, three types of UCAs are commonly used in Europe [29,30]. These are Levovist, SonoVue and Optison.

1. Levovist (SH U 508A): Levovist bubbles contain air with galactose/palmitic acid surfactant (introduced by Schering in 1996). The bubbles in Levovist are coated with a thin layer of palmitic acid. Flash echoes are not observed at a depth of > 7 cm, because the acoustic pressure fall below the threshold of bubble collapse is due to tissue attenuation. Assuming the tissue attenuation is 0.6 dB/MHz/cm, transmission power would attenuate at −10.5 dB or around 420 kPa at a depth of 7 cm. These results suggest that more power output is needed for Levovist to obtain flash echoes deeper than 7 cm [31]. Main indications for the use of Levovist include heart, abdomen (including vesicoureteral reflux) and transcranial studies.

2. SonoVue (second-generation agent): Bubbles of SonoVue contain sulfur hexafluoride with a phospholipid shell (introduced by Bracco, Milan, Italy in 2001). SonoVue is a blood pool perfluoro gas agent, which consists of microbubbles of sulfur hexafluoride stabilized by a phospholipid shell [32]. The microbubbles are isotonic to human plasma and stable and resistant to pressure. SonoVue improves the display of focal tumor vascularity and normal parenchymal liver vascularity [33]. Main indications for the use of SonoVue are cardiac, macrovascular, liver and breast lesions.


UCAs consist of gas bubbles stabilized by a shell; Levovist contains air, whereas SonoVue (sulfur hexafluoride) and Optison (perflutren) contain low solubility gases which improve microbubble stability [29].

Techniques

Harmonic imaging

Because of the difference in acoustic impedance between air and liquid, air microbubbles in the liquid can reflect ultrasound signals which contain significant energy, not only the fundamental frequency from the original transducer, but also higher order harmonics. Using these nonlinear properties of microbubbles, a harmonic imaging study on capillary blood flow was reported in 1992 [34]. In this method, signals are transmitted at the fundamental frequency, but are received as higher order harmonics. That is, an ultrasound scanner is transmitting at one frequency and receiving double or triple times the frequency transmitted. This technique improves the detection rate of the microbubble contrast agents [35,36]. Harmonic imaging makes it possible to visualize capillary blood flow in tissues that cannot be detected by conventional B-mode or color Doppler imaging [35,36].

Pulse inversion imaging

Because of the limitations of resolution due to compromises forced by harmonic imaging that restrict the bandwidth [37], pulse inversion imaging mode was designed to allow low incidence power and nondestructive, continuous imaging of microbubbles in an organ (such as the liver) to produce high-quality contrast-enhanced images. The pulse inversion imaging mode is superior to second harmonic imaging or conventional Doppler imaging [37,38] and may present as harmonic angio images [39]. In pulse inversion imaging, two separate pulses (normal pulse and inverted pulse at 180° out of phase) are transmitted in rapid succession into the tissue. The inverted pulse is a mirror image of the normal pulse. The echoes from these two successive pulses are received by the scanner which forms their sum. The resulting echoes from tissue behave in a linear manner canceling each other, and the sum of these two pulses is zero. For an echo with nonlinear components, such as that from a bubble, the echoes produced from these two pulses will not be simple mirror
images of each other. Because of the asymmetric behavior of the bubble radius with time, the sum of these two pulses is not zero. That means the echo is present and contains nonlinear harmonic components of the signal (including second harmonics). So, the signal can be detected from a bubble but not from tissues [37,40]. Pulse inversion imaging mode has no restriction on bandwidth; the full frequency range of sound emitted from the transducer can be detected and this mode provides an effective result [37,41].

**Low mechanical index (MI) technique**

Ultrasound pulse with an acoustic power has the ability to disrupt the microbubbles of UCAs. Low MI with very low acoustic power (such as <0.2) avoids disruption of the microbubble. This low MI contrast technique allows dynamic imaging with subsequent evaluation of the three different vascular phases using a low solubility gas UCA.

UCA is administered as a bolus injection, followed by a 5–10 mL saline flush. The needle diameter should not be smaller than 20 gauge to avoid loss of bubbles due to mechanical impact during injection. Continuous scanning for 60–90 seconds is recommended to continuously assess the arterial and portal venous phases. Under this assessment until the disappearance of the UCA from the tissues, the microvasculature has been observed [29]. The setting of low MI is an insonating frequency of 3 MHz, acoustic power of −75 to −90 dB, and frame rate of 17–20. The scanning time of a vascular study is up to 3.5 minutes, including the arterial phase of 0–49 seconds, the portal phase of 50–179 seconds and the late phase of >180 seconds.

**High MI technique**

High MI technique in which microbubbles are deliberately destroyed is probably more useful for focal liver lesion detection and can be used for characterization of these lesions. High MI technique requires intermittent scanning of the lesion during all three phases [29]. The destruction of microbubbles by high MI ultrasound has been studied to allow a greater separation between the tissue and the contrast agent. The high MI destruction imaging technique has been referred to as agent detection imaging (ADI). With Doppler techniques, ADI displays microbubble signals as a color overlay on the grayscale tissue image. In studies with ADI, a bubble destruction image showed the normal liver as bright and the metastases as black without any signal. Thus, ADI makes CEUS very sensitive [30].

**Intermittent harmonic imaging with subtraction mode**

Using the second harmonic imaging technique [31], intermittent harmonic (flash echo) imaging with subtraction mode can be performed to evaluate the dynamic perfusion of small lesions in which power Doppler US failed to demonstrate the vessels. Flash echo imaging in subtraction mode is obtained in the following way. The scanner transmits the ultrasound beam at, for example, 2.1 MHz and receives echoes at 4.2 MHz and is set to generate two bursts of high acoustic power (high MI, 1.0–1.2) in rapid succession. The subtraction image is automatically obtained by setting the ultrasound machine to subtract the second frame image from the first frame image. The flash echo image with subtraction mode can be designed to operate depending on the operator’s demand. The real-time, low acoustic power imaging (low MI, 0.2) is used for monitoring during the intervals between flash echo imaging.

**Vascular Phase Study in Liver**

Hepatic artery supply usually starts 10–20 seconds post-injection into a peripheral vein and lasts for approximately 10–15 seconds. This is followed by the portal vein phase, which usually lasts 2 minutes after contrast agent injection. The late phase lasts until clearance of the contrast agent from the hepatic parenchyma, up to approximately 15–20 minutes post-injection for Levovist and 4–6 minutes for SonoVue [29].
1. Arterial phase: The contrast agent reaches the liver first via the hepatic artery and provides information on the degree and pattern of vascularity. Tumors with abundant blood supply show hypervascularity during this phase.

2. Portal vein phase: The contrast agent has passed through the circulation and spreads through the liver via the portal branches. This phase usually lasts 2 minutes after contrast agent injection.

3. Late (parenchymal) phase: The late or parenchymal phase follows the portal phase, in which the agent is slowly distributed throughout the entire liver parenchyma. The origin of the late phase is the subject of ongoing scientific discussion, and suggested mechanisms include sinusoid pooling and reticuloendothelial system/Kupffer cell uptake [42].

The portal and late phases provide information regarding the wash-out of contrast agent from the lesion compared with normal liver tissue. In the case of hemangiomas, a progressive filling can be observed during these phases. The portal and late phase enhancement can provide important information regarding the character of the lesions. Most malignant lesions are hypo-enhancing, while the majority of solid benign lesions are iso- or hyper-enhancing [43–46].

The limitations of CEUS for characterization of liver lesions are subject to the same limitations as other types of ultrasound, and sensitivity is markedly reduced in attenuating livers and deep lesions. As a general rule, if baseline ultrasound is suboptimal, results from CEUS may be disappointing.

Small Liver Lesions of <3 cm

HCC
Pathologically, HCCs receive an arterial blood supply. In small HCCs of distinctly nodular type, most of these tumors show hypervascularity despite the small tumor size. While in small HCCs of indistinctly nodular type, many of them show hypovascularity. Meanwhile, the majority of well differentiated HCCs of indistinctly nodular type (early HCC) receive portal blood supply in addition to the arterial blood supply, because they contain portal tracts within the tumor. The number of arterial vessels per square millimeter in early-stage HCCs of <1.5 cm in diameter is about two-thirds of that in advanced tumors, and it is only less than one-third in tumors smaller than 1.0 cm. Early HCCs are not encapsulated, and HCC cells proliferate as if they are replacing the liver cell cords at the boundaries. The sinusoidal blood spaces are incompletely vascularized, and the sinusoidal spaces of the tumor are continuous with the sinusoids of the surrounding liver tissue. So, a certain proportion of blood flows into the sinusoids of the surrounding liver tissue [47]. The contrast agent will wash out from the tumor to the liver parenchyma rapidly, and the tumor may appear hypoechoic with respect to the surrounding liver in the late phase.

With CEUS, HCCs are characterized by hypervascularity in the arterial phase. Using real-time evaluation with low MI, early intense enhancement is usually identified and the feeding artery is clearly visible in most cases. Tumor vessels usually show a basket-like or an irregular branching pattern extending from the periphery to the center of the tumor [48]. Arterial enhancement of the tumor may be inhomogeneous, because tumors may have septa, different cell differentiation and arteriovenous shunting among the neoformed vessels [15,26]. In small HCCs, the arterial phase shows hyper-echoic enhancement, and in the portal and late phase, enhancement also provides important information regarding the character of the lesions. In the late phase, the most malignant lesions are hypo-enhancing, while the majority of solid benign lesions are iso- or hyper-enhancing [43–46]. In a study by Nicolau et al on the differentiation of benign from malignant focal liver lesions using contrast-enhanced imaging, the results showed that evaluation of all three vascular phases was superior to the evaluation of enhancement in the late phase alone. The sensitivity increased from 78.4% to 98%, and the accuracy from 80.9% to 92.7% [49]. However, these characteristic patterns are sometimes hard to demonstrate in small HCCs, owing to the small tumor
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size, fine feeding arteries, and slow arterial blood flow to the tumor [50]. Contrast-enhanced flash echo with subtraction mode is another way of detecting liver tumors as small as 8 mm in diameter. In the arterial phase, some tumors show faint hyperperfusional status, which is isoechoic with respect to the surrounding liver parenchyma during arterial enhancement and is difficult to identify. Smaller lesion may be shown using flash echo subtraction imaging (Fig. 1) [51]. In a study of 14 small liver tumors (diameter, 0.8–3.0 cm; mean, 1.8 ± 0.5 cm) by Wang et al, contrast-enhanced flash echo with subtraction mode was sensitive and effective in detecting these small liver tumors [51].

In cirrhotic liver, multistage processes can exist, including regenerative nodules, dysplastic nodules and HCC. Differentiation between these processes is somewhat difficult. On a histopathologic basis, evolving malignant change in a cirrhotic nodular lesion shows that the arterial flow supply progressively increases to the lesion [52,53]. This progressive neoangiogenesis provides the clue for clinical diagnosis with imaging techniques [54]. Therefore, the European Association for the Study of the Liver panel of experts determined that the diagnosis of nodules of >2 cm must be confirmed by two different imaging techniques. However, no reference was made to the vascularity of nodules of 1–2 cm in diameter. Many studies have used CEUS in the characterization of liver lesions. In a study of 41 cirrhotic patients with small monofocal lesions (<3 cm in diameter) by Fracanzani et al [16], it was reported that contrast-enhanced Doppler US using Levovist was a noninvasive, sensitive technique in

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**Fig. 1.** Intermittent harmonic (flash echo) imaging with subtraction mode in a patient with a small hepatocellular carcinoma of 1.0 cm in diameter. (A) Conventional ultrasound demonstrates a small hypoechoic lesion (arrow). (B) In the arterial phase of contrast enhanced ultrasound, the hypervascular lesion cannot be differentiated from the enhanced surrounding normal liver parenchyma. (C) Using subtraction mode, the lesion is clearly shown (arrow). (D, E) In the portal and late phases, the lesion shows as hypoechoic (arrow). (F) By subtraction of the late phase image, the lesion is still hypoechoic (arrow).
differentiating malignant and premalignant focal lesions. In this study, the intratumoral arterial blood flow was detected in 19 of 20 HCCs (95%), and in 6/21 nonmalignant nodules (28%) by contrast-enhanced Doppler US. Four of the six false-positive findings were high-grade dysplastic nodules, and the remaining two evolved to HCC during follow-up [16]. The results showed that the likelihood of detecting arterial flow in a nodular lesion in a cirrhotic patient with HCC was high. Bolondi et al [23] reported 72 small nodules (1–2 cm, \( n = 41 \); 2.1–3 cm, \( n = 31 \)) in 59 cirrhotic patients, which depended on the coincident arterial hypervascularity at contrast perfusional sonography using SonoVue and helical CT to detect small HCCs in cirrhotic nodules. The detection rate was only 61% (44/72) in nodules of <3 cm in cirrhotic patients (44% in nodules 1–2 cm, 84% in nodules 2–3 cm). Relying on imaging techniques in nodules of 1–2 cm, the missed diagnosis of HCC was up to 38%, and any nodules of >2 cm should be regarded as highly suspicious for HCC [23]. Thus, even with arterial hypervascularity shown by CEUS, the diagnosis of nodules of 1–2 cm in cirrhotic patients is not satisfactory.

The detection of small HCCs, especially in the cirrhotic liver, is a problem. Small HCCs in cirrhotic liver may be detected as areas of increased enhancement in the arterial phase, and the short duration of the arterial phase does not allow surveillance of the whole liver. The portal and late phases may provide more information in the detection of small lesions in cirrhotic liver [43–46]. Forsberg et al reported that Levovist showed a tissue-specific late phase with selective enhancement of liver and spleen parenchyma [55]. The accumulation of Levovist in parenchyma is known in reticular endothelial (RE) cells [56], and Kono et al suggested that this accumulation is the uptake of Levovist by mechanisms including sinusoid pooling and RE/Kupffer cells [42]. Therefore, pulse inversion imaging allows visualization of liver parenchyma on sonography [57]. Pathologically, HCC and metastatic malignancies in liver lack RE cells, and no HCC or metastasis have shown uptake of Levovist in late-phase pulse-inversion sonography [17]. For the discrimination of malignant versus benign liver lesions, late-phase pulse-inversion contrast-enhanced sonography improved diagnostic sensitivity from 85% to 100% and specificity from 30% to 63% compared with baseline sonography, and with lower interobserver variability [17]. In addition, Wang et al reported the highly specific visualization of small HCCs (≤2 cm) in cirrhotic patients using a combination of arterial enhancement (AE) and absence of delayed phase enhancement (ADE) using Levovist [58]. Scanning for the delayed phase was carried out about 5–6 minutes later after arterial phase evaluation. In the evaluation of 30 small hepatic nodules (diameter, 1–2 cm; mean, 1.5 ± 0.3 cm) using both AE and ADE for HCC diagnosis, the sensitivity, specificity, accuracy, positive predictive value and negative predictive value were 55.6%, 91.7%, 70%, 90.9% and 57.9%, respectively. When using either AE or ADE for the diagnosis of HCC, the same parameters were 94.4%, 66.7%, 83.3%, 81% and 88.9%, respectively. The authors concluded that concurrent delayed phase imaging is useful in the diagnosis of small hypovascular HCCs [58].

For grading of small HCCs on the basis of the presence of Kupffer cells in small tumors, Kitamura et al reported that contrast-enhanced color Doppler sonography appeared to reflect the histopathologic features of HCCs in 20 tumors (mean diameter, 2.8 ± 1.2 cm) and was useful for differentiating liver tumors [59]. von Herbay et al [17] suggested that CEUS could not grade HCCs. However, both highly differentiated and less differentiated HCCs were detected without contrast enhancement in late-phase images [17], and Nicolau et al reported that the echogenicity in the portal and late phases correlated with cellular differentiation [27]. In 104 HCCs (36 cases; diameter, <2 cm), 96.2% of HCCs (including 27 well-differentiated HCCs) showed enhancement in the arterial phase. Four (3.8%) of the well-differentiated cases showed an isoechoic pattern \((p < 0.05)\). Therefore, in the arterial phase, no enhancement may represent a well-differentiated HCC. In the early portal phase, isoechoic echogenicity was found in well- and moderately differentiated
HCCs, and hypoechoic echogenicity in poorly differentiated HCCs. In the late phase, isoechoic echogenicity was found in well-differentiated HCCs and hypoechoic in moderately and poorly differentiated HCCs [27]. In a report by Wang et al on 18 small HCCs (diameter, ≤2 cm), no significant correlations between cellular differentiation and CEUS enhancement patterns were observed [58]. These results were limited by the small number of cases. However, the correlation between cellular differentiation and CEUS enhancement patterns depends upon the vascularity of HCC in the arterial phase, the speed of blood feeding in the portal phase, and the number of Kupffer cells or sinusoid spaces in the late phase. More research is needed to confirm these findings.

**Metastasis**

Hepatic metastatic lesions are not uncommon and are not always multiple. Histologically, most hepatic metastatic lesions are hypovascular. Characteristics of metastatic tumors include intratumoral hypovascularity and hypervascularity in the tumor periphery. Ten to fifteen percent of hepatic metastatic tumors are hypervascular. Conventional grayscale US can detect metastatic lesions as hypo-, hyper- or mixed echogenicity, but conventional US can miss isoechoic lesions and lesion size of <1 cm in diameter [10]. Many studies have confirmed the improvement in accuracy of CEUS in diagnosing liver metastatic lesions [13,17,18,60–62]. The detection rate of hepatic metastatic lesions was reported by Bernatik et al in their study of 28 patients to be 97% [9]. Oldenburg et al reported the sensitivity to be 90% in 128 metastases [10]. Solbiati et al also reported that CEUS improved the detection of miliary metastases (0.5–1 cm) [8]. Characteristic features of hepatic metastatic lesions can be demonstrated in three phases of continuous low-MI imaging CEUS. In the arterial phase, hypovascular metastases appear as hypo-effective lesions, usually with a typical rim enhancement of varying size, whereas hypervascular metastases appear as bright enhancing hyper-effective and homogeneous lesions. Rapid wash-out of arterial enhancement is found in the late arterial and portal phases [63]. Therefore, at the beginning of the portal phase, the arterial enhancement fades and the entire hypovascular lesion becomes hypoechoic. In the late phase, both hypovascular and hypervascular metastases invariably appear dark compared with the enhanced background of normal liver parenchyma. During this late phase, both portal venous and late-phase imaging markedly increase the contrast between the enhanced normal liver. Thus, non-enhancing metastases improve detection, especially of small lesions of <1 cm in diameter and of lesions which are isoechoic at baseline [11]. Benign focal liver lesions (FLL) contain Kupffer cells and/or sinusoids (except hemangiomas), including dysplastic nodules, which also consist of sinusoidal capillarization [47]. So, in the late parenchymal phase, FLL can be enhanced in an isoechoic pattern with respect to the surrounding liver. An isoechoic pattern in relation to the adjacent liver in the last phase is demonstrated in benign lesions, whereas metastases appear more hypoechoic by the enhanced normal liver background and are easily distinguished from normal liver. A high diagnostic accuracy in the differentiation between metastases and benign FLL in the late phase has been reported [17,64,65].

**Hemangiomas**

Hemangiomas are the most frequent benign tumor found in the liver. Pathologically, a hemangioma is composed of cavernous vessels. In the tumor, the blood flow in the vascular space is extremely slow and blood pooling exists [66]. The velocity of flow in the tumor is so slow that Doppler US can not detect any signals [67]. Although most hemangiomas show homogeneous hyperechoic patterns on conventional US, the sonographic features of hemangiomas are not specific. Furthermore, the imaging diagnostic accuracy is low for small hemangiomas even by MRI [68]. CEUS has been shown to increase the detection sensitivity of slow-velocity blood flow in hepatic tumors [50] and provides a progressive filling in hemangiomas in the portal and late phases. Thus, in the arterial phase of CEUS, characteristic images show the presence of...
peripheral globular or rim-like enhancement in typical and atypical hemangiomas [48,69,70]. However, these characteristic patterns are also found in malignant FLL, such as metastases [48,62]. In the portal and late phases, the enhancement of hemangiomas has a specific pattern [12,41,48,71]. In the portal phase, progressive filling may gradually show centripetal enhancement first and then complete filling within several seconds in small hemangioma and within 30–60 minutes in giant hemangioma. Incomplete centripetal enhancement and/or incomplete tumor fill-in may occur in some tumors. In the late phase, owing to the contrast agent, the time elapsed, the filling velocity and intratumoral thrombosis or fibrosis, the enhanced patterns show complete enhancement or non-enhancing central areas (partial thrombosis or fibrosis). As a result of the persistence of contrast in the vascular bed of hemangioma, the enhancement remains hypoechoic compared with the surrounding tissue [29]. In small hemangiomas (<2 cm in diameter), the arterial phase shows diffuse enhancement, which may occur in hypervascular malignant tumors such as HCC or metastases. However, in the portal and late phases, small hemangiomas usually have hyperechoic or stronger enhancement with respect to the surrounding liver tissue, while malignant lesions become hypoechoic [11,12,29]. CEUS can be used in the diagnosis of hemangioma, when centripetal fill-in enhancement is a positive finding in hemangioma. Ding et al reported that the sensitivity of CEUS in the diagnosis of hemangioma was 96.23% and the specificity was 97.5% [72]. When typical contrast-enhanced patterns in the vascular and late phases were regarded as positive findings, Nicolau et al showed that the correct identification of 22 hemangiomas was 81.8% in the vascular phase and 86.4% in the late phase [12].

**Focal nodular hyperplasia (FNH)**

FNH is the second most common benign liver neoplasm. FNH is a hyperplastic lesion composed histologically of all the components of normal liver tissue, and about 45% of cases have a central stellate fibrous scar [73]. In the arterial phase of CEUS, FNH rapidly enhances with atypical centrifugal radiating enhancement (spoke-wheel pattern) [46,12,74], then shows whole-lesion homogeneous hyperechoic enhancement. The spoke-wheel pattern represents a central feeding artery and centrifugal blood supply from the center of the lesion to the periphery.

In the portal phase, enhancement in FNH gradually changes to isoechogenic compared with the surrounding liver parenchyma. In the late phase, because the lesion contains all the components of normal liver tissue, the lesion remains isoechogenic; some lesions even show as slightly hyperechoic with respect to the surrounding normal liver [17,41]. Due to the central stellate fibrosis scar, CEUS does not show enhancement in the portal and late phases and represents a key feature for diagnosing FNH. The characteristic features of FNH on CEUS include: (1) hypervascularity in the arterial phase with a centrifugal blood supply; (2) isoechogeticity in the late phase; and (3) a central scar. Those features aid in the differential diagnosis of FNH from other hypervascular tumors, including hypervascular metastases, HCCs, small hemangiomas and adenomas [12]. Di Stasi et al reported on the characteristic features, and the sensitivity and specificity of diagnosing FNH were 87.6% and 94.5%, respectively [74]. Yen et al [75] reported that the sensitivity of the spoke-wheel sign or central scar for FNH in 35 FNH lesions (1.3–7.0 cm; mean, 2.9 ± 1.4 cm) was 97.1%, 40%, 28.6%, and 50% for CEUS, color/power Doppler US, CT scan, MRI and hepatic angiography, respectively. Regardless of the size of FNH, CEUS demonstrated the spoke-wheel sign or central scar well (Fig. 2) [75].

**Hepatocellular adenoma (HA)**

Among the FLL, HA is relatively rare and mainly found in young women with a history of oral contraceptive use, androgen steroid therapy and glycogen storage disease [76]. Histologically, HA is composed of cords of tumor cells, which closely resemble hepatocytes and contain fat and glycogen. On conventional US, HA showed variable US patterns, such as hypo-, iso-, hyper- or mixed-echoic
images, depending on the presence of intratumoral hemorrhage, necrosis or fatty change [77]. In the arterial phase of CEUS, early and homogeneous hyperechoic enhancement is found in most cases. However, no enhancement will be seen if the tumor contains hemorrhage or necrosis. Due to the subcapsular feeding artery in HA, CEUS using a continuous low-MI image may demonstrate an early and hyper-enhanced tumor periphery. This phenomenon is useful in distinguishing HA from other hypervascular tumors [12]. In the portal and late phases, the enhancement of HA is almost the same as that of liver parenchyma and can remain slightly hypoechoic in relation to the adjacent liver tissue in later stages because of varying numbers and activity of Kupffer cells [61,78]. However, larger studies regarding the value of CEUS in HA have not been carried out [11].

**Focal fatty change and spared area in diffuse steatosis of liver**

On conventional US, focal fatty change and focal spared areas are usually demonstrated adjacent to the right main portal vein at area 4, the gallbladder bed or the falciform ligament. However, a single well-demarcated nodule can be found anywhere in the liver. Because this type of lesion has normal liver components, CEUS shows the same enhancement pattern with respect to the normal liver in all phases and remains isoechoic in the post-vascular phase [62,79].

**CEUS evaluation of small HCCs after percutaneous ablation therapy**

HCCs of <2 cm are well differentiated and not associated with abundant neoangiogenesis [80,81]. Although contrast-enhanced color Doppler sonography was reported to be useful in the detection of residual HCC after percutaneous local therapy [82,83], the sensitivity of detection was low because of slow blood flow [84] and reduced vascularity in the residual mass. Flash echo contrast sonography with subtraction (FECS) mode allows microbubble contrast agents to flow into the capillaries before the microbubbles are imaged and destroyed [31]. Using this method, Wang et al reported the results of assessing perfusion and the therapeutic effects after percutaneous ablation in small HCCs (Fig. 3) [51, 85,86]. The agreement between FECS and CT, FECS and hepatic angiography, and all three imaging modalities in a study of 35 small tumors (mean, 2.0±0.5 cm) were 80%, 85.7% and 77.1%, respectively. The sensitivity, specificity, accuracy, and positive and negative predictive values of FECS in detecting viable tumors were 53.8% (7/13), 90.9% (20/22), 77.1% (27/35), 77.8% (7/9) and 76.9% (20/26), respectively [86]. These results were lower than those reported by Ding et al [87]. The explanation by
Wang et al for the lower sensitivity in detecting viable tumor tissue was the smaller tumor size when compared with those of other studies [87–90] and the longer follow-up interval [87,90]. Although CEUS has its limitations in the depiction of tumor vascularity for HCC located more than 7 cm from the abdominal wall [31,51,85], CEUS has potential in the evaluation of the therapeutic effects of percutaneous ablation for HCC, even in small tumors [31,86].

**Conclusion**

Owing to the easy application of contrast agents into peripheral vessels and improvements in technologic devices and techniques, CEUS can clearly demonstrate the vascular pattern and parenchymal contrast in liver lesions. The effectiveness of CEUS in diagnosing liver tumors (even small tumors) is not less than that of CT scan, MRI or angiography. CEUS also improves the diagnostic accuracy of focal liver lesions, even for those as small as 1–2 cm. This safe, convenient, low cost and non-invasive diagnostic modality should be promoted in routine clinical practice.

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