Indeterminate Focal Liver Lesions Incidentally Discovered at Gray-Scale US

Role of Contrast-Enhanced Sonography

Tommaso Vincenzo Bartolotta, MD, PhD, Adele Taibbi, MD,* Massimo Midiri, MD,* Domenica Matranga, PhD,* Luigi Solbiati, MD,† and Roberto Lagalla, MD**

Objectives: To assess the role of contrast-enhanced ultrasound (CEUS) in the characterization of focal liver lesions (FLLs) incidentally discovered but indeterminate at gray-scale ultrasound (US).

Materials and Methods: One hundred forty-two consecutive patients with 174 FLLs (169 benign and 5 malignant) incidentally discovered but indeterminate at gray-scale US, underwent CEUS after the administration of SonoVue. Two readers independently reviewed CEUS scans and: (1) classified each lesion as malignant or benign on a 5-point scale of confidence by means of definite diagnostic criteria; (2) provided if possible a specific diagnosis; (3) were requested if further imaging was needed for lesion characterization. Sensitivity, specificity, and areas under the receiver-operating characteristic curve (A_z) as well as interobserver agreement were calculated.

Results: At CEUS, both readers correctly differentiated benign from malignant lesions in 168 of 174 (96.5%) cases ($P < 0.0001$). A specific correct diagnosis was provided in 123 of 174 (70.7%) and 127 of 174 (72.9%) cases for reader 1 and 2, respectively ($P < 0.0001$). A further imaging study to characterize the lesion after CEUS was requested in 67 cases (38.5%) for reader 1 ($P < 0.001$) and 46 cases (26.4%) for reader 2 ($P < 0.001$). Receiver-operating characteristic analysis after CEUS revealed A_z value of 1 for both readers and sensitivity and specificity values of 100% and 97.04% for reader 1 and 100% and 96.45 for reader 2 respectively ($P < 0.0001$). Inter-reader agreement at CEUS was good (weighted k = 0.779).

Conclusion: CEUS improves the diagnostic performance of radiologists in the characterization of indeterminate FLLs incidentally discovered at US and reduces the need for further radiologic work-up.

Key Words: liver, ultrasound (US), neoplasms, diagnosis, contrast media.

(*Invest Radiol* 2011;46: 106–115)

Incidental focal liver lesions (FLLs) are increasingly being detected at ultrasound (US) abdominal scan performed for various reasons in patients without cancer history or symptoms of liver disease. The majority of these masses are benign and devoid of particular clinical significance, especially when considering that the prevalence of benign hepatic lesions in general population approaches up to 52% in autoptic studies.[1]

Despite technical advances, gray-scale US still shows low specificity in the diagnosis of FLLs. The introduction of contrast-enhanced ultrasound (CEUS) represents a significant breakthrough in liver sonography.[2,3] The unique feature of CEUS of noninvasively assessing in real-time liver perfusion throughout the vascular phase has led to a dramatic improvement in diagnostic accuracy of US in either detection and characterization of FLLs when compared with conventional gray-scale US.[4–6] Hence, CEUS impact on clinical practice and patient management is currently under evaluation with encouraging results.[7]

We hypothesized that CEUS might be an effective tool in the characterization of FLLs incidentally discovered but indeterminate at gray-scale US in patients without cancer history or symptoms of liver disease. We also hypothesized that CEUS may reduce the need for further radiologic work-up in this peculiar clinical scenario.

MATERIALS AND METHODS

Patient Population

This prospective study had our institutional review board approval and all patients gave their full informed consent before the CEUS examination. The procedure followed was in accord with the Declaration of Helsinki.[8]

Between June 2003 and February 2008, 142 consecutive patients (93 women and 49 men; age range: 18–79 years, mean: 48.5 years) with 174 FLLs (size range: 0.5–13.1 cm; mean ± SD: 3.3 ± 2 cm) who were referred to our institution for an abdominal US scan entered this study and underwent CEUS of the liver on the basis of the following inclusion criteria: (1) The presence of at least 1 FLL incidentally discovered but indeterminate at gray-scale US; (2) Absence of known history of cancer, clinical doubt of hepatic mass, and/or suspicious chronic liver disease, including positivity for hepatitis B/C virus antibody. US examinations were performed for 1 or more of the following reasons: routine US examination in inpatients (n = 72), type II diabetes (n = 63), hypercholesterolemia (n = 46), suspected gallbladder (n = 36) or renal lithiasis (n = 21), abdominal discomfort (n = 15) or pain (n = 12), previous abdominal trauma (n = 3), increased serum creatinine value (n = 1). The following exclusion criteria were also considered: (1) According to the clinical setting and literature data, the presence of lesions showing US features of simple cyst, typical hemangioma and/or focal fatty sparing at US[2,7]; (2) US findings suggestive of severe liver fibrosis or cirrhosis, such as irregular hepatic surface, coarse, and/or nodular echotexture, enlarged caudate or left lobe, decrease in liver volume, because some US findings may bias radiologist reading[9]; (3) Presence of ascites at baseline US scan, which can suggest cirrhosis as well as extrahepatic abdominal malignancy[9]; (4) Presence of critical illness and/or severe heart disease; (5) Lack of final diagnosis proved by means of an adequate standard of reference (SOR).

One hundred and twenty patients had 1 lesion, whereas in 22 patients who had more than 1 lesion (14 patients with 2 lesions, 6 patients with 3 lesions, and 2 patients with 4 lesions), each lesion was studied separately. One hundred twenty-four (71.3%) lesions

Received September 12, 2009; accepted for publication (after revision) July 18, 2010.
From the *Department of Radiology, University of Palermo, Palermo, Italy; and †Department of Radiology, General Hospital, Busto Arsizio Varese, Italy.
Each author certifies that he or she did not receive any funds for this work from any of the following organizations: National Institutes of Health (NIH); Wellcome Trust; Howard Hughes Medical Institute (HHMI); and other(s).
Reprints: Tommaso Vincenzo Bartolotta, MD, PhD, Via Del Carabiniere 32, 90146 Palermo, Italy. E-mail: tv.bartolotta@unipa.it.

ISSN: 0020-9996/11/4602-0106

were located in the right liver and the remaining 50 (28.7%) in the left liver. Ninety-seven lesions (55.7%) were located within a normal liver at US, whereas the remaining 77 masses (44.2%) were located in a highly echogenic "bright liver." The echogenicity of liver parenchyma was graded into 3 levels as follows: (1) echogenicity increased more than the renal cortex; (2) poor visualization of the portal veins or the posterior portion of the right lobe; and (3) nonvisualization of the right lobe and the portal veins.[10]

US Technique

Two experienced radiologists (more than 5 years experience in CEUS of the liver), who were aware of the patients' clinical histories, performed US scanning by means of either an HDI 5000 (ATL, Bothell, WA) or an iU22 unit (Philips Ultrasound, Bothell, WA), both of them provided with a C5–2 convex array probe and Pulse Inversion imaging software. A baseline survey examination, including a color/power and pulsed Doppler analysis, was performed. Once set, the US scan parameters—such as focal zone and time gain compensation—were not changed throughout the study. The US contrast agent used in the present study was SonoVue (Bracco, Milan, Italy), which was injected intravenously as a 2.4 mL bolus (equivalent to a 0.003 mL/Kg for 70 Kg body weight) followed by 10 mL of normal sterile saline flush by using a 20 or 22-gauge peripheral intravenous cannula. A low frame-rate (5 Hz) and a very low mechanical index (MI), ranging from 0.05 to 0.08, were used for real time imaging. One focus was positioned below the level of the lesion. Each examination lasted about 5 minute after bolus injection. No adverse events have been registered in our patients during or immediately after the injection of contrast agent. In patients with multiple lesions, a further 2.4 mL bolus of SonoVue was administered for each lesion, with an interval time at least of 15 minutes to allow for contrast clearance of the previous contrast medium injection.

Digital cineloops were registered both during baseline and postcontrast US scanning in the arterial, (ie, 10–40 seconds from beginning of contrast agent bolus injection), portal venous (ie, 55–90 seconds from beginning of injection), and extended portal venous or late phase (ie, until 235–270 seconds from beginning of injection) phases. All cineloops were digitally stored as raw-data in a PC-based workstation connected to the US units via a standard Ethernet link.

On-Site Image Analysis

Each focal liver lesion was measured and located in a liver segment according to Couinaud classification system.

Immediately after the completion of each CEUS scan, the 2 examiners subjectively evaluated, by consensus, the dynamic enhancement pattern of each lesion in comparison with adjacent liver parenchyma.

The following parameters were considered[2,4,11,12]:

Baseline echogenicity of the lesions in comparison both with adjacent liver parenchyma and muscle tissue of the anterior abdominal wall (hyperechoic, hypoechoic, isoechoic, mixed, presence of central scar);

Echotexture of the lesions, divided into homogeneous and inhomogeneous;

Changes in the echogenicity and enhancement patterns after contrast injection, subjectively classified as:

1. Absent (no difference in echogenicity)
2. Peripheral globular (enhancing peripheral nodular areas)
3. Rim-like (continuous ring of peripheral enhancement)
4. Dotted (tiny hyperechoic spots of enhancement distributed throughout the lesion);
5. Spoke-wheel (enhancement of the central portion of the lesion with a central vessel branching from the center toward the periphery of the lesion)
6. Diffuse homogeneous (uniform enhancement of entire lesion)
7. Diffuse inhomogeneous (heterogeneous enhancement of entire lesion)

Progression of enhancement was also evaluated (centripetal and centrifugal contrast enhancement).

Off-Site Image Analysis

Two independent and experienced radiologists (more than 10 years in the use and interpretation of CEUS) randomly reviewed all cineloops off-line on screen. Both readers were not involved in the scanning and were blinded to the final diagnosis, as well as to the identification, clinical histories, and other imaging findings of the patients, but they could not be blinded to the liver parenchyma echostructure. Six consecutive interpretation sessions with a 7-day interval to avoid recall bias were held to complete the review process of all patient contrast-enhanced scans. For each lesion, the 2 readers were asked the same 3 questions after reviewing the CEUS scan. First, they were asked to provide a diagnosis of benign or malignant lesion, according to established criteria developed on the basis of enhancement patterns previously described at CT, Magnetic Resonance Imaging (MRI) (Table 1),[13–16] US, and CEUS.[2,4,5,17–20] Both readers used a 5-point scale to grade diagnostic confidence 1, definitely benign; 2, probably benign; 3, indeterminate (not assessable); 4, probably malignant; and 5, definitely malignant. Second, on the basis of the same criteria, they were asked to characterize, if

TABLE 1. Diagnostic Criteria at Contrast-Enhanced Ultrasound

Lesion Type	CEUS
Cyst	Lack of contrast enhancement throughout the vascular study
Hemangioma	Globular peripheral enhancement or rim enhancement in the arterial phase, followed by progressive centripetal fill-in in the extended portal-venous phase; also "inside-out" pattern
Focal nodular hyperplasia	"Spoke-wheel" sign in the early arterial phase, homogeneously hypervascular in the delayed arterial phase, iso/hypervascular in the portal-venous and late phases; hypoechoic unenhancing central scar
Hepatocellular adenoma	Subcapsular arterial vessels with centripetal or mixed fill-in; enhancement similar to the surrounding liver parenchyma in the extended portal-venous phase, often inhomogeneous
Focal fatty sparing	Isovascular to the surrounding liver parenchyma throughout the vascular study
Focal fatty area	Isovascular to the surrounding liver parenchyma throughout the vascular study
Regenerative nodule	Hypo- or isovascular in the arterial phase, isovascular to the remaining liver parenchyma in the extended portal-venous phase
Metastasis	Hypovascular appearance in the extended portal-venous phase regardless contrast-enhancement behavior in the arterial phase
Cholangiocarcinoma	Inhomogeneous, mainly peripheral, enhancement in the arterial phase; hypovascular in the extended portal-venous phase

CEUS indicates contrast-enhanced US.

possible, the lesion and to provide a specific diagnosis. Finally, they were asked if there was any need for a further cross-sectional imaging (CT or MR) study to characterize the lesion.

Standards of Reference

Table 2 provides information about the 174 lesions, 169 benign and 5 malignant, that were examined, on the basis of the final diagnosis. This latter was obtained by histologic evaluation of resected specimen (n = 2: 1 hepatocellular adenoma, 1 intrahepatic cholangiocarcinoma), core-biopsy performed with an 18-G needle (n = 7: 2 hepatocellular adenomas, 1 focal nodular hyperplasia [FNH], 4 metastases) and typical helical CT and/or MRI findings (n = 165: 90 hemangiomas, 55 FNHs, 10 focal fatty sparing areas, 8 focal fatty areas, 2 hydatid cysts). Strict imaging criteria depicting typical contrast-enhancement pattern were employed.[13–16] CT studies were performed by means of a multidetector row (64-slice) Philips Brilliance scanner (Royal Philips Electronics, Andover, MA) with the acquisition of unenhanced and contrast-enhanced images—after the administration via a 18 or 20-G needle cannula in an antecubital vein of the right arm of a dose of 1.5 mL per kilogram of body weight of iomeprol (400 mg I/mL) (Iomeron Bracco, Milan, Italy) at a rate of 4 mL/s by power injector—including hepatic arterial-dominant phase (25–30 seconds after the automated bolus detection), portal venous-dominant phase (60 seconds after the injection of contrast agent), and equilibrium phase (3–5 minutes or even more when needed). MRI was performed with a 1.5 T MR unit (Signa Excite, General Electric, Healthcare, Milwaukee, WI), using a phased-array multicoil as a receiver coil. The MRI protocol included precontrast axial breath-hold and respiratory-triggered T2-weighted FSE sequences with and without fat-saturation, unenhanced (in-phase and out-of-phase) and precontrast fat-saturated spoiled 3D gradient-recalled echo T1-weighted sequences. A triphasic dynamic contrast-enhanced study was obtained after the administration of an IV bolus of 0.1 mmol/kg of gadobenate dimeglumine (MultiHance, Bracco, Italy) injected a flow rate of 2 to 2.5 mL/s and flushed by 20 mL of sterile saline solution using an automatic MR-compatible injector. The scanning delay for triphasic dynamic 3D gradient-recalled echo imaging was 13 seconds after the automated bolus detection for the arterial phase, and 60 seconds, and 180 seconds after initiating contrast injection for portal venous, and equilibrium phases, respectively. The dynamic study was followed by a delayed, hepatospecific phase obtained 2 hours after the injection of contrast material, with the same scanning parameters.

For diagnoses made through core-biopsy, all CEUS studies were always performed before the biopsy, and for diagnoses made through CT or MRI, the interval between the CT or MRI and the CEUS was 0 to 30 days (mean interval: 15 days).

Statistical Analysis

Statistical analysis was performed by a biostatistician involved in the study design by using a computer software package (Intercooled Stata for Windows, v. 9.2., StateCorp, TX).

Interobserver agreement between radiologists for each sonographic interpretation with contrast enhancement was evaluated using weighted kappa statistics with weights calculated in the linear set. Agreement was graded as poor (k = <0.20), moderate (k = 0.20 to <0.40), fair (k = 0.40 to <0.60), good (k = 0.60 to <0.80), or very good (k = 0.80 to 1.00).

The individual performance of each radiologist for distinguishing benign and malignant lesions for both sonographic interpretations was evaluated and compared using areas under the receiving-operating characteristic curve.[21]

In terms of the number of correctly characterized lesions, the number of lesions in which sonography played a confirmatory diagnostic role and the number of cases for which the radiologists incorrectly classified a lesion but stated that no further test was necessary, the significances of differences between the results obtained with and without contrast-enhanced sonography for each radiologist were assessed using z test on frequencies.

RESULTS

On-Site Image Analysis

Table 3 summarizes baseline echogenicity of the 174 incidental lesions in comparison either with liver parenchyma or muscle tissue of the anterior abdominal wall.

All of the 90 hemangiomas showed hypoechoic echotexture, either inhomogeneous (n = 50) or homogeneous (n = 40). Precontrast color/power Doppler examination revealed absence of detectable flow in 74 of 90 hemangiomas. Thirteen hemangiomas showed some peripheral vessel, either arterial (n = 10) or venous (n = 3). Two hemangiomas presented some intralesional arterial vessel and the last one showed both peripheral and intralesional arterial vessel.

Of 56 FNHs, 42 showed hypoechoic echotexture, either homogeneous (n = 25) or inhomogeneous (n = 17). Twelve FNHs were isoechoic and the remaining 2 were hyperechoic, 1 homogeneous and 1 inhomogeneous, respectively. Precontrast Doppler examination revealed a characteristic spoke-wheel arterial pattern of vessels in 17 of 56 FNHs, some intralesional arterial vessel in 23 of 56 FNHs and lack of vascularization in the remaining 16 of 56 FNHs.

Two of 3 adenomas were inhomogeneous hypoechoic lesions without any detectable signal at color/power Doppler analysis. The remaining adenoma was inhomogeneously hyperechoic

TABLE 2. General Features of the 174 Incidental Focal Liver Lesions

Lesion Type	Lesion Size (cm)*	No. Lesions	No. Patients	No. Male/ Female	Patient Age (yr)†
Metastasis	1–4.2 (2.6)	4	3	1/3	54 ± 15 (28–63)
Cholangiocarcinoma	2.5	1	1	0/1	63
Hemangioma	0.5–11.5 (3.2)	90	71	32/39	52.9 ± 12.6 (31–79)
Focal nodular hyperplasia	1.1–8.5 (3.4)	56	45	9/36	41.8 ± 15.3 (18–77)
Hepatocellular adenoma	1.5–12 (5)	3	2	0/2	27.5 ± 3.5 (24–31)
Focal fatty sparing	0.5–3 (2)	10	10	3/7	50.6 ± 12.9 (44–75)
Focal fatty area	1.4–5 (2.9)	8	8	3/5	46 ± 14.5 (32–70)
Hydatid cyst	5.5–13.1 (9.3)	2	2	1/1	58.5 ± 3.5 (55–62)

*All data, except the size of the cholangiocarcinoma, are size ranges. The numbers in parentheses are the mean sizes.
†All data, except the age of the patient with cholangiocarcinoma, are mean ages ± SDs, with age ranges in parentheses.

with some intralesional venous vessel detectable at Doppler examination.

The 2 hydatid cysts were multiseptated, showing a "honeycomb-like" appearance with lack of vascularization at baseline Doppler evaluation.

TABLE 3. Baseline Echogenicity of the 174 Incidental Lesions in Comparison With Liver Parenchyma and Muscle Tissue of the Anterior Abdominal Wall

	Lesion Echogenicity					
	Liver			Muscle		
Lesion Type*	Hyper	Iso	Hypo	Hyper	Iso	Hypo
Metastasis (4)	—	—	4	2	1	1
Cholangiocarcinoma (1)	—	—	1	—		1
Hemangioma (90)	—	—	90	—	51	39
Focal nodular hyperplasia (56)	2	12	42	14	29	13
Hepatocellular adenoma (3)	1		2	1	2	—
Focal fatty sparing (10)	—	—	10	—	6	4
Focal fatty area (8)	8	—	—	8	—	
Hydatid cyst (2)	—	—	2	—	—	2

*Number of lesions are in parentheses.

All the 10 skip areas presented as roundish hypoechoic lesion mimicking a liver mass and did not meet the standard criteria for an appropriate characterization at B-mode US (ie, polygonal shape, location near the portal vein or the gallbladder).[2,7] All the 8 focal fatty areas presented as roundish hyperechoic lesion mimicking a liver mass.

All the 4 metastases showed hypoechoic echotexture; 2 of them were inhomogeneous and 2 homogeneous. Precontrast color/power Doppler examination revealed absence of detectable flow in all the metastatic lesions, but 1, which showed some intralesional arterial vessel.

The 1 cholangiocarcinoma showed homogeneous hypoechoic echotexture on gray-scale US and some intralesional arterial vessel on Doppler US scan.

Table 4 summarizes contrast-enhancement patterns of the 174 FLLs studied with CEUS.

After administration of SonoVue, 64 of 90 (71.1%) hemangiomas showed a typical contrast-enhancement pattern: a peripheral hyperechoic nodules in the arterial phase, followed by progressive centripetal fill-in, which was incomplete in 48 of 64 cases and complete in the remaining 16 cases. Of 90 (14.4%) hemangiomas, smaller than 2 cm in diameter, 13 showed rapid and complete fill-in in the arterial phase, which persisted in the portal and delayed phases. At CEUS, 5 of 90 (5.5%) hemangiomas did not show a typical contrast-enhancement pattern (Fig. 1).

TABLE 4. Contrast-Enhancement Patterns of 174 Incidental Focal Liver Lesions

Lesions	Arterial Phase	Portal-Venous Phase	Late Phase
Hemangioma (n = 90)			
48	Globular peripheral	Centripetal progression	Incomplete fill-in
16	Globular peripheral	Centripetal progression	Complete fill-in
7	Central hyperechoic foci	Centrifugal progression	Complete fill-in
9	Hyperechoic	Isoechoic	Isoechoic
3	Hyperechoic	Hyperechoic	Hyperechoic
3	Hypoechoic	Hypoechoic	Hypoechoic
1	Peripheral rim	Centripetal progression	Complete fill-in
2	Peripheral rim	Hypoechoic	Hypoechoic
1	Isoechoic	Isoechoic	Isoechoic
FNH (n = 56)			
40	Hyperechoic	Isoechoic	Isoechoic
15	Hyperechoic	Hyperechoic	Isoechoic
1	Hyperechoic	Hyperechoic	Hyperechoic
Adenoma (n = 3)			
2	Hyperechoic	Hyperechoic	Hyperechoic
1	Diffuse inhomogeneous	Diffuse inhomogeneous	Diffuse inhomogeneous
Hydatid cyst (n = 2)			
2	Hypoechoic	Hypoechoic	Hypoechoic
Skip areas (n = 10)			
8	Isoechoic	Isoechoic	Isoechoic
2	Slightly hypoechoic	Isoechoic	Isoechoic
Focal fatty areas (n = 8)			
6	Isoechoic	Isoechoic	Isoechoic
2	Slightly hyperechoic	Slightly hyperechoic	Slightly hyperechoic
Metastasis (n = 4)			
3	Hyperechoic	Hypoechoic	Hypoechoic
1	Peripheral rim-dotted	Hypoechoic	Hypoechoic
Cholangiocarcinoma			
1	Hyperechoic	Hypoechoic	Hypoechoic

A typical central starlike fill-in in the arterial phase was seen in 9 of 56 FNHs, and a hypoechoic unenhancing scar was seen in 10 of 56 FNHs (Fig. 2). Furthermore, 6 other FNHs showed both signs. Of 15 FHNs showing a central starlike fill-in pattern in the arterial phase of CEUS, 7 FNHs presented an arterial pattern of vessels at precontrast Doppler examination (spoke-wheel).

Skip or fatty areas were essentially isoechoic (n = 16) or slightly hyperechoic in the portal phase (n = 2) to the adjacent liver parenchyma (Fig. 3).

The 2 hydatid cysts, respectively, a type CE2 and CE4 of WHO classification, showed lack of contrast-enhancement.[22]

All the 5 malignant lesions showed a clear-cut wash-out in the portal phase regardless the contrast-enhancement patterns in the arterial phase (Fig. 4).

Off-Site Image Analysis

After reviewing the CEUS scans, reader 1 (Table 5, Fig. 5A) correctly characterized as benign or malignant 168 of 174 (96.5%) lesions (163 benign, 5 malignant). For the remaining 6 lesions (all benign) reader 1 provided a wrong diagnosis in 5 cases (4 hemangiomas and 1 adenoma), whereas 1 lesion (1 hemangioma) was considered not assessable. The diagnostic confidence score for reader 1 was the following: 5 (n = 5), 4 (n = 5), 3 (n = 1), 2 (n = 15), 1 (n = 148) respectively.

CEUS enabled reader 2 (Table 5, Fig. 5B) to correctly characterize as benign or malignant 168 of 174 (96.5%) lesions (163 benign, 5 malignant). For the remaining 6 lesions (all benign: 5 hemangiomas and 1 adenoma) reader 2 provided a wrong diagnosis in all cases. The diagnostic confidence score for reader 2 was 5 (n = 5), 4 (n = 6), 3 (n = 0), 2 (n = 3), 1 (n = 160) respectively. Inter-reader agreement at CEUS was (weighted k) = 0.779 with good agreement value. In terms of specific diagnosis, the total number of correctly characterized lesions was 123 of 174 (70.7%) for reader 1 and 127 of 174 (72.9%) for reader 2 when comparing CEUS to SOR ($P < 0.0001$) (Table 6). In particular, 44 lesions for reader 1 and 40 lesions for reader 2 were correctly classified as benign but without specific characterization. One intrahepatic cholangiocarcinoma was correctly assessed as malignant but characterized as metastasis by both readers. The remaining 6 lesions (5 hemangiomas and 1 adenoma) for both readers were not correctly characterized (5 lesions and 6 lesions for reader 1 and 2, respectively) or not assessable (1 hemangioma for reader 1).

The numbers of cases for which a further cross-sectional imaging study was requested after CEUS was 67 (38.5%) for reader 1 ($P < 0.001$) and 46 (26.4%) for reader 2 ($P < 0.001$).

DISCUSSION

In the present study, focused in patients with no cancer history or symptoms of liver disease, we found that sulfur hexafluoride-enhanced US, when compared with baseline gray-scale US, improved the radiologist performance in the characterization of incidentally discovered but indeterminate FLLs in terms of differentiation between benign and malignant lesions, as showed by both A_z values and specificity. CEUS also showed a "good" inter-reader agreement and significantly reduced the number of cases in which a further imaging study to characterize the lesion was considered necessary: 38.5% for reader 1 and 26.4% for reader 2. To a lesser extent, CEUS was also able to provide a specific diagnosis in a statistically significant number of cases (70.7% for reader 1 and 72.9% for reader 2). Both readers were unable to precisely characterize 44 and 40 lesions, respectively. In particular, 43 lesions for reader 1 and 39 lesions for reader 2 were correctly classified as benign and 1 lesion for both readers

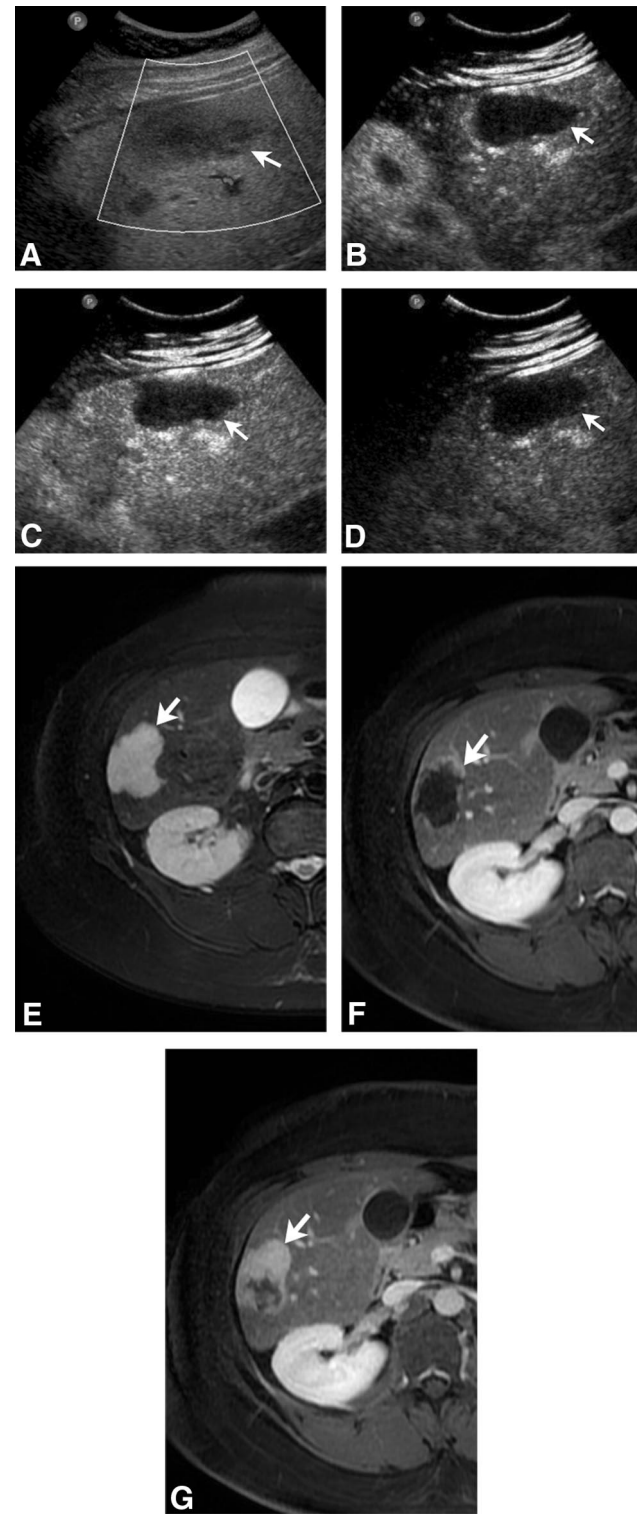

FIGURE 1. Atypical hemangioma in a 36-year-old woman. A, Baseline US shows a hypoechoic lesion sized 4.6 cm in the sixth hepatic segment (arrow). B–D, The lesion appears hypoechoic throughout the vascular study at CEUS (arrows). E, T2-w MR axial image shows a hyperintense lesion (arrow). F, G, Contrast-enhanced T1-w MR axial images clearly depict a peripheral globular enhancement with progressive centripetal fill-in (arrows).

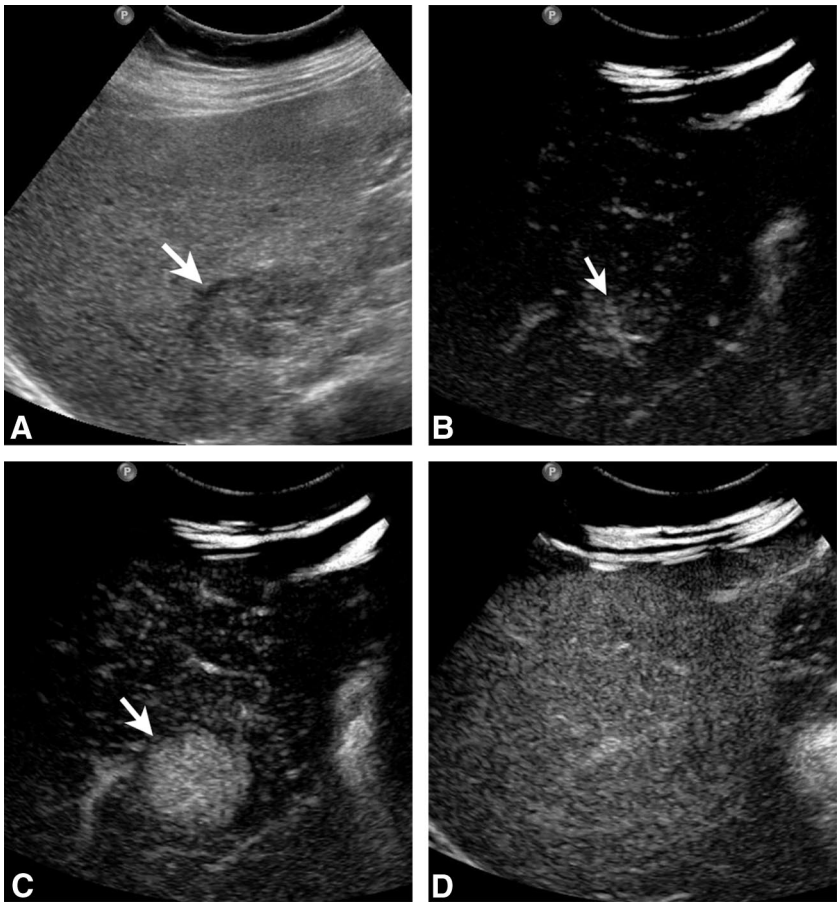

FIGURE 2. Focal nodular hyperplasia in a 51-year-old woman. A, Baseline US shows an inhomogeneous hypoechoic lesion sized 3.9 cm in the fifth hepatic segment (arrow). B, At CEUS, in the early arterial phase (21 seconds after SonoVue injection), the lesion presents the "spoke-wheel" sign (arrow), followed by a strong and homogeneous enhancement in delayed arterial phase (34 seconds after SonoVue injection) (arrow) (C). D, The lesion becomes isoechoic with respect to the surrounding liver parenchyma during the extended portal-venous phase.

was correctly assessed as malignant but a further imaging study was requested for specific characterization. The majority of these lesions were benign masses, significantly smaller (2.5 ± 1.4 cm; $P = 0.003$) than the average of whole series. These lesions mainly appeared iso- or hyperechoic in the arterial phase at CEUS and presented a sustained contrast-enhancement in the extended portal-venous phase. Such a contrast-enhancement pattern, without any further clue—ie, spoke-wheel sign, globular peripheral enhancement, central scar, feeding vessel—lacks of specificity and does not allow a precise characterization, though suggesting benignity.[11] Actually, arterial phase lasts few seconds and those signs may be missed if the right plane is not properly imaged. To facilitate the assessment of the filling pattern and vessel morphology, multiple injections of contrast or flash-replenishment techniques might be helpful.[19,23] Real-Time Temporal Maximum-Intensity-Projection (MIP) is able to show both vascular structure and the direction of lesional filling of hepatic lesions at CEUS.[23] Imaging of focal nodular hyperplasia and adenoma will benefit most from the MIP technique because filling direction and vascular structure are the main components in differentiation of these lesions.[23] Furthermore, advances in flow quantification and advanced computer assisted pattern analysis may provide a more accurate and reproducible method to characterize FLLs and monitor patient response to antiangiogenic therapies.[24–26] Therefore, despite some Author have reported a specificity of CEUS in precise lesion characterization slightly higher than the ours, our experience suggest that, at least when considering small hypervascular benign lesions without patient's medical history and laboratory data, CEUS performs better in differentiating benign from malignant lesions than in providing specific histotype definition.[27,28] In a study, a histotype diagnosis was obtained in 66% to 52% with MR imaging and 52% to 53% with CEUS, respectively.[29] Nevertheless, from the clinical point of view, providing a diagnosis of benignity of an incidentally discovered mass during the same US session is still an important goal. In our series CEUS allowed a precise characterization to be made in a percentage approaching three-fourths of all lesions. Actually, at least 1 of the 6 benign lesions (a bleeding hepatic adenoma) erroneously characterized as malignant mass would have been probably better assessed by both blinded readers when considering, in the real clinical setting, the acute onset of abdominal pain in a 30-year-old woman assuming oral contraceptives. The remaining misdiagnosed 5 lesions were all hemangiomas appearing hypoechoic throughout the vascular phase (n = 3) or showing a peripheral rim of contrast-enhancement not followed by a clear centripetal fill-in (n = 2). All these latter hemangiomas but one were located in fatty liver and had a mean diameter lesser than the average of the whole series (2.6 ± 1.4 cm). MRI and/or CT correctly characterized all these hemangiomas, but we do not have a proved explanation for this discrepancy, even though the different behavior of ultrasound contrast agent, which is a blood pool agent, and extracellular gadolinium based and iodinated contrast agents, may play a significant role, more than the presence of a bright liver.[30–32]

Though previously reported experiences have shown the positive impact of CEUS in the management of patients with indeterminate liver masses, those studies included lesions arising in patients with known history of cancer and/or at high risk of hepatocellular carcinoma.[33,34] In these latter patients, CEUS may play an important role, but usually it is included in a more complex

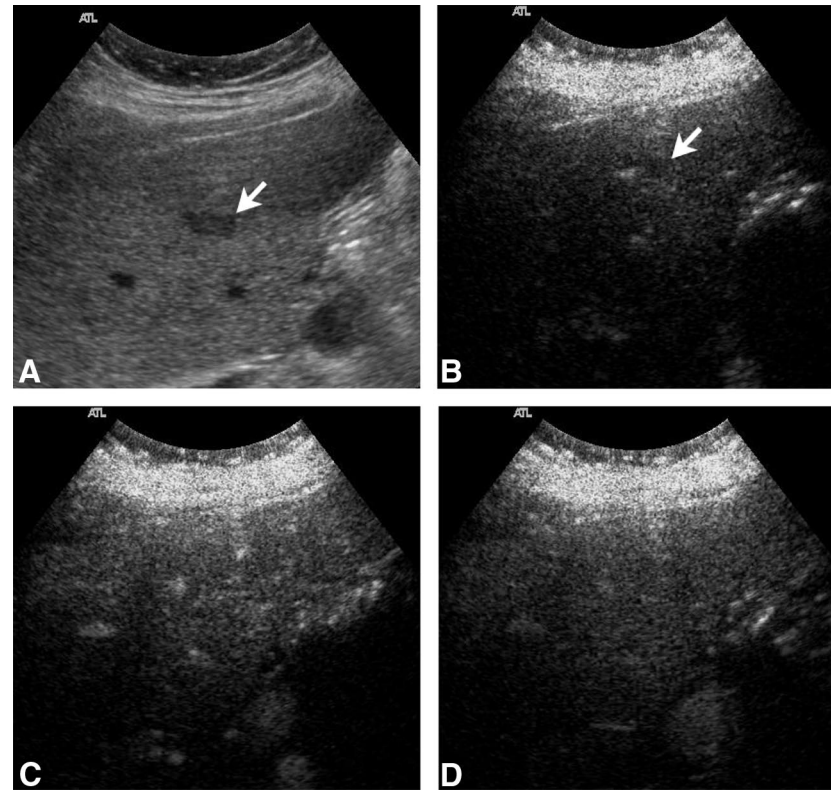

FIGURE 3. Focal fatty sparing in a 58-year-old woman. A, Baseline US shows a round-shaped hypoechoic area in the fifth hepatic segment sized 1.3 cm (arrow). B, At CEUS, the pseudolesion is slightly hypoechoic during the arterial phase (arrow) becoming isoechoic during the portal-venous and late phases (arrows) (C, D).

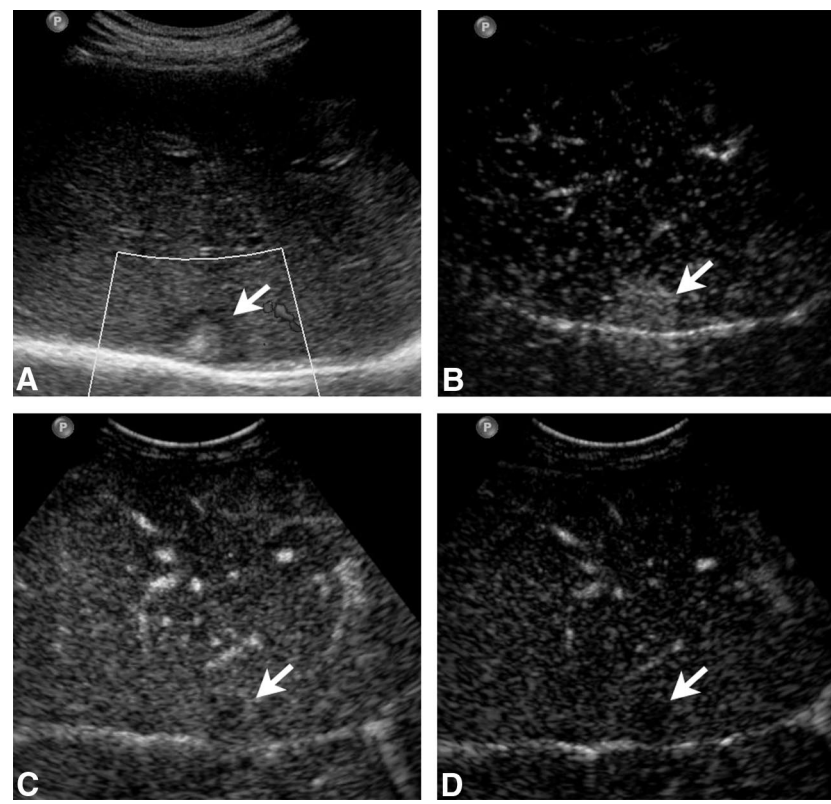

FIGURE 4. Metastasis from rectal cancer in a 74-year-old man. A, Baseline US reveals an inhomogeneously hyperechoic lesion with peripheral hypoechoic rim sized 2.2 cm in the seventh hepatic segment (arrow). B, In the arterial phase, the lesion shows a clear-cut and homogeneous contrast-enhancement at CEUS (arrow). C, During the remaining vascular phases the tumor shows a progressive wash-out appearing hypoechoic with respect to the surrounding liver parenchyma, mostly in the late phase (D) (arrows).

diagnostic algorithm, encompassing various imaging modalities aimed not only to characterize liver masses but also to assess the tumoral burden and to stage the disease.[7,35] On the contrary, looking at our specific patient population, our results indicate that CEUS may play a confirmatory role in the characterization of incidentally discovered FLLs providing a fast and reliable diagnosis in the majority of cases, thus making unnecessary any other further imaging investigations and easing patient's anxiety. Hence, as other authors have recently outlined in studies focusing on cost analysis, our findings suggest that CEUS might be of immediate practical value for daily clinical practice and of substantial importance for patient care.[36–39]

TABLE 5. Individual Performances for Differentiating Benign and Malignant Lesions at CEUS at Off-Site Retrospective Analysis

Radiologist	A_z	Sensitivity	Specificity
Reader 1	1 (1–1)	100 (100–100)	97.04 (94.5–99.6)
Reader 2	1 (1–1)	100 (100–100)	96.45 (93.7–99.2)

All data, except those for areas under the receiver operating characteristics curve (A_z), which are actual values, are percentage.
Numbers in parentheses are 95% CIs.

The main limitation of this study is that the final diagnosis was established in the majority of cases without pathologic evaluation because of ethical concerns. However, all the lesions that were not examined at histologic analysis were well characterized at multiphase contrast-enhanced CT and/or MRI on the basis of typical contrast-enhancement patterns considered as established diagnostic criteria. A bias selection is present in our study, because we only evaluated patients suitable for US scan. Nevertheless, this bias does not affect the results of the present study but reflects the limitation of US in general. Indeed, a limitation of CEUS is that multiple injections of contrast agent are required to characterize several lesions situated in different lobes or even segments of the liver. To this purpose, cross-sectional dynamic imaging with CT or MR is probably better suited and even more practical. Nonetheless, in this study, we did

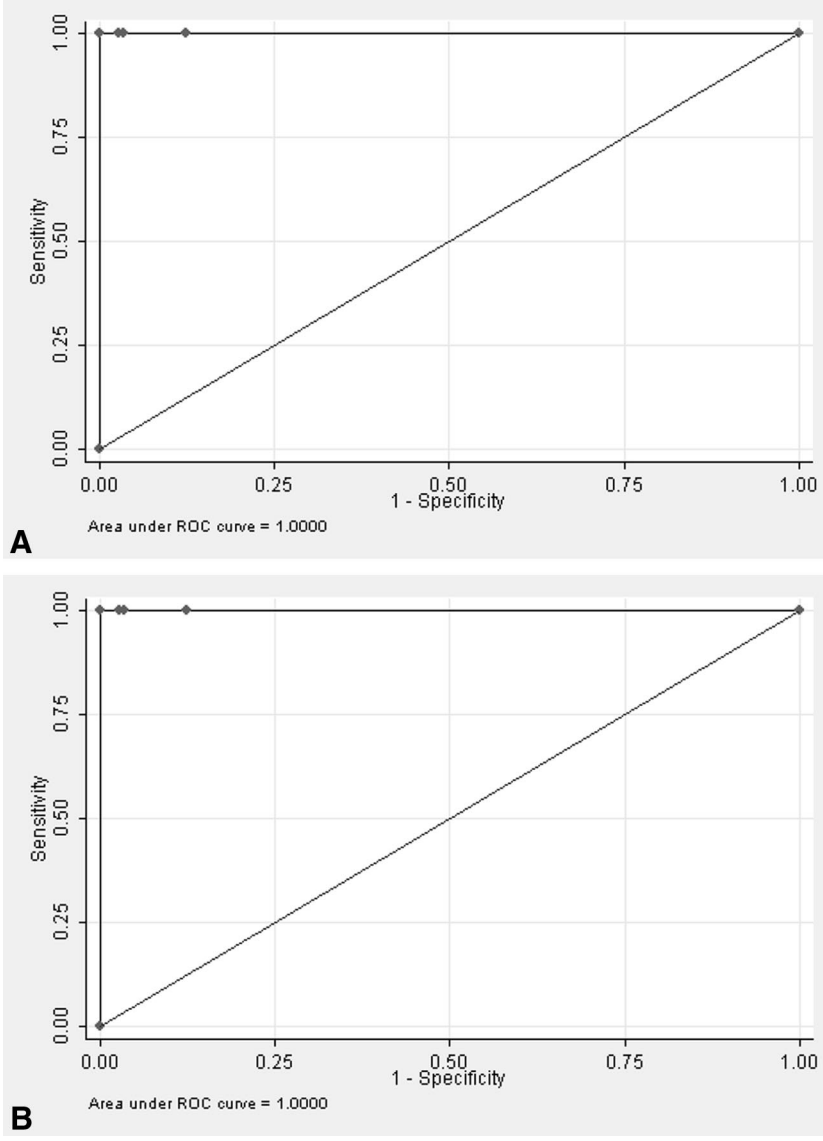

FIGURE 5. Graphs illustrate the diagnostic confidence after review of contrast-enhanced US scans. Receiver operating characteristic curves are plotted to discriminate between benign and malignant focal liver lesions after review of contrast-enhanced US scans (continuous line) for (A) reader 1 and (B) reader 2. The curves are shown against a diagonal (right) line, which represents a review method with which malignant and benign lesions cannot be differentiated.

TABLE 6. Results for Specific Lesion Characterization With Contrast-Enhanced Ultrasound

	Benign (n = 169)		Malignant (n = 5)		Total (n = 174)	
Radiologist	No. Cases Characterized	No. Cases Correctly Characterized	No. Cases Characterized	No. Cases Correctly Characterized	No. Cases Characterized	No. Cases Correctly Characterized
Radiologist 1	168/169 (99.4%)	119/169 (70.4%)	5/5 (100%)	4/5 (80%)	173/174 (99.4%)	123/174 (70.7%)
P value*	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Radiologist 2	169/169 (100%)	123/169 (72.8%)	5/5 (100%)	4/5 (80%)	174/174 (100%)	127/174 (72.9%)
P value*	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

*z test.

not aimed to detect new lesions but we used CEUS to characterize lesions already seen at baseline US.

In conclusion, our results show that sulfur hexafluoride-enhanced US improves the diagnostic performance of radiologists in the characterization of incidentally discovered FLLs indeterminate at baseline US and reduces the need for further radiologic work-up, indicating a precise role of CEUS in this peculiar clinical setting.

REFERENCES

1. Karhunen PJ. Benign hepatic tumours and tumour like conditions in men. *J Clin Pathol*. 1986;39:183–188.
2. Bartolotta TV, Taibbi A, Midiri M, et al. Focal liver lesions: contrast-enhanced ultrasound. *Abdom Imaging*. 2009;34:193–209.
3. Quaia E. Microbubble ultrasound contrast agents: an update. *Eur Radiol*. 2007;17:1995–2008.
4. Quaia E, Calliada F, Bertolotto M, et al. Characterization of focal liver lesions with contrast-specific US modes and sulphur hexafluoride-filled microbubble contrast agent: diagnostic performance and confidence. *Radiology*. 2004;232:420–430.
5. Catala V, Nicolau C, Vilana R, et al. Characterization of focal liver lesions: comparative study of contrast-enhanced ultrasound versus spiral computed tomography. *Eur Radiol*. 2007;17:1066–1073.
6. Quaia E, D'Onofrio M, Palumbo A, et al. Comparison of contrast-enhanced ultrasonography versus baseline ultrasound and contrast-enhanced computed tomography in metastatic disease of the liver: diagnostic performance and confidence. *Eur Radiol*. 2006;16:1599–1609.
7. Lencioni R; European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB). Impact of European federation of societies for ultrasound in medicine and biology (EFSUMB) guidelines on the use of contrast agents in liver ultrasound. *Eur Radiol.* 2006;16:1610–1613.
8. World Medical Association. Declaration of Helsinki. Ethical principles for medical research involving human subjects. Available at: www.wma.net/e/policy/pdf/17c.pdf. Accessed September 1, 2003.
9. Colli A, Fraquelli M, Andreoletti M, et al. Severe liver fibrosis or cirrhosis: accuracy of US for detection—analysis of 300 cases. *Radiology*. 2003;227:89–94.
10. Kim SH, Lee JM, Lee JY, et al. Value of contrast-enhanced sonography for the characterization of focal hepatic lesions in patients with diffuse liver disease: receiver operating characteristic analysis. *Am J Roentgenol*. 2005;184:1077–1084.
11. Von Herbay A, Vogt C, Willers R, et al. Real-time imaging with the sonographic contrast agent SonoVue: differentiation between benign and malignant hepatic lesions. *J Ultrasound Med*. 2004;23:1557–1568.
12. Bartolotta TV, Midiri M, Quaia E, et al. Benign focal liver lesions: spectrum of findings on SonoVue-enhanced pulse-inversion ultrasonography. *Eur Radiol*. 2005;15:1643–1649.
13. Nino-Murcia M, Olcott EW, Jeffrey RB, et al. Focal liver lesions: pattern-based classification scheme for enhancement at arterial phase. *Radiology*. 2000;215:746–751.
14. Horton KM, Bluemke DA, Hruban RH, et al. CT and MR imaging of benign hepatic and biliary tumors. *Radiographics*. 1999;19:431–451.
15. Ros PR, Menu Y, Vilgrain V, et al. Liver neoplasms and tumor-like conditions. *Eur Radiol*. 2001;11(suppl 2):S145–S165.
16. Ros PR. Benign liver lesions. *Eur Radiol*. 2000;10(suppl 2):S175–S184.
17. Nicolau C, Vilana R, Catalá V, et al. Importance of evaluating all vascular phases on contrast-enhanced sonography in the differentiation of benign from malignant focal liver lesions. *Am J Roentgenol*. 2006;186:158–167.
18. Bartolotta TV, Taibbi A, Galia M, et al. Centrifugal (inside-out) enhancement of liver hemangiomas: a possible atypical appearance on contrast-enhanced US. *Eur J Radiol*. 2007;64:447–455.
19. Kim TK, Jang HJ, Burns PN, et al. Focal nodular hyperplasia and hepatic adenoma: differentiation with low-mechanical-index contrast-enhanced sonography. *Am J Roentgenol*. 2008;190:58–66.
20. Bartolotta TV, Midiri M, Scialpi M, et al. Focal nodular hyperplasia in normal and fatty liver: a qualitative and quantitative evaluation with contrast-enhanced ultrasound. *Eur Radiol*. 2004;14:583–591.
21. Obuchowski NA. Receiver operating characteristic curves and their use in radiology. *Radiology*. 2003;229:3–8.
22. WHO Informal Working Group. International classification of ultrasound images in cystic echinococcosis for application in clinical and field epidemiological settings. *Acta Trop*. 2003;85:253–261.
23. Wilson SR, Jang HJ, Kim TK, et al. Real-time temporal maximum-intensity-projection imaging of hepatic lesions with contrast-enhanced sonography. *Am J Roentgenol*. 2008;190:691–695.
24. Lassau N, Lamuraglia M, Chami L, et al. Gastrointestinal stromal tumors treated with imatinib: monitoring response with contrast-enhanced sonography. *Am J Roentgenol*. 2006;187:1267–1273.
25. Stang A, Keles H, Hentschke S, et al. Real-time ultrasonography-computed tomography fusion imaging for staging of hepatic metastatic involvement in patients with colorectal cancer: initial results from comparison to US seeing separate CT images and to multidetector-row CT alone. *Invest Radiol*. 2010;45:491–501.
26. Shiraishi J, Sugimoto K, Moriyasu F, et al. Computer-aided diagnosis for the classification of focal liver lesions by use of contrast-enhanced ultrasonography. *Med Phys*. 2008;35:1734–1746.
27. Liu GJ, Xu HX, Xie XY, et al. Does the echogenicity of focal liver lesions on baseline gray-scale ultrasound interfere with the diagnostic performance of contrast-enhanced ultrasound? *Eur Radiol*. 2009;19:1214–1222.
28. Bartolotta TV, Taibbi A, Galia M, et al. Characterization of hypoechoic focal hepatic lesions in patients with fatty liver: diagnostic performance and confidence of contrast-enhanced ultrasound. *Eur Radiol*. 2007;17:650–661.
29. Soussan M, Aubé C, Bahrami S, et al. Incidental focal solid liver lesions: diagnostic performance of contrast-enhanced ultrasound and MR imaging. *Eur Radiol*. 2010;20:1715–1725.
30. Burns PN, Wilson SR. Focal liver masses: enhancement patterns on contrast-enhanced images—concordance of US scans with CT scans and MR images. *Radiology*. 2007;242:162–174.
31. Wilson SR, Kim TK, Jang HJ, et al. Enhancement patterns of focal liver masses: discordance between contrast-enhanced sonography and contrast-enhanced CT and MRI. *Am J Roentgenol*. 2007;189:W7–W12.
32. Bartolotta TV, Midiri M, Quaia E, et al. Liver haemangiomas undetermined at grey-scale ultrasound: contrast-enhancement patterns with SonoVue and pulse-inversion US. *Eur Radiol*. 2005;15:685–693.
33. Bleuzen A, Tranquart F. Incidental liver lesions: diagnostic value of cadence contrast pulse sequencing(CPS) and SonoVue. *Eur Radiol*. 2004;14(suppl 8):P53–P62.
34. Lanka B, Jang HJ, Kim TK, et al. Impact of contrast-enhanced ultrasonography in a tertiary clinical practice. *J Ultrasound Med*. 2007;26:1703–1714.
35. Bruix J, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. *Hepatology*. 2005;42:1208–1236.

36. Romanini L, Passamonti M, Aiani L, et al. Economic assessment of contrast-enhanced ultrasonography for evaluation of focal liver lesions: a multicentre italian experience. *Eur Radiol*. 2007;17(suppl 6):99–106.
37. Faccioli N, D'Onofrio M, Comai A, et al. Contrast-enhanced ultrasonography in the characterization of benign focal liver lesions: activity-based cost analysis. *Radiol Med*. 2007;112:810–820.
38. Strobel D, Seitz K, Blank W, et al. Tumor-specific vascularization pattern of liver metastasis, hepatocellular carcinoma, hemangioma and focal nodular hyperplasia in the differential diagnosis of 1349 liver lesions in contrast-enhanced ultrasound (CEUS). *Ultraschall Med*. 2009;30:376–382.
39. Moriyasu F, Itoh K. Efficacy of perflubutane microbubble-enhanced ultrasound in the characterization and detection of focal liver lesions: phase 3 multicenter clinical. *Am J Roentgenol*. 2009;193:86–95.