Eur Radiol (2007) 17: 1066–1073
DOI 10.1007/s00330-006-0444-6

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Characterization of focal liver lesions: comparative study of contrast-enhanced ultrasound versus spiral computed tomography

Received: 10 October 2005
Revised: 9 August 2006
Accepted: 14 August 2006
Published online: 27 October 2006

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Abstract The purpose of this study was to compare the diagnostic accuracy of contrast-enhanced ultrasound (CEUS) with spiral computed tomography (SCT) for the characterization of focal liver lesions (FLL) and to determine the degree of correlation between the two techniques. Seventy-seven FLL (45 hepatocellular carcinomas; 12 metastases; ten hemangiomas; two regenerating/dysplastic nodules; eight focal nodular hyperplasias) detected with ultrasound (US) were prospectively evaluated by CEUS using a second-generation contrast agent and SCT (with an interval of no more than one month between the two techniques). Independent observers made the most probable diagnosis and the results were compared with the final diagnoses (histology $n = 59$; MRI $n = 18$). Statistical analysis was performed by the Chi-square and Kappa tests. CEUS provided a correct, specific diagnosis in 69/77 (90%) of the FLL, while SCT did so in 67/77 (87%). The sensitivity, specificity, and diagnostic accuracy for malignancy were 91%, 90%, and 91%, respectively, for CEUS and 88%, 89%, and 88%, respectively, for SCT. No statistically significant difference was found between CEUS and SCT in the characterization of FLL ($p > 0.05$). In addition, agreement between the two imaging techniques was good ($k = 0.75$). We conclude that CEUS and SCT provide a similar diagnostic accuracy in the characterization of FLL, with a good degree of correlation between the two techniques.

Keywords Ultrasound contrast media · Liver neoplasms · Computed tomography · Ultrasound · Liver neoplasm · Diagnosis

Introduction

Focal liver lesions (FLL) are a frequent finding upon ultrasound (US) imaging, either in studies in which they are suspected or in those carried out because of nonspecific abdominal symptoms [1]. However, the accuracy of this technique in the characterization of FLL is poor, due to the variability of the US patterns. Doppler US provides useful information about tumor vascularity [2–4] but its effectiveness is, unfortunately, limited by lesion depth, low vascular flow, or small vessel size, and, moreover, it is subject to motion artifacts caused by either respiratory or cardiac activity [4, 5]. Therefore, once FLL are detected by US, other imaging techniques or biopsy are needed for characterization.

Spiral computed tomography (SCT) is a technique which is frequently used for the characterization of FLL [6–9]. Since FLL have different vascular patterns, the diagnosis of these lesions by SCT is based mainly on the ability of this technique to define the enhancement pattern after the intravenous injection of a contrast agent. Nevertheless, the limitations of SCT are well known: the increase in the cost and time of diagnosis; the involvement of radiation; the contrast agent used may be harmful in

patients with renal failure or in those allergic to iodinate contrast agents. For these reasons, rapid, precise diagnosis with the sole use of US would be advantageous.

Recent advances in US, including the availability of contrast agents and the development of specific contrast-imaging methods, have led to a larger role of US imaging [10–14] in the characterization of FLL. SonoVue (Bracco, Italy) is a second-generation contrast agent made of microbubbles stabilized by phospholipids and containing sulfur hexafluoride. This agent is more stable and resistant to pressure than those of the first generation, while the use of specific software allows the detection of both macro- and microvascular flow. SonoVue can be used with a low mechanical index, thus, allowing the continuous real-time imaging of contrast [10, 15]. Previous studies using contrast-enhanced ultrasound (CEUS) have demonstrated its ability to reproduce pattern enhancement in FLL similar to that of SCT [11, 16], although, to our knowledge, no study has yet correlated the diagnostic accuracy of both techniques in the same series of patients.

The aim of our study was to compare the diagnostic accuracy of real-time evaluation by CEUS using SonoVue versus SCT in the characterization of FLL and to determine the degree of correlation between the two techniques.

Materials and methods

Patients

From December 2002 to August 2003, 213 patients with FLL detected on conventional US were prospectively evaluated. We excluded patients from this protocol if they were less than 18 years of age, were pregnant, or nursing. Only FLL evaluated with an interval of no more than one month between CEUS and SCT were included. Moreover, we included only malignant FLL whose diagnoses had been confirmed by pathologic study. Thus, a total of 77 patients were included in the study (32 women, 45 men; mean age 62 ± 11 years; 53 with a history of chronic liver disease). In patients with multiple lesions, only one lesion was considered for the study, with a total of 77 FLL being evaluated. For patients with more than one FLL who underwent biopsy, the histologically demonstrated lesion was selected for analysis; otherwise, the largest lesion was selected.

The study was performed with the approval of the Ethics Committee of our institution and full informed consent was obtained from all of the patients before inclusion in the study.

Final diagnosis

Of the 77 lesions (mean diameter, 3.5 ± 2.2 cm), 57 were malignant and 20 were benign. The 57 malignant lesions included 45 hepatocellular carcinomas (HCC: 13 well differentiated, 30 moderately differentiated, two poorly differentiated; with an overall mean diameter of 2.8 ± 1.1 cm) and 12 metastases (known primary malignancy: five colorectal carcinomas, one pulmonary carcinoma, one mammary carcinoma, one lymphoma, one gastric adenocarcinoma, two adenocarcinomas of unknown origin, one neuroendocrinal carcinoma; overall mean diameter, 3.3± 2.8 cm). The 20 benign lesions included ten hemangiomas (mean diameter, 3.8 ± 3.1 cm), two regenerating/dysplastic nodules (mean diameter, 2.5 ± 1 cm), and eight focal nodular hyperplasias (FNH; mean diameter, 6.8±2.3 cm).

All malignant lesions were histologically confirmed after either biopsy ($n = 52$), partial hepatic resection ($n = 3$), or explantation ($n = 2$). Of the 20 benign FLL, the final diagnosis was obtained by biopsy in two regenerating nodules/dysplastic nodules and by MRI and follow-up over a period of not less than 12 months in the remaining benign lesions.

Ultrasonography

US studies were performed with Sequoia 512 equipment (Acuson, Mountain View, CA). First, a baseline US of the liver was performed in the fundamental mode by using a grayscale and a multifrequency 4× C1 convex array probe in order to identify each FLL. We then carried out CEUS using the specific software Coherent Contrast Imaging with the same convex array probe. The settings were as follows: insonating frequency, 3 MHz; acoustic power, −75 to −90 dB; frame rate, 17–20; and double focus. A low mechanical index (<0.2) was selected, in order to avoid microbubble disruption. CEUS studies were carried out after the administration of 2.4 ml of a second-generation US contrast agent (Sonovue, Bracco, Italy) as a bolus via a 21-gauge peripheral intravenous cannula, followed by a 5-mL saline flush. The enhancement patterns of the FLL were studied during the vascular phase up to 3.5 min, including the arterial (0–49 s), portal (50–120 s), and late phases (>120 s). Images were stored as digital cineloops or on S-VHS videotapes.

Spiral computed tomography

SCT studies were performed using a SCT scanner (Somatom Plus 4, Siemens Medical Systems, Erlangen, Germany). When the indication for the SCT technique was suspected HCC, hypervascular metastasis, or FLL characterization, the dynamic study included the acquisition of nonenhanced images followed by three-phase enhanced images at the hepatic arterial, portal-venous, and the delayed phases. When the indication was for the suspicion of not hypervascular metastasis, the dynamic study only included the portal and late phases. We carried out the

scans in a cranial-caudal direction with a 5-mm collimation in the arterial phase and an 8-mm collimation in the other phases (pitch, 1.5), for a single held breath at a spiral acquisition of up to 15 s (in accordance with the size of the liver). Computer-assisted bolus-tracking software was used to determine the optimal scan delay for each patient. The acquisition of the arterial phase started 6 s after the automatic detection of peak aortic enhancement. Portal and late venous phases were scanned 70 and 180 s after initiation of the injection of the contrast agent. The contrast agent used was 100 ml of iodinated low osmolarity contrast (Iopromide, 300 mg I/ml, Ultravist, Schering AG, Berlin, Germany) administered via the antecubital vein with a power injector at a rate of 4 ml/s.

Image analysis

All CEUS and SCT images were interpreted by experienced independent radiologists, all with more than five years of experience in US liver contrast agent and liver CT imaging, respectively. The studies employing each technique were evaluated by two observers. In the cases of discrepancies in the diagnoses, a third radiologist was asked to evaluate the study without knowledge of the prior interpretation and his diagnosis was considered to be the correct one. At the time of analysis, the observers were unaware of the final diagnosis and the results of the other imaging techniques. However, they were able to visualize the presence or absence of US/SCT signs of chronic liver disease. Each observer was asked to choose the most likely specific diagnosis of a given lesion from a list of possibilities. On the basis of the observers' responses, we classified the lesions as malignant or benign for later statistical analysis of the data. According to the literature [8, 11, 13, 17], we defined the diagnostic criteria for the different FLL as summarized in Table 1, using similar enhancement patterns for both techniques.

Statistical analysis

Statistical analyses were performed using a computer software package (SPSS 10.0 Inc. 1989–1995, Chicago, IL). For each imaging modality, the sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy in determining the benign or malignant nature of the lesions were calculated by using the reference standard. The significance of difference was analyzed by the Chi-square test and a $p < 0.05$ was considered to indicate a statistically significant difference. Analysis of lesion characterization by CEUS and SCT was tested by assessing agreement between paired imaging studies with the Kappa test. Agreement was graded as poor ($k < 0.20$), moderate ($0.20 < k < 0.40$), fair ($0.40 < k < 0.60$), good ($0.60 < k < 0.80$), or very good ($0.80 < k1.00$).

Table 1 Diagnostic criteria for focal liver lesions (FLL)

Lesion	Vascular phase	Enhancement pattern
Hepatocellular carcinoma[a,b,c]	Arterial	Heterogeneous or homogeneous hyperenhancement
	Early portal	Iso/hypo enhancement, slow washout
	Late portal	Iso- or hypoenhancement
Metastasis[b]	Arterial	Hypo- to high enhancement
	Early portal	Hypoenhancement, quick washout, or rim-like
	Late portal	Hypoenhancement
Hemangioma	Arterial	Peripheral and nodular enhancement
	Early portal	Slow centripetal filling
	Late portal	Slow centripetal filling, hyper- or isoenhancement
Focal nodular	Arterial	Homogeneous hyperenhancement
		Centrifugal contrast enhancement
Hyperplasia[c]	Early portal	Hyper/isoenhancement
	Late portal	Hyper/isoenhancement.
Regeneration nodules/dysplastic nodules	Arterial	Low or isoenhancement
	Early portal	Isoenhancement
	Late portal	Isoenhancement

[a]In cirrhotic patients, HCC was defined as a hypervascular lesion in the arterial phase that was hypoattenuating in the late phase. Hypervascular lesions in the arterial phase that were isoattenuating in the late phase were also suggestive of HCC. Additionally, nodules in cirrhotic patients with the presence of a fatty intranodular component were classified as HCC, even in the absence of hyperenhancement in the arterial phase.

[b]With the hyper-hypo-hypo pattern, CEUS and SCT categorized nodules as metastasis in patients without any signs of chronic liver disease, while these lesions in individuals with such signs were classified as HCC.

[c]With the hyper-iso-iso pattern, CEUS and SCT categorized nodules as FNH in patients without any signs of chronic liver disease, while these lesions in individuals with such signs were classified as HCC.

Results

Specific focal liver lesions

A correct specific diagnosis was obtained in 69 out of the 77 patients (90%) with CEUS and in 67 out of the 77 (87%) with SCT ($p > 0.05$). The agreement between the two imaging techniques was good ($k = 0.75$). A comparison of the number of correctly diagnosed lesions by CEUS and SCT is summarized in Table 2.

Malignant FLL

HCC Forty-one out of 45 HCCs were correctly classified by CEUS and 39 out of 45 by SCT (Fig. 1). All four HCC misdiagnosed by CEUS were well differentiated and were not correctly diagnosed due to the absence of enhancement in the arterial phase.

Six HCC (three of the well differentiated HCC undiagnosed by CEUS and three more that were moderately differentiated HCC) did not show enhancement in the arterial phase and were not diagnosed by the SCT technique. One well differentiated HCC that did not show enhancement in the arterial phase with CEUS was correctly diagnosed with SCT due to the presence of an intratumoral fatty component.

Metastases Both techniques classified 11 out of 12 metastases correctly, due to a typical enhancement pattern. The only lesion erroneously classified by both CEUS and SCT corresponded to hypervascular metastasis of a gastric adenocarcinoma, which presented enhancement in the arterial phase without a clear washout in the portal and late phases. This lesion was classified as FNH by both techniques.

Benign FLL

Hemangiomas Nine out of ten of the lesions were correctly classified by both techniques (Fig. 2). The single lesion

Table 2 Number of lesions correctly diagnosed with contrast-enhanced ultrasonography (CEUS) and spiral computed tomography (SCT)

Number of lesions correctly diagnosed (% correct)			
	CEUS	SCT	Total
Hepatocellular carcinoma	41 (91)	39 (87)	45 (100)
Metastasis	11 (92)	11 (92)	12 (100)
Hemangioma	9 (90)	9 (90)	10 (100)
Focal nodular hyperplasia	8 (100)	8 (100)	8 (100)
Regeneration/dysplastic nodule	0 (0)	0 (0)	2 (100)
Total	69 (90)	67 (87)	77 (100)

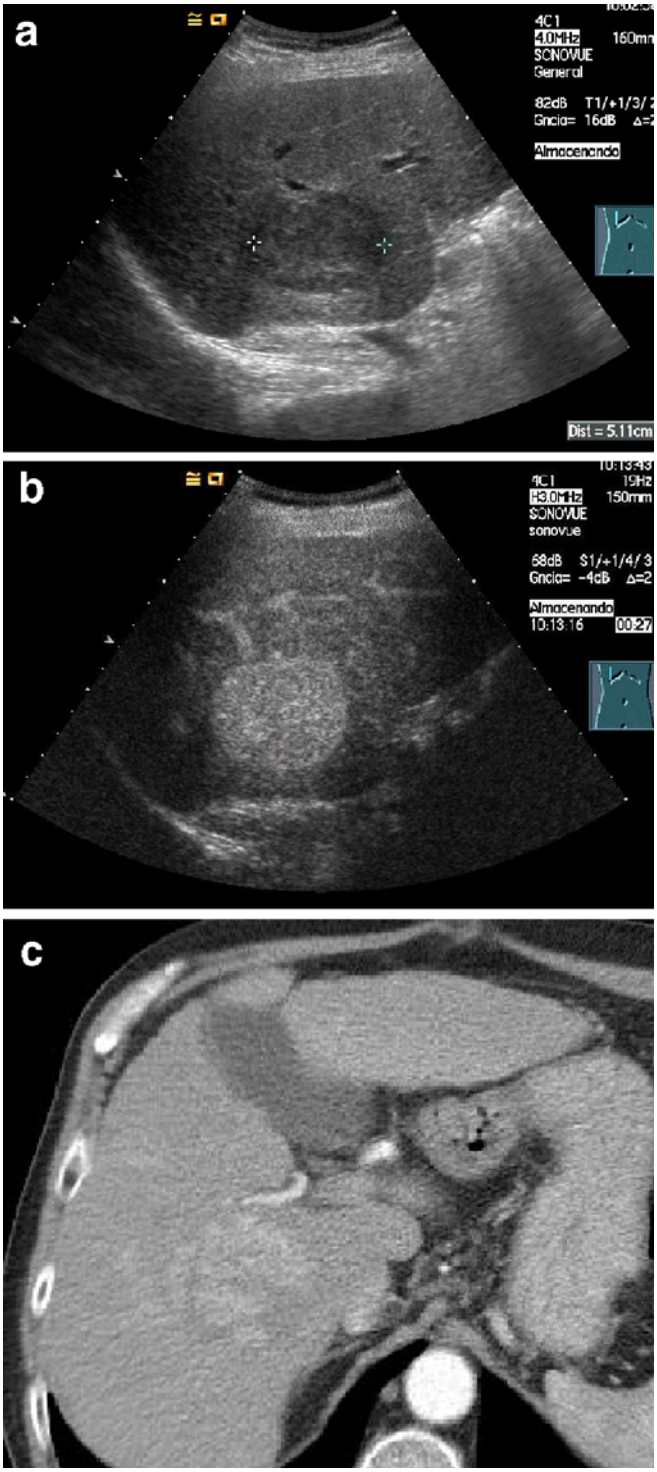

Fig. 1a–c Typical appearance of hepatocellular carcinomas (HCC) in a 65-year-old man with chronic liver disease. Good agreement is observed between the two imaging techniques. **a** On baseline ultrasonography (US) scans, the tumor (*cursors*) appears hypoechoic. **b** US scan obtained during the arterial phase (27 s after microbubble contrast agent injection) shows hyperenhancement. **c** Spiral computed tomography (SCT) scan obtained during the arterial phase shows contrast enhancement of the same lesion

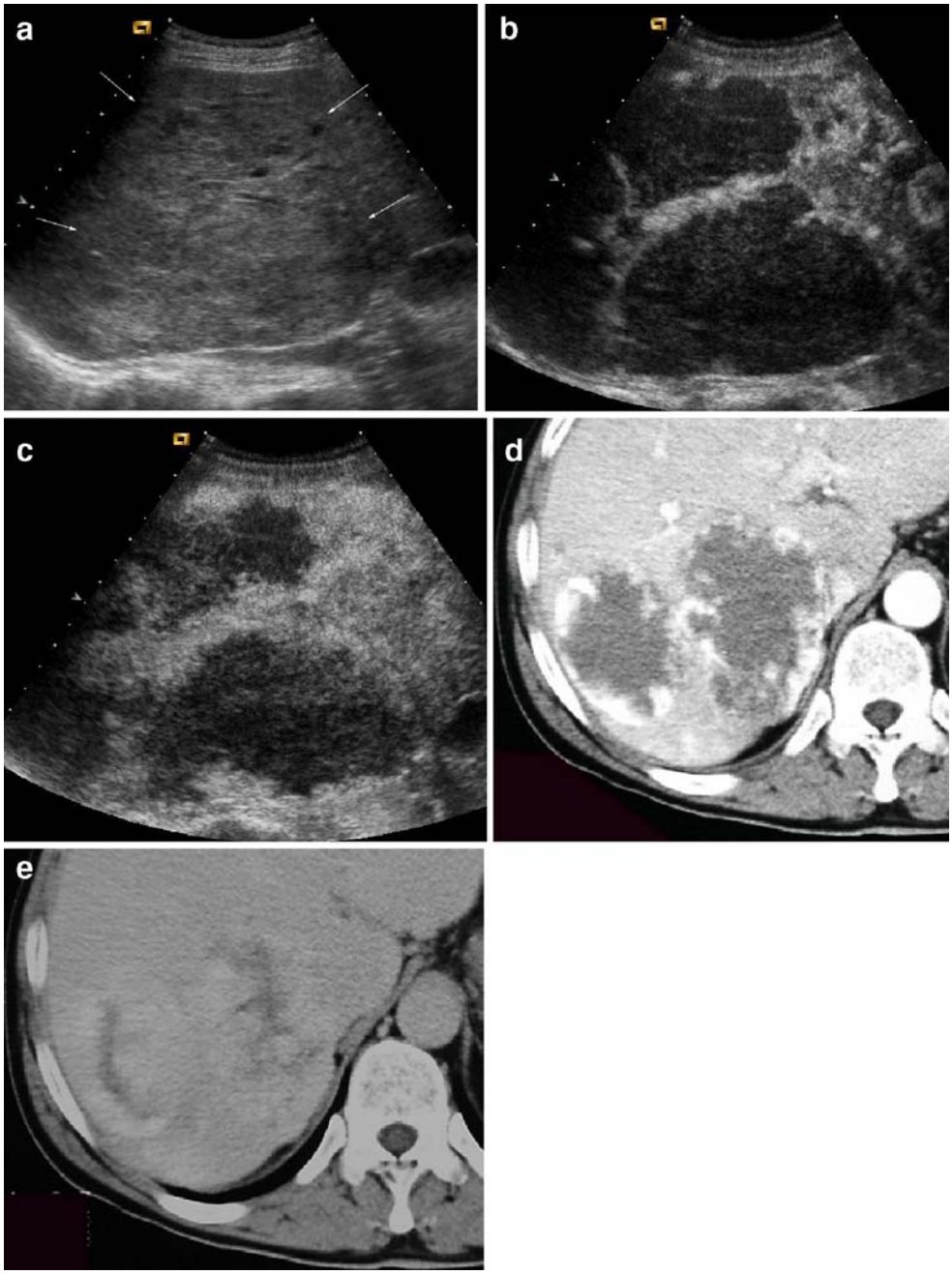

Fig. 2a–e Images obtained in a 55-year-old woman show a typical appearance of two liver hemangiomas (only the largest one was included in the study). **a** Baseline US scan shows two heterogeneous lesions (*arrows*). **b** Contrast-enhanced ultrasonography (CEUS) scans obtained 35 s after microbubble contrast agent injection show nodular peripheral enhancement and progressive centripetal fill-in (**c**) during the portal phase. SCT scans show similar findings in arterial (**d**) and portal (**e**) phases

incorrectly classified corresponded to a hemangioma of size 2.5 cm that showed enhancement in all phases by both techniques and was also classified as FNH.

Focal nodular hyperplasia Both imaging techniques correctly classified 8 out of 8 of the lesions as FNH (Fig. 3). Six out of eight (75%) of these lesions presented a central scar with both techniques.

Regenerative nodules and dysplastic nodules Both imaging techniques incorrectly classified two FLL according to dysplastic nodules diagnosed by biopsy. Both displayed hyperenhancement in the arterial phase and were, thus, classified as HCC by the two imaging techniques.

Benign versus malignant lesions

The overall accuracy for the differentiation between benignancy and malignancy was 91% (70/77) when using CEUS and 88% (68/77) with SCT. A comparison of the sensitivity, specificity, positive- and negative-

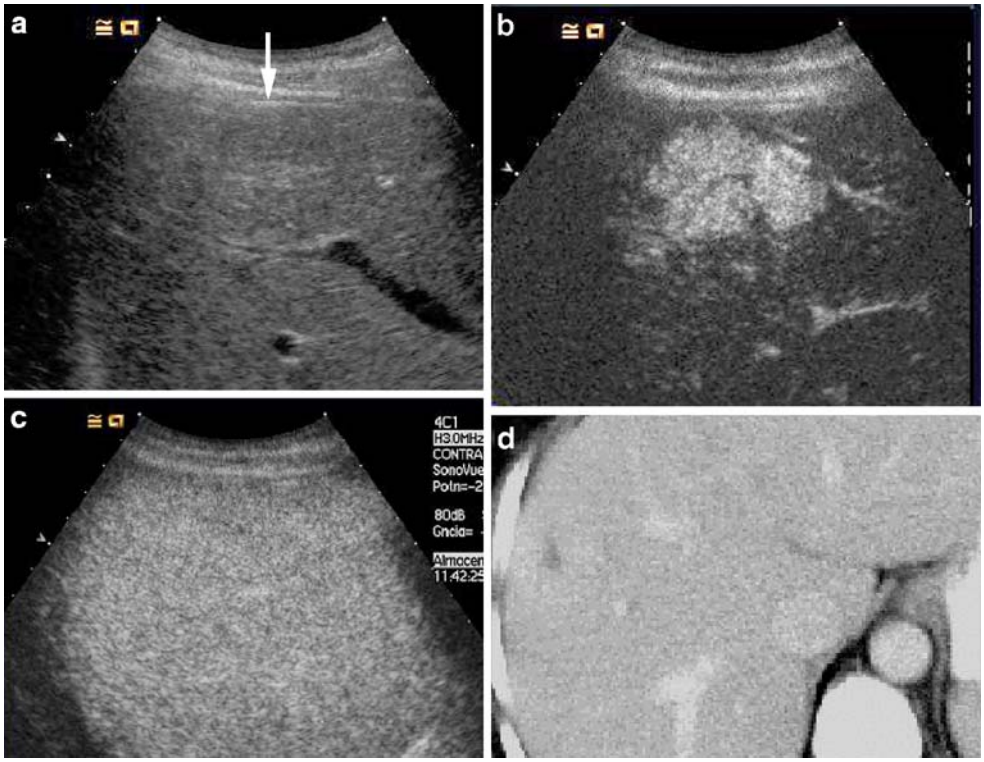

Fig. 3a–d Images obtained in a 45-year-old woman show a typical contrast enhancement pattern of focal nodular hyperplasia (FNH) after contrast agent injection with both techniques. **a** Baseline US scan shows a isoechoic lesion in the anterior segment of the right hepatic lobe (*arrow*). **b** US scan shows an homogeneous contrast enhancement, except for a central hypoechoic area in the arterial phase. **c** The lesion remains isoechoic 120 s after the injection (late phase). **d** SCT scans in the portal phase show similar enhancement findings, with the central hypoenhancing area that represents the central scar

predictive values, and accuracy in determining the malignant nature of the FLL with CEUS and SCT is summarized in Table 3.

No statistically significant difference was found between CEUS and SCT in the characterization of FLL.

Discussion

The characterization of FLL as benign or malignant is crucial for the correct selection of patients to receive invasive versus noninvasive management. SCT is an imaging technique which is frequently used for the characterization of FLL [6, 9]. However, it has several limitations.

Previous studies [18, 19] have demonstrated the high accuracy of the use of CEUS in real time to characterize FLL. The results of our study indicate that the accuracy of CEUS imaging is similar to that of SCT when similar diagnostic criteria are used in both techniques. Additionally, a good agreement ($k = 0.75$) between the two techniques was found. Although both techniques rely on the evaluation of enhancement patterns of FLL [8, 9, 14, 20], one consideration of the characteristics of each technique may explain the diagnostic discrepancies between the two, as shown in four cases. SCT showed better results in one case which consisted of an HCC with fatty degeneration. In this case, unlike CEUS, the ability of SCT to detect a fatty component [21] conferred greater diagnostic precision, provided that the presence of a fatty component is a relevant criterion in the differential diagnosis. By contrast, CEUS showed better results in three cases due to the ability of detecting enhancement in the arterial phase in both cases. Gaiani et al. [22] have recently investigated the accuracy of CEUS with a second-generation contrast agent compared with SCT in the assessment of hypervascularity of HCC, considering SCT as the reference standard showing a good diagnostic agreement in the detection of arterial hypervascularity. Nonetheless, the characteristics of the design of their study

Table 3 Summary of the sensitivity, specificity, positive-predictive value (PPV), negative-predictive value (NPV), and accuracy in determining the malignant nature of focal liver lesions by contrast-enhanced ultrasonography (CEUS) and spiral computed tomography (SCT)

	CEUS[a]	SCT[a]
Sensitivity	91	88
Specificity	90	89
PPV	96	96
NPV	78	75
Accuracy	91	88

[a]Values are expressed as percentages

limited the detection of the false negatives of the SCT technique. In our study, the SCT technique had three false negatives according to moderately differentiated HCC because it did not show arterial enhancement. By contrast, CEUS was able to detect enhancement in the arterial phase and a correct diagnosis was made in these cases. It is important to underline that a single SCT was used in our study. Similar findings with the uses of single SCT have been previously described [23]. Quite likely, multi-detector CT would show better results. It is well known that the arterial enhancement of some HCCs or hypervascular metastases may last only a few seconds, therefore, depending on the time of arterial phase acquisition, this enhancement cannot be detected using SCT. By contrast, real-time evaluation using CEUS imaging allowed us to achieve continuous assessment of enhancement throughout all of the arterial, portal, and late phases. This continuity is made possible by using the combination of a second-generation contrast agent and specific software, such as Contrast Coherent Imaging, which uses a low mechanical index that avoids disruption of the microbubbles, unlike the necessity of intermittent imaging with the high mechanical index of the first-generation contrast agents [11].

Nonetheless, several limitations are inherent in this study.

First, because of ethical considerations, we were unable to use pathologic study as the reference standard in all of the cases. Although all of the malignant and two of the benign lesions (two regeneration nodules/dysplastic nodules) were analyzed this way, the remainder of the benign FLL were included only if they showed a typical presentation on MRI, in the sequences both with and without contrast. This approach presupposes that the lesions characterized by MRI as the reference standard exhibit a typical vascular pattern that would contribute to the high diagnostic accuracy of benign lesions, such as FNH and hemangiomas.

Second, the observers in our study were able to determine the presence or absence of chronic liver disease. As has been described previously [24], HCC can present as hyperenhancement in the arterial phase and as isoenhancement in the remaining phases with the use of CEUS. Thus, in a percentage of cases, the overlapping of the relief pattern with the FNH cases would occur. Likewise, HCC and hypervascular metastasis may have similar patterns and knowledge of the presence or absence of chronic liver disease is mandatory in order to assess the most probable diagnosis. The accuracy of SCT for the characterization of FLL in our study was greater than that previously published by Oudkerk et al. [17]. In their study, lesion classification was correct in only 57% with SCT. This may be due to differences in imaging interpretation since, in their study, the readers were blinded to clinical information. Nonetheless, we believe that analysis when taking this information into account may better reflect the diagnostic accuracy of both techniques in clinical practice.

In conclusion, CEUS and SCT provide a similar diagnostic accuracy in the characterization of FLL, with a good degree of correlation between the two techniques. Thus, we think that CEUS can be routinely used as the first step in the diagnostic algorithm for the characterization of FLL detected on baseline US. Further studies are necessary to evaluate the usefulness of CEUS in the detection and staging of FLL.

Acknowledgment V. Catala was supported, in part, by a grant from the Carolina Foundation.

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