Contrast-Enhanced Ultrasound (CEUS) For The Evaluation Of Focal Liver Lesions – A Prospective Multicenter Study Of Its Usefulness In Clinical Practice

Kontrastverstärkte Sonografie zur Bewertung von fokalen Leberläsionen – eine prospektive Multizenter-Studie und deren Nutzen in der klinischen Praxis

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Key words

- contrast-enhanced ultrasound
- focal liver lesions
- liver tumor

Abstract

Purpose: To assess the value of contrast-enhanced ultrasound (CEUS) for differentiating malignant from benign focal liver lesions (FLLs) and for diagnosing different FLL types.

Material and Methods: CEUS performed in 14 Romanian centers was prospectively collected between February 2011 and June 2012. The inclusion criteria were: age > 18 years; patients diagnosed with 1 – 3 de novo FLLs on B-mode ultrasound; reference method (computed tomography (CT), magnetic resonance imaging (MRI) or biopsy) available; patient's informed consent. FLL lesions were characterized during CEUS according to the European Federation of Societies for Ultrasound in Medicine and Biology guidelines. For statistical analysis, indeterminate FLLs at CEUS were rated as false classifications.

Results: A total number of 536 cases were included in the final analysis, 344 malignant lesions (64.2 %) and 192 benign lesions (35.8 %). The reference method was: CT/MRI – 379 cases (70.7 %), pathological exam – 150 cases (27.9 %) and aspiration of liver abscesses – 7 cases (1.4 %). CEUS was conclusive in 89.3 % and inconclusive in 10.7 % of cases. To differentiate between malignant and benign FLLs, CEUS had 85.7 % sensitivity, 85.9 % specificity, 91.6 % positive predictive value, 77.1 % negative predictive value and 85.8 % accuracy. The CEUS accuracy for differentiation between malignant and benign liver lesions was similar in tumors with diameter ≤ 2 cm and those with diameter > 2 cm.

Conclusion: CEUS represents a useful method in clinical practice for differentiating between malignant and benign FLLs detected on standard ultrasonography, and the results of this study are in concordance with previous multicenter studies: DEGUM (Germany) and STIC (France).

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Bibliography

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Zusammenfassung

Ziel: Bewertung des kontrastverstärkten Ultraschalls (CEUS) zur Differenzierung zwischen malignen und gutartigen fokalen Leberläsionen (FLL) und bei der Diagnose verschiedener FLL-Typen.

Material und Methoden: CEUS wurde in 14 rumänischen Zentren von Februar 2011 bis Juni prospektiv durchgeführt und erfasst. Die Einschlusskriterien waren: Alter > 18 Jahre; Diagnose von 1 – 3 FLL de novo im B-Bild; verfügbare Referenzmethode (Computertomografie – CT, Magnetresonanz-Tomografie – MRT oder Biopsie); Einverständniserklärung des Patienten („informed consent"). Die FLL-Läsionen wurden während des CEUS gemäß den Richtlinien der „European Federation of Societies for Ultrasound in Medicine and Biology" charakterisiert. Für die statistische Auswertung wurden durch CEUS nicht bestimmbare FLLs als falsche Klassifizierungen gewertet.

Ergebnisse: Insgesamt wurden 536 Fälle in die Endanalyse eingeschlossen, 344 maligne (64,2 %) und 192 benigne Läsionen (35,8 %). Die Referenzmethoden waren: CT/MRT – 379 Fälle (70,7 %), pathologische Untersuchung – 150 Fälle (27,9 %) und Aspiration von Leberabszessen – 7 Fälle (1,4 %). In 89,3 % der Fälle war CEUS eindeutig und in 10,7 % nicht eindeutig. Bei der Differenzierung zwischen malignen und gutartigen FLLs betrug die Sensitivität des CEUS 85,7 %, die Spezifität 85,9 %, der positive Vorhersagewert 91,6 %, der negative Vorhersagewert 77,1 % und die Genauigkeit 85,8 %. Die Genauigkeit des CEUS bei der Differenzierung zwischen malignen und benignen Leberläsionen war bei Tumoren mit einem Durchmesser von < 2 cm und > 2 cm Durchmesser gleich.

Schlussfolgerung: CEUS ist in der klinischen Praxis eine nützlich, um maligne und benigne FLL, die in einer Standard-US-Untersuchung entdeckt wurden, zu differenzieren. Die Ergebnisse dieser Studie stimmen mit früheren Multizenter-Studien aus Deutschland (DEGUM) und Frankreich (STIC) überein.

Introduction

Focal liver lesions (FLLs) are being increasingly discovered, because of the widespread use of imaging modalities, especially ultrasonography – an imaging method widely used in clinical practice due to its accessibility and relatively good accuracy, similar to computed tomography (CT) and magnetic resonance imaging (MRI). Some of the FLLs are detected incidentally in asymptomatic patients raising the question of subsequent investigations required for diagnosis, e. g. what investigations to use, how complex and how invasive. Ultrasound is a quite sensitive method for detecting FLLs, but it is not specific enough. The information provided by B-mode ultrasound is enough to establish the diagnosis of simple cysts, typically localized focal fat accumulations or fatty sparing [1]. Unfortunately, in daily clinical practice, many lesions cannot be characterized by B-mode ultrasound alone. Power and color Doppler can be useful for diagnosing some liver lesions, for example for focal nodular hyperplasia. Nevertheless, power and color Doppler have a low sensitivity to visualize small tumor vessels, being also susceptible to motion artifacts [2].

The introduction of contrast-enhanced ultrasound (CEUS) with perfluoro-containing agents allows the vascular characterization of lesions, and, according to their pattern, it can establish the diagnosis. The usefulness of this technique for ultrasound diagnosis of FLLs is summarized in the available guidelines: the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) guidelines published in 2004 [3], updated in 2008 [4] and recently in October 2012 [5].

Two large multicenter studies [6, 7] have demonstrated that CEUS is very accurate for the characterization of FLLs, but the data is still questioned [8]. There are also differences when referring to clinical practice, and different levels of operator experience. A multicenter retrospective study including 1244 focal liver lesions in four Romanian centers with extensive ultrasound experience showed that CEUS is a reliable method for the positive diagnosis of focal liver lesions in clinical practice [9].

Consequently the Romanian Society of Ultrasound in Medicine and Biology (SRUMB) initiated this multicenter trial with CEUS, aiming to prospectively establish its value in the assessment of *de novo* FLLs in clinical practice.

Patients And Methods

A multicenter prospective study was conducted over 16 months (February 1, 2011 – June 1, 2012) in 8 university centers (14 individual departments), and the trial was registered at clinicaltrials.gov (Identifier NCT01 329 458).

Patients

The study included consecutive patients (older than 18 years) with one to three newly discovered FLLs during B-mode ultrasound, regardless of the FLL size. The following characteristics were documented for each patient: the indication for CEUS study and a short history including the presence of chronic liver diseases or various malignancies. In each included patient, the B-mode examination was followed by the contrast study (CEUS). Contrast-enhanced CT or MRI or histopathologic exam was available for each patient and considered as a "gold standard" for establishing the final diagnosis.

The exclusion criteria were the following: patients with contraindication for a contrast-enhanced study (subjects with acute myocardial infarction, with class III/IV cardiac insufficiency, or with significant rhythm disorders, as well as pregnant women); patients diagnosed with simple cysts on B-mode ultrasound (biliary) or those diagnosed with hydatid cysts; patients with known FLL, for example after percutaneous treatment, in which the contrast study was used for the follow-up of the patient.

A dedicated website (http://study.umfcv.ro) was developed by the University of Medicine and Pharmacy of Craiova for this study, and the collected data were registered online for each individual patient.

Informed consent for the contrast-enhanced study was obtained from every patient. The study protocol was approved by the local Ethical Committee of each center and was in accordance with the Helsinki Declaration of 1975. Furthermore, perfluoro-containing contrast agents (SonoVue, Bracco Spa, Milan, Italy) have been approved for use in vascular and liver examinations in European Medicines Agency (EMEA) countries from 2002.

Conventional and contrast-enhanced studies

The B-mode and the CEUS studies were performed in each patient with the same ultrasound machine. Different machines were used in different centers, but all had capabilities for low-mechanical index examinations. The amount of contrast agent, as well as the type of ultrasound machine and the operator were also documented. All contrast studies were performed using the dedicated contrast software of each ultrasound machine used in the study. CEUS was interpreted by experts from each center, who were blinded to the CT/MRI or histology results.

The number, size, ultrasound pattern and location of the FLLs were documented after B-mode ultrasound. CEUS was performed with convex probes using a low mechanical index (0.09 – 0.11) in order to minimize microbubble disruption. The contrast agent was SonoVue® (Bracco SpA, Milan, Italy) (2.4 ml), which was injected through a peripheral intravenous cannula of sufficient size, followed by a 10-mL saline flush, as per standard protocol [4]. Lesion enhancement patterns were studied in 3 phases: arterial (10 – 30 seconds after injection), portal (30 – 120 seconds) and late phase (> 120 seconds) according to EFSUMB recommendations [4]. The contrast study for each patient lasted 5 minutes after bolus injection and was documented by at least 4 video files no longer than 30 seconds each, containing: B-mode examination, the arterial phase, the portal phase and the late phase.

The contrast vascular patterns were defined by comparing the enhancement behavior of the tumor as compared with the surrounding liver parenchyma and were classified as:

1. homogeneous hyperenhancement, meaning that the whole FLL showed global homogeneous contrast enhancement;
2. heterogeneous hyperenhancement, meaning that the FLL presented mixed irregular areas of contrast enhancement;
3. rim-like hyperenhancement, meaning a peripheral hyperenhancement of the lesion which was limited to less than 25 % of the tumor's diameter;
4. isoenhancement, meaning that the FLL enhanced similarly to the adjacent parenchyma at the same depth;
5. hypoenhancement, meaning that the lesion's enhancement intensity was less than that of the adjacent parenchyma at the same depth;
6. wash-out, meaning hypoenhancement in the portal or late phases preceded by hyper- or isoenhancement in the arterial phase

A CEUS diagnosis was established after the contrast study based on the patterns described in the 2008 EFSUMB guidelines regarding the use of CEUS for liver applications [4], as follows:

1. Hemangioma: centripetal fill-in enhancement in the arterial phase, partial/complete centripetal filling in portal phase and complete enhancement in the late phase;
2. Focal nodular hyperplasia (FNH): rapid arterial hyperenhancement with typical centrifugal radiating or "spoke-wheel" pattern, followed by homogeneous hyperenhancement in the late arterial phase with the persistence of hyperenhancement in the portal phase and iso/hyperenhancement in the late phase;
3. Adenoma: early and homogeneous hyperenhancement in the arterial phase, isoenhancement in portal phase and iso/hypoenhancement in the late phase;
4. Focal fatty alterations: the same enhancement pattern with respect to the surrounding liver in all vascular phases;
5. Liver cysts:cno contrast enhancement in any of the vascular phases;
6. Regenerative nodule: the same vascular pattern as the surrounding liver parenchyma in all three vascular phases;
7. Abscess: rim-like enhancement in the arterial phase, hypo/isoenhancing rim in portal phase and hypo-enhancing rim in the late phase;
8. Hepatocellular carcinoma (HCC): complete hyperenhancement in the arterial phase, isoenhancement in the portal phase and iso/hypoenhancement in the late phase;
9. Hypervascular metastasis: fast complete hyperenhancement in the arterial phase, hypoenhancement in the portal phase and hypo/non-enhancement in the late phase;
10. Hypovascular metastasis: rim-like hyperenhancement in the arterial phase, hypoenhancement in the portal phase and hypo/non-enhancement in the late phase;
11. Cholangiocarcinoma: rim-like hyperenhacement in the arterial phase, hypo/non-enhancement in the portal and late phase.

A CEUS examination was considered conclusive if, following contrast, the FLL had a typical enhancement pattern according to the EFSUMB guidelines [4], and inconclusive if the enhancement pattern was not in concordance with these guidelines. The CEUS diagnosis was compared with the final diagnosis which was established based on all available imaging and clinical data: contrast-enhanced CT, and/or MRI, and/or histology.

Fig. 1, 2 present a benign and a malignant FLL diagnosed by CEUS.

Statistical analysis

Statistical analysis was performed using the MedCalc program (MedCalc Software, version 12.3.0, Belgium). The distribution of numerical variables was first tested by the Kolmogrov-Smirnov test. In the case of numerical variables with normal distribution, the mean value and standard deviation were calculated, while in the case of non-normal distribution, median values and interquartile range intervals were presented. Differences between numerical variables were analyzed by parametric (t-test) or non-parametric tests (the Mann–Whitney test) according to the normal or non-normal distribution of the variables. Qualitative variables were presented as numbers and percentages. The Chi-square (X^2) test (with Yates' correction for continuity) was used for comparing two proportions expressed as a percentage ("n" designates the total number of patients included in a particular subgroup). A *p*-value less than 0.05 was regarded as significant for each statistical test.

The accuracy of CEUS for FLL characterization was assessed in terms of lesion status and specific lesion type. The sensitivity (Se) was calculated as true positive cases divided by the total number of cases in which the disease was present; the specificity (Sp) was

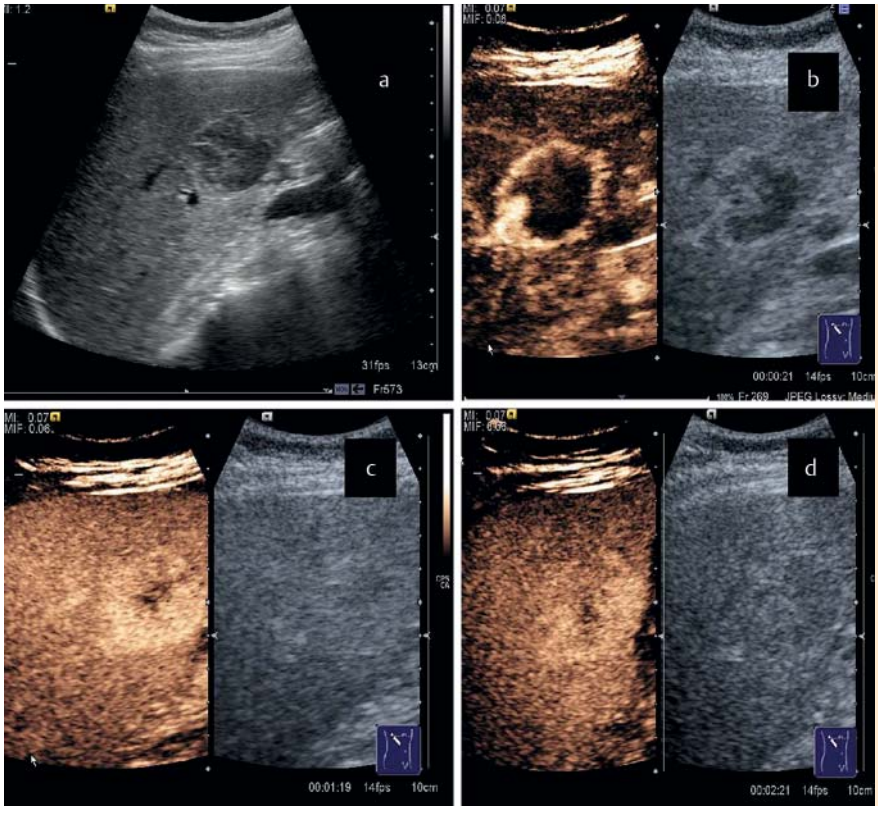

Fig. 1 CEUS in a benign lesion (hemangioma). **a** Conventional ultrasound: hypoechoic liver mass, with hyperechoic rim, well delimited; **b** Arterial phase: peripheral nodular hyperenhancement; **c** Portal phase: partial centripetal fill-in; **d** Late phase: almost complete enhancement.

Abb. 1 CEUS bei einer gutartigen Läsion (Hämangiom). **a** Herkömmliche Sonografie: Echoarme Raumforderung in der Leber, mit echoreichem Rand, gut umgrenzt; **b** Arterielle Phase: Periphäre nodulare Signalanhebung; **c** Portale Phase: partielle zentripetale Füllung; **d** Spätphase: fast vollständige Kontrastaufnahme.

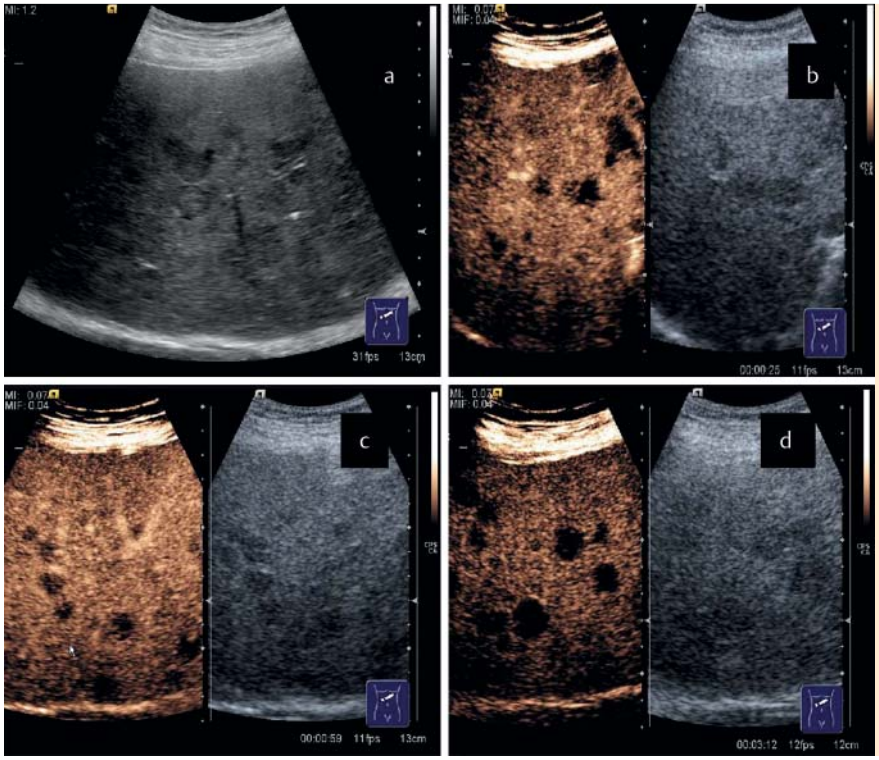

Fig. 2 CEUS in malignant lesions (hypovascular metastases). a Conventional ultrasound: multiple hypoechoic liver masses; **b** Arterial phase: rim enhancement; **c** Portal phase: wash-out of the rim area; **d** Late phase: continued wash-out.

Abb. 2 CEUS bei malignen Läsionen (hypovaskuläre Metastasen). **A** Herkömmliche Sonografie: Multiple echoarme Raumforderungen in der Leber; **b** Arterielle Phase: Kontrastaufnahme des Randes; **c** Portale Phase: Wash-out im Randbereich; **d** Spätphase: fortgesetztes Wash-out.

calculated as true negative cases divided by the total number of cases in which the disease was absent; the positive predictive value (PPV) was calculated as true positive cases divided by all CEUS positive cases; the negative predictive value (NPV) was calculated as true negative cases divided by all CEUS negative cases and accuracy was calculated as the sum of true positive and true negative cases divided by the total number of cases. We included in the statistical analysis all cases reported, while the inconclusive CEUS cases were considered as wrongly diagnosed.

For the cost-effectiveness analysis, we compared the costs of three strategies: 1) CEUS as the first imaging method followed by CT or MRI for inconclusive cases; 2) contrast-enhanced CT as the first imaging method in all cases; 3) contrast-enhanced MRI as the first imaging method in all cases. For this analysis we used the mean costs of imaging techniques practiced in Romania: CEUS – 42 Euros (32 Euros – the cost of ½ vial of Sonovue + 10 Euros – staffing costs); CT – 65 Euros and MRI – 150 Euros.

Results

Initially, 866 FLLs were included in the online database. From these, the following cases were excluded for not meeting the inclusion criteria: non-hepatic lesions – 4 cases (0.4 %), simple cysts evident on B-mode ultrasound (biliary or hydatid) – 8 cases (0.9 %), patients with more than 3 lesions – 21 cases (2.4 %), no reference method available – 297 cases (34.3 %). Thus, 536 FLLs (61.8 % of all FLL) in 525 patients were included in the final analysis.

The final diagnosis was established in most cases by contrast-enhanced CT/MRI – 379 cases (70.7 %), followed by the histology in 150 cases (27.9 %), and puncture with aspiration from liver abscesses in 7 cases (1.4 %).

The patient characteristics included in the final analysis are presented in **Table 1**.

Half of the lesions (53.4 %) were hypoechoic on B-mode ultrasound, followed by hyperechoic (35.8 %) and isoechoic (10.8 %) lesions, while 59.9 % were inhomogeneous and 40.1 % homogenous. From all 536 FLLs analyzed, the final diagnosis established the malignant etiology in 344 cases (64.2 %) and the benign nature in 192 FLLs (35.8 %).

The value of CEUS in benign vs. malignant differentiation

The CEUS study was conclusive for benign vs. malignant differentiation in 89.3 % of cases, and inconclusive in 10.7 %. Of the FLLs in which CEUS was conclusive, 56.1 % were malignant and 33.2 % benign.

When all included cases were analyzed, considering those that were inconclusive on CEUS as cases wrongly diagnosed, the method had 85.7 % Se, 85.9 % Sp, 91.6 % PPV, 77.1 % NPV and 85.8 % accuracy. When we analyzed only the cases categorized as conclusive for benign/malignant differentiation, CEUS had 95.7 % Se, 96.4 % Sp, 98 % PPV, 92.6 % NPV and 96 % accuracy.

The size of the FLL was specified in 519 FLLs. This group was divided into lesions ≤ 2 cm: 127 cases (24.4 %), and lesions > 2 cm: 392 cases (75.6 %). The diagnostic performance according to FLL size is presented in **Table 2**.

The CEUS accuracy for the differentiation between malignant and benign liver lesions was similar in tumors with a diameter ≤ 2 cm and those with a diameter > 2 cm, in all cases and also in only conclusive CEUS cases: 86.6 % vs. 85.4 %, p = 0.84 and respectively 95.5 % vs. 95.9 %, p = 0.93. In our study, only 24 FLL (4.6 %) had the size smaller or equal with 1 cm. For these lesions, CEUS accuracy for differentiation between malignant and benign FLL was 75 % in all cases and 94.7 % in conclusive CEUS cases.

The median size of FLLs in conclusive vs. inconclusive benign/malignant lesions was similar: 3.5 cm (0.5 – 18 cm) vs. 3.5 cm (0.6 – 11 cm), p = 0.50. Also, the proportion of malignant lesions was similar in conclusive vs. inconclusive benign/malignant CEUS cases: 64.3 % vs. 68.4 %, p = 0.64.

Table 1 Patient characteristics.

Parameter	Data
median age (years)	59 (19 – 89)
gender: – women	n = 208 (39.6 %)
– men	n = 317 (60.4 %)
the median size of the examined FLL (cm)	3.5 (0.5 – 18)
number of FLLs examined/patient: – one	n = 525 (97.9 %)
– two	n = 11 (2.1 %)
CEUS indication:	
– incidental finding in subjects without liver pathology	n = 237 (44.2 %)
– FLL in patients with chronic hepatopathies (including liver cirrhosis)	n = 207 (38.6 %)
– FLL in patients with oncologic history	n = 86 (16.1 %)
– patients with inconclusive CT/MRI	n = 6 (1.1 %)
final diagnosis:	
– hepatocellular carcinoma (HCC)	n = 209 (38.9 %)
– metastasis	n = 109 (20.4 %)
– hemangioma	n = 102 (19.1 %)
– focal fatty alteration	n = 30 (5.5 %)
– cholangiocarcinoma	n = 25 (4.7 %)
– focal nodular hyperplasia (FNH)	n = 19 (3.5 %)
– regenerating nodules	n = 17 (3.1 %)
– liver abscess	n = 13 (2.5 %)
– adenoma	n = 7 (1.3 %)
– complex cysts	n = 2 (0.3 %)
– lymphoma	n = 1 (0.2 %)
– scar area	n = 1 (0.2 %)
– vascularization disorder	n = 1 (0.2 %)

The value of CEUS for the diagnosis of different types of lesions

CEUS accuracy for diagnosing different types of benign and malignant FLLs ranged between 79.8 % and 98.3 %, the highest accuracy being obtained for focal nodular hyperplasia (FNH) and the lowest for hepatocellular carcinoma (HCC) (**Table 3**).

Cost-effectiveness analysis

- ***Strategy I:*** CEUS performed in all cases followed by CT or MRI for inconclusive malignant/benign cases
  - CEUS cost: 536 cases × 42 Euros = 22,512 Euros
  - CT cost for inconclusive cases: 57 cases × 65 Euros = 3705 Euros
  - MRI cost for inconclusive cases: 57 cases × 150 Euros = 8550 Euros
  - CEUS in all cases followed by CT for inconclusive cases: 22,512 Euros + 3705 Euros = 26,127 Euros
  - CEUS in all cases followed by MRI for inconclusive cases: 22,512 Euros + 8550 Euros = 31,062 Euros
- ***Strategy II:*** CT performed as first-line imaging in all cases
  - CT cost: 536 cases × 65 Euros = 34 840 Euros
- ***Strategy III:*** MRI performed as first-line imaging in all cases
  - MRI cost: 536 Euros × 150 Euros = 80 400 Euros

all cases included, considering those inconclusive on CEUS as cases wrongly diagnosed					
lesion size	**Se (%)**	**Sp (%)**	**PPV (%)**	**NPV (%)**	**Accuracy (%)**
≤ 2 cm	80.5	93.3	93.1	81.1	86.6
> 2 cm	86.7	82.6	91.2	75	85.4
only cases categorized on CEUS as conclusive for benign/malignant differentiation					
lesion size	**Se (%)**	**Sp (%)**	**PPV (%)**	**NPV (%)**	**Accuracy (%)**
≤ 2 cm	92.9	98.2	98.1	93.3	95.5
> 2 cm	96.2	95.4	97.8	92.1	95.9

Table 2 CEUS diagnostic performance in benign vs. malignant differentiation according to lesion size.

	all cases included, considering those inconclusive on CEUS as wrongly diagnosed					
FLL	**no. of lesions**	**Se (%)**	**Sp (%)**	**PPV (%)**	**NPV (%)**	**Accuracy (%)**
hemangioma	102	81.3	87.1	59.7	95.2	86
FNH	19	94.7	87.6	21.9	99.7	87.8
regenerating nodules	17	76.4	87.2	16.4	99.1	86.9
focal fatty alteration	30	96.6	86.7	30.2	99.7	87.3
liver abscess	13	76.9	88.9	14.7	99.3	86.9
HCC	209	70.3	85.9	76.1	81.9	79.8
metastasis	109	87.1	82.9	56.5	96.1	83.7
cholangiocarcinoma	25	60	85.1	16.4	97.7	83.9
	cases categorized on CEUS as conclusive for benign/malignant differentiation					
FLL		**Se (%)**	**Sp (%)**	**PPV (%)**	**NPV (%)**	**Accuracy (%)**
hemangioma	92	90.2	97.6	90.2	97.6	96.2
FNH	19	94.7	98.4	72	99.7	98.3
regenerating nodules	14	92.8	97.4	52	99.7	97.2
focal fatty alteration	28	100	97.7	74.3	100	97.9
Liver abscess	10	100	98.4	62.6	100	98.5
HCC	181	81.2	94.2	89.6	89.2	89.3
metastasis	102	93.1	94.1	81.1	98.1	93.9
cholangiocarcinoma	24	62.5	95.6	42.8	97.9	93.9

Table 3 CEUS performance for the positive diagnosis of different types of FLL.

Discussion

In a period when medicine is becoming more and more expensive, ultrasound evaluation is an inexpensive and accessible method, useful in many medical fields. Ultrasound is a sensitive method for the evaluation of the liver and especially for FLLs, but is not specific enough. The introduction of CEUS (especially with perfluoro-containing agents) was a huge step forward. Vascular characterization in the arterial, portal and late phase allows in many cases a correct diagnosis of discovered FLL.

CEUS can be performed in many centers and situations immediately after the B-mode ultrasound during which the liver lesion was discovered. Thus, in the large majority of cases, in approximately 30 minutes the final diagnosis can be obtained. Considering contrast-enhanced CT, the medical and non-medical world is increasingly concerned about exposure to ionizing radiation. Also, unlike MRI and especially contrast-enhanced CT, CEUS can be safely used in patients with acute or chronic renal failure. Moreover, it should be mentioned that adverse events following the administration of perfluoro-containing agents are rare and mild [10, 11] as compared with other contrast imaging techniques [12], but it should be specified that severe adverse events after CEUS injections can occur in patients with severe cardiac conditions, such as acute myocardial infarction, class III/IV cardiac insufficiency, or with significant rhythm disorders [10, 11]. And last but not least, it should be specified that CEUS as a first-line imaging method in all cases followed by CT or MRI for inconclusive benign/malignant cases is less expensive than contrast-enhanced CT or MRI used as a first-line imaging method: in our study 26,127 Euros for CEUS in all cases + CT for inconclusive cases vs. 31,062 Euros for CEUS in all cases + MRI for inconclusive cases vs. 34,840 Euros for CT as the first-line imaging method in all cases vs. 80,400 Euros for MRI as the first-line imaging method in all cases. These results are in line with other published studies [13, 14], and with the recently published recommendations of NICE [15]. The CEUS and CT/MRI costs used in our present study are smaller than that used by Schuler et al [16], but as specified these are the mean costs practiced in Romania for different imaging techniques [14].

Our aim was approximately the same as in the DEGUM (German) [6] and the multicenter French study – STIC [7] multicenter trials. The reference method for the final FLL diagnosis was dynamic contrast-enhanced CT or MRI in most cases (70.7 %), similarly to the French multicenter study [7], but different from the German multicenter study [6], in which histology was the "gold standard" in most cases.

Although the proportion of incidental findings was much higher than the proportion of FLLs in cirrhotic and oncologic patients in the German study [6], the number of incidental findings in our study in subjects without known liver pathology or oncologic history was only slightly higher than that of FLLs in patients with chronic hepatopathies (mainly liver cirrhosis). Similarly to the German study [6] and different from the French study [7], the reference method showed a higher proportion of malignant than benign FLLs.

Regarding the "intent to diagnose" and considering all solid FLLs with wash-out in the portal and/or late phase as malignant, and all lesions without wash-out in any vascular phase as benign, CEUS was inconclusive in 10.7 % of cases in our cohort of 536 FLLs, a percentage higher than that observed in the German multicenter study (6.8 %) [6], thus these cases must be referred for another imaging method for the final diagnosis. The mean FLL size and the proportion of malignant lesions were similar in conclusive and inconclusive CEUS cases. Unfortunately, one limitation of our study was the fact that the lesion depth was not recorded, so we could not study the influence of this factor in the inconclusive CEUS cases. Another limitation is the fact that we could not analyze the accuracies of the different centers included in the study because the distribution of patients between the centers included in the study was different (some of the centers comprised a large number of patients and some of the centers only a few patients) and also the pathology was different (some centers with a large number of HCCs or regenerative nodules and some centers with many benign lesions or liver metastases).

In the present multicenter Romanian study, CEUS has approximately 85 % Se, Sp and accuracy to differentiate between malignant and benign FLLs when all cases were considered, percentages similar to those observed in the French multicenter study [7] and slightly lower than those presented in the German study [6]. Since our results showed that CEUS is conclusive in about 90 % of cases in Romanian clinical practice, we decided to analyze the performance of CEUS in those cases. We observed that Se, Sp, PPV and accuracy for differentiating benign vs. malignant liver tumors were higher than 95 %. Thus, if CEUS examination is conclusive (with a typical enhancement pattern according to the EFSUMB guidelines [4]), we can be very confident in our results and another imaging technique is not required for FLL characterization.

Unlike the German and French studies [6, 7], we did not analyze the comparative value of CEUS and CT/MRI for FLL characterization (considering histology as the reference method for the final diagnosis) since contrast-enhanced CT and/or MRI was also available only in one third of cases in which histology and CEUS were performed. Also, it should be specified that histology evaluation was performed for the most part of cases without conclusive results in CEUS and CT/MRI.

The FLL size (≤ 2 cm and > 2 cm) did not influence CEUS accuracy for differentiating malignant from benign lesions, results similar to those obtained in the German multicenter study [6]. Also, good CEUS accuracy was observed for differentiating malignant from benign lesions with size ≤ 1 cm, especially in CEUS conclusive cases, our results being in line with others published studies which analyzed FLL smaller than 1 cm [17].

The good performance of CEUS for FLL characterization was demonstrated in a meta-analysis published in 2011 [18], which included 25 studies. The reference method for the final diagnosis was histology in all cases, while CT or MRI was also available in a subgroup of patients. The summary Se and summary Sp were similar for CEUS, contrast-enhanced CT and MRI for FLL characterization: 0.87, 0.86, 0.85 and 0.89, 0.82, 0.87, respectively. In another recently published meta-analysis [19], which included 45 studies with 8147 FLLs, CEUS had a summary Se of 0.93 and a summary Sp of 0.90 for differentiating between malignant and benign lesions. In this meta-analysis also, CEUS performed as well as CT/MRI.

Regarding the value of CEUS for the diagnosis of different types of malignant and benign FLLs and considering all FLLs included in the study, our results for diagnosing focal nodular hyperplasia and liver metastasis were similar to those observed in the French multicenter study [7], in which slightly better results were obtained for diagnosing hemangioma and HCC. One explanation for the lower CEUS performance in our study for diagnosing HCC, can be the significantly higher number of HCCs in our study as compared with the French study [7]: 38.9 % vs. 24.1 %, and

maybe the histological differentiation of HCC knowing that well-differentiated HCCs show wash-out in the portal and late phase in only approximately 20 % of cases [20].

When we considered only conclusive CEUS cases, we observed an excellent performance for diagnosing different benign FLLs: focal fatty alteration (100 % Se, 97.7 % Sp, 100 % NPV and 97.9 % accuracy), focal nodular hyperplasia (94.7 % Se, 98.4 % Sp, 99.7 % NPV and 98.3 % accuracy), hemangioma (90.2 % Se, 97.6 % Sp, 97.6 % NPV and 96.2 % accuracy) or regenerating nodules in cirrhotic patients (92.8 % Se, 97.4 % Sp, 99.7 % NPV, and 97.9 % accuracy). Our results are in line with other published data [21 – 24] and show that it is sufficient to perform a CEUS examination after a standard ultrasound, thus reducing the time and the costs for a confident final diagnosis.

Regarding the characterization of liver masses in oncologic patients, CEUS had an excellent performance with Se, Sp, and accuracy higher than 93 % and NPV > 98 % for diagnosing liver metastases, results consistent with published data [25]. These results are important when we consider that oncologic patients need to be evaluated periodically and that other imaging techniques, such as contrast-enhanced CT or MRI, are expensive and have a higher rate of allergic reactions than CEUS [12], and that CT also exposes the patient to ionizing radiation.

The value of CEUS for the characterization of HCC in the CEUS-conclusive cases was very good, with Se > 80 %, Sp > 95 % and with PPV, NPV and accuracy > 89 %. Other published studies showed good performance of CEUS for diagnosing HCC in cirrhotic patients [19, 26, 27].

All these data suggest that CEUS should be reintroduced in the noninvasive guidelines for HCC, after it was eliminated from the guidelines of the American Association for the Study of Liver Disease (AASLD) in 2010 [28] and subsequently from the HCC guidelines of the European Association for the study of the Liver (EASL) [29] mainly because of the risk of confusing intrahepatic cholangiocarcinoma and HCC [30]. However, even if in the Vilana study [30] approximately 50 % of the intrahepatic cholangiocarcinomas showed a similar CEUS pattern to that of HCC (homogeneous hyperenhancement in the arterial phase followed by homogeneous wash-out in portal or late phase), it should be mentioned that cholangiocarcinomas are rare in cirrhotic patients, limited to 1 – 2 cases/year in big hepatology centers [30]. Thus, the present multicentric trial clearly showed that we can confidently use in clinical practice CEUS as first line imaging method for FLLs as hemangioma, FNH, focal fatty alteration, liver metastasis, HCC in cirrhotic patients [6, 7, 31].

In our present study, conclusive CEUS had a lower performance for diagnosing cholangiocarcinoma as compared with other malignant and benign FLLs, but this is a quite rare tumor in clinical practice. Hence, it was encountered in less than 5 % of all FLLs, while most probably CEUS cannot replace histology for cholangiocarcinoma diagnosis. Nevertheless, one limitation of our study is that compared with others studies [32, 33] we did not presented an analysis regarding the comparison between CEUS and CT/MRI in cases in which histology was the “gold-standard” method, because histology evaluation was performed for the most part of cases without conclusive results in both CEUS and CT/MRI. Unlike the German and French studies [6, 7], we did not compare directly these imaging techniques for FLL characterization since only in one third of cases in which histology and CEUS were performed, contrast-enhanced CT and/or MRI were also available.

In conclusion, CEUS was conclusive for differentiation between malignant and benign FLLs in approximately 90 % of all cases. If only conclusive cases were considered, CEUS proved to be a very accurate method to differentiate malignant vs. benign lesions and also to diagnose different types of FLL. Therefore, there can be confidence in our results in CEUS-conclusive cases in which other contrast imaging techniques are not required, thus reducing the costs and the time for obtaining the final diagnosis.

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