Impact of reader's experience in contrast-enhanced ultrasonography (CEUS) management of patients with indeterminate liver lesions

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Authors: E. Rodolfino, R. Basilico, V. Calamita, M. Maccarone, A. R. Cotroneo; Chieti/IT
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Purpose

The technological improvement in diagnostic imaging has led to an increase in the frequency of unexpectedly discovered liver lesions.

Because we all know that most of focal liver lesions are benign, it is crucial to define the benign or malign etiology of an hepatic incidentaloma which, therefore, has become a modern problem, both from the diagnostic and the therapeutic point of view. Most of hepatic incidentalomas are detected by conventional sonography which cannot usually achieve definitive diagnosis and these limitations have led to a widespread use of other imaging modalities having a major impact on costs and patient management. The availability of real time contrast enhanced US (CEUS) can change the strategy in the characterization of such lesions (1).

CEUS has been shown to overcome the limitations of unenhanced imaging and allows a define improvement in liver tumor characterization (2).

Ultrasound contrast agents are microbubbles presenting a pure intravascular distribution and do not leak in the interstitial space but persist in the sinusoids and portal vessels. This property helps to provide accurate information about the vascularity of the lesion. The enhancement resulting exclusively from the hepatic arterial supply is timed from 10 to 20 seconds after intravenous contrast agent injection and lasts for 10 to 15 seconds. The portal phase lasts until 2 minutes after contrast agent injection whereas the late phase lasts up to 4 to 6 minutes after injection until microbubbles clearance from the liver parenchyma (2-3). Lesion vascularity assessed by CEUS allows a differential diagnosis between malignancies and benign lesions; moreover many focal liver lesions (FLLs) have special enhancement patterns on CEUS which allow precise lesion type diagnosis. In particular, the evaluation of the degree of lesion enhancement during arterial, portal and late phases is essential to achieve a diagnosis because, during the portal and late phases, malignant tumors prevalently show a hypoenhancing appearance whereas benign tumors tend to show an isoenhancing or a hyperenhancing appearance due to persistent ultrasound contrast agent uptake (4,5,6). However, because the lesions do not always show typical enhancement pattern and dynamic study may also be influenced by the structure features of the liver parenchyma (steatosis, cirrhosis etc), the reader's experience could affect the diagnostic work-up of patients with undetermined liver lesions at baseline US (7).

The purpose of our study is to assess the impact of reader's experience on the diagnostic performance of CEUS in the management of patients with indeterminate liver lesions detected at conventional US.
**Methods and Materials**

Seventy consecutive patients, 27 females and 43 males with a mean age of 53 years (range 25-86 years) with 73 nodules classified as indeterminate at conventional US with color or power Doppler by two radiologists in consensus, were included in the study.

All examinations were performed by a HDI 5000 scanner (Philips, Bothell, WA) and an IU 22 scanner (Philips, Bothell, WA) with PIm installed on C5-2 MHz probe and a MI preset at 0.1 for HDI 5000 and at 0.06 for IU 22.

Contrast US examinations were performed by using continuous low mechanical index technique after e.v. bolus injection of 1 or 2 doses of 2.4 ml of a second generation contrast agent (SonoVue, Bracco, Italy) through a 18-20 gauge intravenous cannula followed by a 5 mL normal saline flush.

Three blinded readers with respectively 10, 3 and 1 year of experience in CEUS, independently reviewed CEUS studies stored in digital cine loops.

They were asked to differentiate benign from malignant lesions and to give the most likely etiologic diagnosis. They were also asked to address the patients to further diagnostic procedures when contrast examinations were inconclusive.

Final diagnosis was based on pathology (15 lesions), confirmatory imaging (MRI or CT) in 40 lesions and on 6-month follow-up ultrasound examinations in 18 lesions.
Results

Final diagnoses were 14 FNHs, 30 hemangiomas, 2 regenerative nodules, 6 focal fatty sparing, 2 focal fatty change, 2 adenomas, 9 metastases, 4 HCCs, 1 sclerosing haemangioendotelioma, 1 hidatic cyst, 1 hyperproteic cyst and 1 abscess.

In the differential diagnosis between benign and malignant lesions high sensitivity and negative predictive values were achieved by all the three readers but the most experienced one performed better also regarding specificity, diagnostic accuracy and positive predictive values. Particularly, the values of sensitivity, specificity, diagnostic accuracy, positive predictive value and negative predictive value for the three readers were as follows: reader 1 (93%-90%-97%- 83%- 96%); reader 2 (85%-70%-75%- 63%- 95%); reader 3 (85%-68%- 74%- 60%- 91%).

High diagnostic accuracy values were obtained by all readers evaluating hemangioma which was the most frequent disease in our series. In fact, in the diagnosis of hemangioma reader 1, reader 2 and reader 3 respectively showed diagnostic accuracy values of 95.6%, 87.6% and 84.7%. Lesions considered indeterminate at CEUS and therefore addressed to further examinations were: for reader 1, 8 out of 73, for reader 2, 16 out of 73 and for reader 3, 22 out of 73 nodules.

For the most experienced reader CEUS was inconclusive in the following 8 lesions: 3 hemangiomas, 1 sclerosing hemangioma, 1 atypical FNH, 1 abscess and 1 hidatic cyst.

Some examples of lesions with "typical" CEUS pattern:

Case 1
Fig. 1a- Seventy-nine year old man with gastric cancer; baseline US scan shows an inhomogeneous hyperechoic lesion defined as indetermined.

References: Department of Radiology, University of Chieti - Chieti/IT
Fig.: 1b,1c- At CEUS examination the lesion shows a peripheral globular pattern during the arterial phase (Fig.1b) and a partial centripetal filling in during the portal venous phase (Fig.1c): this vascular pattern was consistent with hemangioma.

References: Department of Radiology, University of Chieti - Chieti/IT

Case 2

Fig.: 2a,2b- Baseline US examination shows a well-defined slightly hyperechoic mass (Fig.2a); at Color-Doppler US some vessels are visible at the periphery and inside the lesion, without a typical color pattern (Fig.2b).

References: Department of Radiology, University of Chieti - Chieti/IT

Fig.: 2c,2d- At CEUS examination the lesion typically presents an early enhancement with a hypervascular appearance during the arterial phase (Fig.2c) and the portal phase (Fig.2d).
**Case 3**

**Fig.**: 2e,2f- The lesion shows a persistent enhancement during the late phase (Fig.2e), with a central hypoechoic scar (Fig.3f). The lesion was consistent with a focal nodular hyperplasia.

**References**: Department of Radiology, University of Chieti - Chieti/IT

**Case 4**

**Fig.**: 3a,b,c- During the arterial phase of CEUS examination, an hypoechoic small lesion shows a rapid and homogeneous uptake of contrast agent (Fig.3a). During the portal phase (Fig.3b) and the late phase (Fig. 3c) the lesion shows a sustained contrast enhancement, remaining hyperechoic respect to the surrounding liver parenchyma. It was a high flow capillary hemangioma.

**References**: Department of Radiology, University of Chieti - Chieti/IT
Fig.: 4a,4b- 75-year old male patient with a bladder cancer. At baseline US examination of the liver an homogeneous hyperechoic lesion suspected to be an haemangioma was detected (Fig.4 a). At Power Doppler imaging the lesion appeared quite hypervascular with tortuous vessels at the periphery and partly inside (Fig.4b). Because of the discrepancy between gray-scale US and power Doppler imaging, the diagnosis at conventional US was unclear and the patient was included in the study. 

References: Department of Radiology, University of Chieti - Chieti/IT

Fig.: 4c,4d,4e- Contrast enhanced US examination shows a marked and homogeneous enhancement of the lesion during the arterial phase (Fig.4c) with a rapid wash-out during the portal (Fig.4d) and late phases (Fig.4e). These findings were consistent with a hypervascular lesion such as HCC; the hypothesis of metastasis was excluded due to the hypovascular nature of bladder cancer. The diagnosis was confirmed at pathology. 

References: Department of Radiology, University of Chieti - Chieti/IT

Some examples of CEUS inconclusive diagnosis for less experienced readers

Case 5
Fig.: 5a,5b- At baseline US examination a huge, inhomogeneous liver lesion with a hyperechoic wall was well depicted (Fig.5a). Power Doppler examination shows vessels randomly distributed at the periphery and inside the lesion (Fig.5b).

*References:* Department of Radiology, University of Chieti - Chieti/IT

Fig.: 5c,5d- After contrast US administration, the lesion shows inhomogeneous enhancement during the arterial phase (Fig.5c) which lasts until the late phase (Fig.5d). These features are consistent with a benign lesion: it was an hepatic adenoma confirmed at surgical specimen (Fig.5e)

*References:* Department of Radiology, University of Chieti - Chieti/IT
Fig.

References: Department of General Surgery, University Hospital Chieti/ Italy

Case 6
**Fig. 6a:** A 55-year old woman with a bronchogenous carcinoma. At baseline US examination a small, hypoechoic, nodular lesion in a fatty liver is detected in the left hepatic lobe.

**References:** Department of Radiology, University of Chieti - Chieti/IT

**Fig. 6b,6c,6d:** At CEUS examination the lesion shows a marked contrast enhancement during the arterial phase (Fig. 6b) with a persistent contrast agent uptake also during the late phase (Fig. 6c). The lesion shows a complete wash-out only 4 minutes after contrast agent injection (Fig. 6d). It was a hypervascular metastasis confirmed at pathology.

**References:** Department of Radiology, University of Chieti - Chieti/IT
Some examples of CEUS inconclusive diagnosis for all the three readers

Case 7

**Fig.** 7a,7b- A 50-year old woman with breast cancer and a small hypoechoic lesion in fatty liver: at CEUS examination the lesion shows a rim enhancement during both the arterial (Fig.7a) and portal phases (Fig.7b) similar to metastasis. All readers required a further diagnostic procedure.

**References:** Department of Radiology, University of Chieti - Chieti/IT

**Fig.** 7c,7d,7e- At multiphasic CT scan the lesion appear homogeneously during the arterial phase (Fig.7c) without a wash-out during both the portal (Fig.7d) and late phases (Fig.7d). It was an hemangioma confirmed also at 6-month follow-up.

**References:** Department of Radiology, University of Chieti - Chieti/IT
Case 8

**Fig.**: 8a- A 26-six year old woman with fever and right upper abdominal pain. Baseline ultrasound examination shows a cystic lesion with a hyperchoic area inside. Contrast-enhanced ultrasound (CEUS) displays a completely avascular lesion without a solid nodule inside. All readers classified the lesion as indeterminate and required the CT examination.

**References**: Department of Radiology, University of Chieti - Chieti/IT
**Fig.:** 8b, 8c, 8d- Arterial and portal phases contrast-enhanced CT scan show a large hypoattenuating lesion with a noncalcified, high-attenuation wall and low-attenuating surrounding liver parenchyma due to oedema (Fig. 8b,c). During the late phase, the lesion wall shows the same attenuation as the surrounding parenchyma (Fig. 8d). The lesion was consistent with complicated hydatic cyst.

*References:* Department of Radiology, University of Chieti - Chieti/IT

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**Case 9**

**Fig.:** 9a, 9b- A 65-year old female patient with a transverse colon cancer and an inhomogeneous liver lesion at segment VII (Fig.9a). After contrast US administration the lesion shows a peripheral enhancement with a similar nodular morphology (Fig. 9b).

*References:* Department of Radiology, University of Chieti - Chieti/IT
Fig.: 9c,9d- The lesion remains markedly hypoechoic during both portal (Fig.9c) and late phase (Fig.9d). In the suspicious of colon metastasis, all the readers addressed to further examinations.

References: Department of Radiology, University of Chieti - Chieti/IT

Fig.: 9e,9f- At CT scan the lesion shows no enhancement both during the arterial (Fig. 9e) and the portal phases (Fig. 9f).

References: Department of Radiology, University of Chieti - Chieti/IT
Fig.: 9g,9h- The lesion begins to show a globular enhancement during a 180 s delayed phase (Fig. 9g) and a centripetal, incomplete enhancement during a more delayed phase (Fig. 9h). The lesion was a sclerosing hemangioma confirmed at surgical resection.

References: Department of Radiology, University of Chieti - Chieti/IT

Case 10
Fig.: 10a,b,c- An ultrasound routine examination of a patient with inhomogeneous hyperechoic lesion (Fig.10a). At power Doppler imaging the lesion presents central and radial vessels consisting with arteries with low resistance (Fig.10b-c). The conventional US diagnosis was uncertain so the patient underwent contrast US examination. References: Department of Radiology, University of Chieti - Chieti/IT

Fig.: 10d,10e,10f- At CEUS examination the lesion shows early and marked homogeneous enhancement during the arterial (Fig.10a) and portal phases (Fig.10b) but become hypoechoic in the late phase (Fig.10c) as hypervascular malignant lesions. References: Department of Radiology, University of Chieti - Chieti/IT
**Fig.** 10g, 10h - The lesion resulted to be a metastasis from neuroendocrine tumor of the pancreas as shown at CT (Fig. 10g) and surgical specimen (Fig. 10e).

**References:** Department of Radiology, University of Chieti - Chieti/IT
Conclusion

The development of microbubble contrast agents has had a major impact on the role of ultrasound in the liver, especially for the characterization of focal lesions. CEUS has similar sensitivity to contrast-enhanced CT for the characterization of both benign and malignant lesions (8). However, the characterization of liver lesions by CEUS relies on subjective interpretation of real time enhancement of the lesions (8-9). Therefore a specific training regarding how to technically perform CEUS examinations and how to assess the hemodynamic behaviour of liver lesions is needed.

In fact, our results show that sensitivity, specificity and diagnostic accuracy values in differentiating benign from malignant lesions by means of CEUS examinations depend on reader's experience. The differences in readers' performances are more evident in the interpretation of lesions characterized by an "atypical" pattern at CEUS than for lesions with "typical" CEUS pattern such as most hemangiomas. Reader's experience also greatly affect the number of lesions considered "indetermined" and consequently the diagnostic work up of patients (10-11).

In conclusion, contrast-enhanced ultrasound is a reliable technique in making the diagnosis of indeterminate lesions detected at conventional US, but training is required in order to reduce the use of more expensive and invasive examinations. In fact, for most of benign lesions, CEUS can represent the last step of the diagnostic work-up.
References


