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Contrast Enhanced Ultrasound for the characterization of focal liver lesions

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Abstract

Aim: to present the practice of two experienced centres concerning the use of contrast enhanced ultrasound (CEUS) in the characterization of focal liver lesions (FLL). **Material and method:** A prospective, bicentric study, between 09.2009-09.2010 was undertaken and 729 FLL (506-Center A, 223-Center B) were evaluated. A CEUS examination was considered conclusive, if the FLL had a typical enhancement pattern according to EFSUMB Guidelines. **Results:** From the 729 cases with FLL, 389 (53.4%) were patients without known and 340 (46.6%) with known chronic liver disease. CEUS was conclusive for the diagnosis in 597/729 cases (82%) and allowed the positive diagnosis of benign vs. malignant lesion in 662/729 (90.8%) FLL. For each center independently (Center A vs. Center B) the situation was as follows: conclusive for the diagnosis 390/506 (77.1%) vs 207/223 (92.8%) ($p<0.0001$), conclusive for the differentiation benign/malignant 449/506 (88.7%) vs. 213/223 (95.5%) ($p=0.0032$). **Conclusion:** In our bicentric study, CEUS was conclusive for diagnosis in 82% of FLL and the benign or malignant character of a lesion was demonstrated in 90.8% of cases. Thus, when faced with an uncharacteristic FLL on standard ultrasound, our local strategy in both centers was to perform CEUS as a first-line investigation thus avoiding other expensive examinations.

Keywords: Contrast Enhanced Ultrasound (CEUS), Focal Liver Lesions (FLL), Ultrasound Contrast Agent (SonoVue)

Rezumat

Scop: prezentarea experienţei practice a două centre experimentate în utilizarea ecografiei cu substanţă de contrast (CEUS) în caracterizarea leziunilor hepatice circumscrise (FLL). **Material şi metodă:** am efectuat un studiu prospectiv bicebtric în perioada 09.2009-09.2010, şi am evaluat 729 FLL (506-Centrul A, 223- Centrul B). O examinare CEUS a fost considerată concluzivă dacă FLL a avut un conportament tipic după administrarea de contrast conform ghidului EFSUMB. **Rezultate:** din cele 729 cazuri cu FLL, 389 (53.4%) au fost pacienţi fără hepatopatie cunoscută iar 340 (46.6%) cu patologie hepatică cronică cunoscută. CEUS a fost concluziv pentru diagnostic în 597/729 cazuri (82%) şi a permis diferenţierea benign vs. malign în 662/729 (90.8%) FLL. Pentru fiecare centru independent (Centrul A vs. Centrul B) datele au fost următoarele: concluziv pentru diagnostic 390/506 (77.1%) vs 207/223 (92.8%) ($p<0.0001$), concluziv pentru diferenţierea benign/malign 449/506 (88.7%) vs. 213/223 (95.5%) ($p=0.0032$). **Concluzii:** în studiul nostru bicentric CEUS a fost concluziv pentru diagnostic în 82% din FLL, iar caracterul benign sau malign al leziunilor a fost demonstrat în 90.8% din cazuri. Astfel, în faţa unei FLL incerte în ecografia standard, strategia locală în ambele centre este efectuarea CEUS, ca investigaţie de primă linie (evitând alte investigaţii costisitoare).

Cuvinte cheie: ecografie cu substanţă de contrast, leziuni hepatice focale, substanţă de contrast (SonoVue)

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Introduction

Focal Liver Lesions (FLL) are quite frequently discovered in daily practice, due to the routine use of imaging methods (ultrasound - US, computer tomography - CT or magnetic resonance imaging - MRI). On the other hand, due to screening strategies for patients with liver cirrhosis, FLL are discovered sometimes very early in these patients, and they must be evaluated, in order to

establish a therapeutic strategy (including transplantation, surgical resection or percutaneous echoguided procedures).

In the latter years, Contrast Enhanced Ultrasound (CEUS) has become a reliable imaging method for the assessment of FLL. Incidental lesions discovered on standard US must be evaluated by means of different imaging methods, and, sometimes, this can be a stressful event for the patients, during the waiting time for a new method of evaluation (contrast CT or MRI). CEUS evaluation of FLL can be an advantage, especially due to the relatively low cost of this method, and because it can be performed immediately after the standard abdominal ultrasound, so that approximately 5 minutes after the injection of US contrast agent (the total duration of this investigation), a confident diagnosis can be obtained in many cases.

The European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) issued the first Guidelines regarding the use of CEUS [1] in 2004, revised in 2008 [2], in which the main indications of this method are presented. Relatively recently, two large prospective multicentre studies were published, proving the value of this method in patients with FLL. The first study, performed by the German Society of Ultrasound (DEGUM) [3] compares CEUS to the liver biopsy, and the second study, performed by the French Society of Ultrasound, compares CEUS to contrast CT or MRI and/or liver biopsy considered to be the "gold standard" [4].

Considering all these data, questions arise: how useful is CEUS in daily practice for the evaluation of FLL, and secondly if, by using this method, we can decrease the medical costs for the diagnosis, knowing that contrast CT and MRI are expensive and, also, that a CT scan exposes the patients to possibly harmful radiations.

The aim of our study is to present a bicentric experience (Department of Gastroenterology and Hepatology Timişoara and IIIrd Medical Clinic Cluj-Napoca), concerning the use of contrast enhanced ultrasound (CEUS) for the characterization of FLL and to find when it would be possible to avoid using other expensive imaging methods, such as contrast enhanced CT or MRI.

Material and method

We performed a prospective, bicentric study, between September 2009-September 2010 and we evaluated 729 FLL (506 examinations in Center A and 223 examinations in Center B) using an US contrast agent. A CEUS examination was considered conclusive, if the FLL had a typical enhancement pattern after contrast injection according to the EFSUMB guidelines.

In all the cases in which standard ultrasound was not sufficient for a correct diagnosis, we performed CEUS, interpreted according to the EFSUMB Guidelines [2]. Following CEUS, we divided the patients in two groups: one in which CEUS evaluation was conclusive and no other diagnostic methods were needed; and another in which CEUS was inconclusive and other diagnostic methods were performed (contrast CT or MRI, or biopsy of the lesion).

In addition, we divided our patients into a group of subjects without diffuse hepatic disease [excluded using clinical, biological, ultrasound and elastographic criteria (including transient elastography - TE and Acoustic Radiation Force Impulse - ARFI)] and a group of patients with chronic hepatopathies (liver cirrhosis or chronic hepatitis).

Exclusion criteria for performing CEUS were: subjects with acute cardiac infarction, with class III/IV cardiac insufficiency, with cardiac rhythm disorders and pregnant women. The study was approved by the Local Ethics Committee. After informed consent was obtained, CEUS was performed and all patients were monitored for adverse events, until two hours after the procedure.

A baseline US survey examination, including a color/power Doppler analysis, was performed. For CEUS examination, a very low mechanical index (< 0.08 MHz) was used for real-time imaging. Each examination lasted about 5 min after the bolus injection. The US contrast agent used in the present study was SonoVue® (Bracco, Italy). Each patient received an intravenous bolus injection of SonoVue® for each lesion to be characterized (usually 2.4 ml), via a 20-gauge intravenous catheter placed in the ante-cubital vein, and followed by 10 ml saline flush. To characterize the lesion, the hemodynamic behavior of SonoVue® enhancement during the arterial phase (15-30 seconds), portal venous (30-120 seconds) and late vascular phases (120-300 seconds) was evaluated. All sonographic examinations were digitally recorded.

The location and size of the lesion were assessed on unenhanced and CEUS scans. In addition, the vascularity and pattern of SonoVue® enhancement of the lesion (hypoenhancing, hyperenhancing, isoenhancing), as compared with the adjacent liver parenchyma during the arterial, portal venous and late phases were evaluated.

Ultrasound diagnosis, in terms of the nature (malignant or benign) and type of the lesion (hemangiomas, focal nodular hyperplasia - FNH, liver adenoma, liver fatty alteration, hepatocellular carcinoma - HCC or metastases) were based on SonoVue® enhanced US (CEUS). The number, location, size and characterization of the lesions were recorded. Experienced physicians (level II or III in the EFSUMB classification: www.efsumb.org) evaluated

all the SonoVue® enhanced images, formulating a final diagnosis.

The data we obtained from our patients were collected in a Microsoft Excel file, the statistical analysis being performed using GraphPad Prism 5 program. Fisher's exact test was used to compare proportions.

Results

From the 729 cases with FLL, 389 (53.4%) were patients without known liver disease and 340 (46.6%) with known chronic liver disease.

CEUS was conclusive for the diagnosis in 597/729 cases (82%) (fig 1); 266 cases (44.6%) were conclusive for the diagnosis in patients with chronic liver disease and 331 cases (55.4%) in patients without chronic liver disease. CEUS allowed the positive diagnosis of benign vs. malignant lesion in 662/729 (90.8%) of all FLL (fig 2).

For each center independently the situation was as follows: conclusive for the diagnosis in center A: 390/506 (77.1%) vs. center B: 207/223 (92.8%) (p<0.0001) (fig 1), conclusive for the differentiation benign vs. malignant 449/506 (88.7%) vs. 213/223 (95.5%) (p=0.0032) (fig 2).

The main lesions found in this study in patients without chronic liver disease were: metastasis (130 cases – 39.3 %), hemangiomas (87 cases – 26.3 %), FNH (28 cases – 8.5 %), fatty free alterations (41 cases – 12.4 %), complex cysts (19 cases – 5.7%), adenomas (9 cases – 2.7%), abscesses (6 cases – 1.8%), cholangiocarcinomas (7 cases – 2.1%) and other type of lesions such as: hematomas (2 cases - 0.6 %), hepatoblastomas (2 cases – 0.6 %) (fig 3-6).

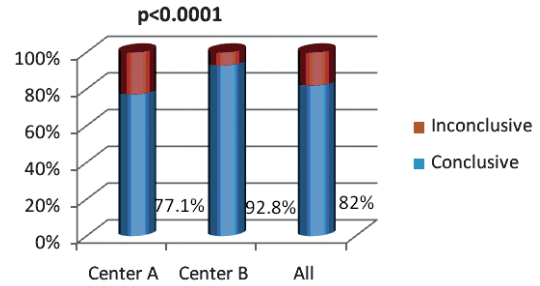

Fig 1. CEUS conclusive for the diagnosis

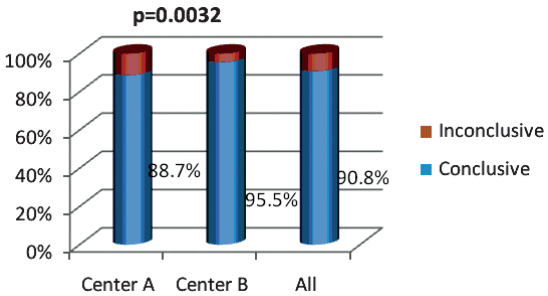

Fig 2. CEUS for the differentiation between benign and malignant FLL

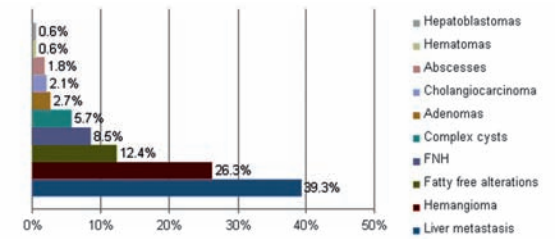

Fig 3. The type of lesions diagnosed by CEUS in patients without chronic liver disease

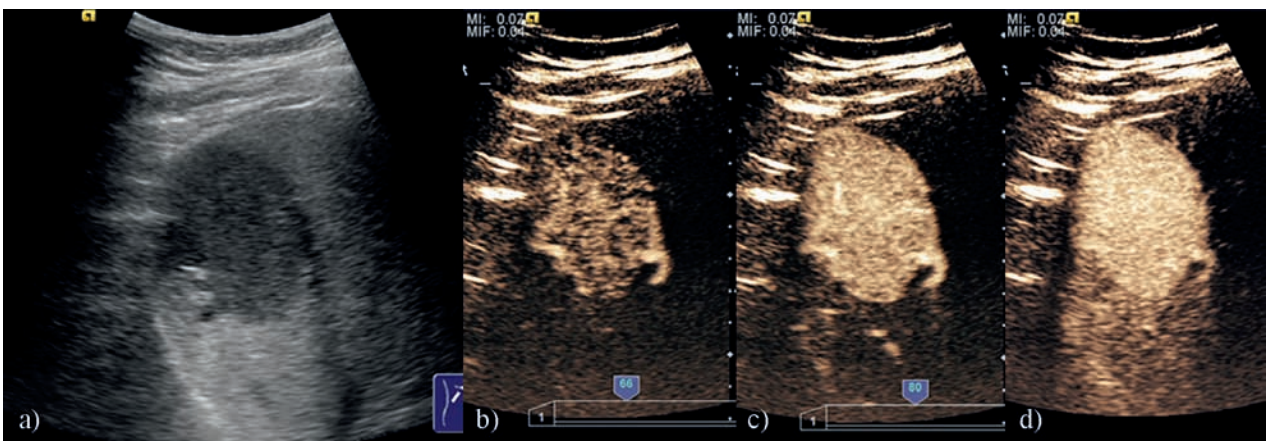

Fig 4. FHN – CEUS examination: a. Hypoechoic lesion in the right liver lobe at standard ultrasound; b. Arterial phase, 8 sec after injection – starting of the lesions' enhancement, visible feeding artery; c. Arterial phase, 9 sec after injection – rapid enhancement of the lesion d. Arterial phase, 12 sec after injection – Complete enhancement of the lesion

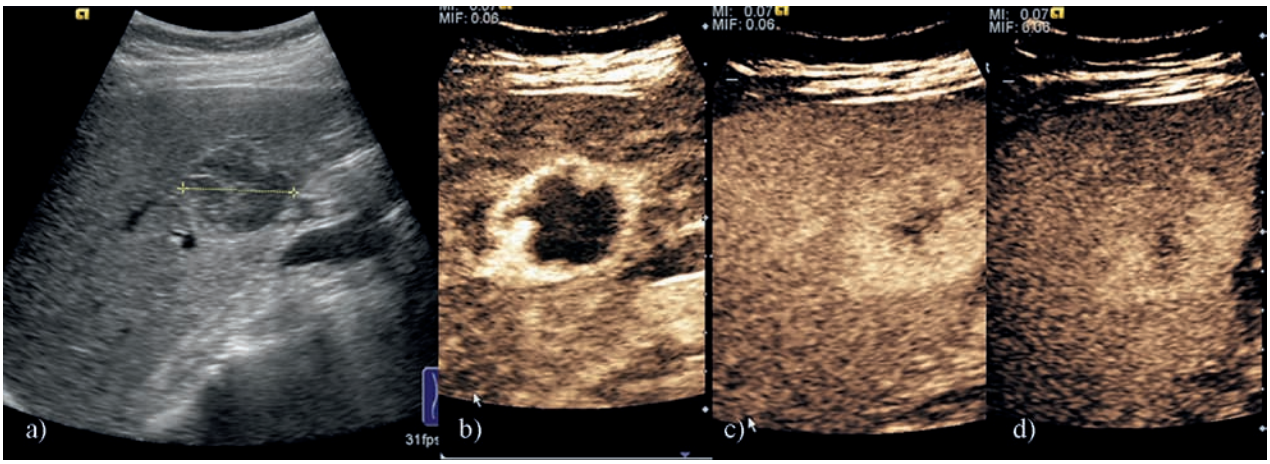

Fig 5. Hemangioma - CEUS examination: a. Standard ultrasound - in the right liver lobe a hypoechoic, inhomogeneous mass with hyperechoic rim; b. Arterial phase – peripheral, rim enhancement; c. Portal-venous phase – the nodule continues to present centripetal progression of enhancement, while the small central area remains unenhanced; d. Late phase – the nodule is still hyperenhancing, with the small central area unenhanced.

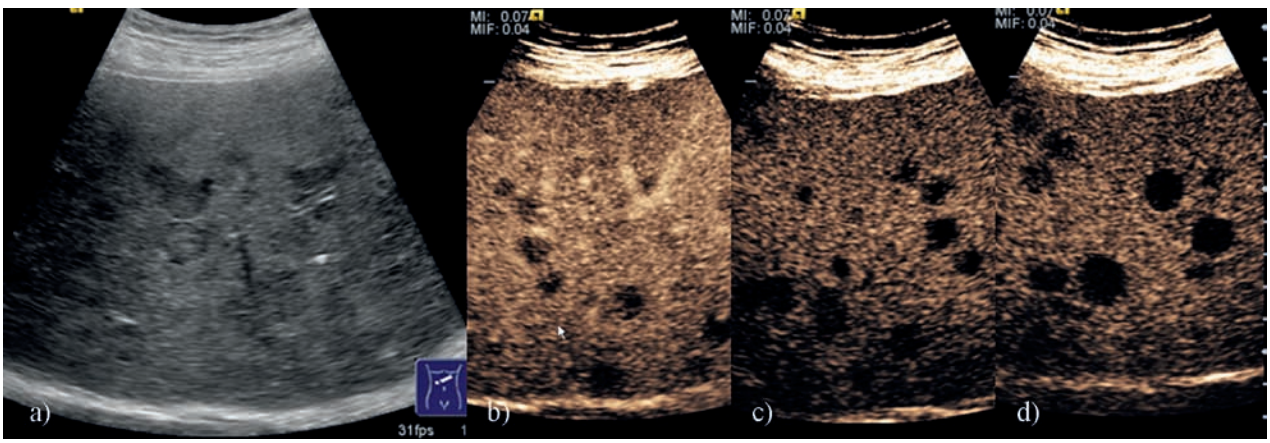

Fig 6. Liver metastases – CEUS examination: a. Standard ultrasound – globally inhomogeneous liver structure, with multiple, small hypoechoic nodules; b. Portal-venous phase – multiple hypoenhancing nodules; c, d Late phase – hypoenhancing small nodules.

In the inconclusive cases we used other diagnostic modalities such as contrast enhanced CT or MRI or liver biopsy. The most frequent inconclusive lesions at CEUS, in which the diagnosis was established by another method were hepatocellular carcinomas, regenerative nodules, cholangiocarcinomas and atypical hemangiomas.

Discussions

The EFSUMB Guidelines [1,2] formulated indications regarding the use of CEUS and several published papers [3-7] demonstrated the real practical value of this method.

We decided to perform this prospective bicentric study in order to evaluate the relevance of this method for daily practice in Romania. Ultrasound in Romania is well developed in some university centers, due to the long experience in using this method and maybe due to the fact that is performed mainly by clinicians. In our prospective study, for patients with new FLL discovered by US, by using CEUS we obtained the final diagnosis in 82% of cases. Thus, only 18% of the patients will need a second line imaging technique evaluation (multislice contrast enhanced CT or contrast enhanced MRI) or, sometimes, echoguided liver biopsy.

One other task of our study was to find the value of CEUS for the differentiation between the malignant or benign character of a FLL. Some benign lesions such as hemangiomas, FNH or fatty liver alterations are easily diagnosed, but sometimes it is quite difficult to formulate

a correct diagnosis of hepatic adenoma [8]. On the other hand, published data showed that the sensitivities and specificities of CEUS for the diagnosis of hemangioma or FNH are very high: the accuracy of standard US for the diagnosis of atypical hemangioma was 43%, while after SonoVue® it increased to 93% [8]. Also, the sensitivities and specificities of CEUS for the diagnosis of focal nodular hyperplasia (FNH) and hemangioma were 100% and 87%, resulting in an accuracy of 94.5% [9].

In patients with liver cirrhosis or advanced fibrosis, we encountered difficulties for the correct CEUS diagnosis of some of the HCCs (usually small or undifferentiated ones). The arterial enhancement is very often present, but the "wash out" in the portal or late phase can sometimes be not very evident, making the diagnosis of HCC difficult. The diagnosis of cholangiocarcinoma is usually difficult with CEUS; published data showed that the accuracy of CEUS for the characterization of cholangiocarcinoma was only 57% in one study [8] and 57.9% in the DEGUM study [3].

A recently published multinational study [9] included 134 patients with one FLL detected in baseline ultrasound (US). Second line imaging methods included CEUS (n=134), contrast-enhanced CT (n=115) and/or dynamic contrast-enhanced MRI (n=70). Compared to CT and/or dynamic MRI, CEUS for characterization of FLL was 30.2% more sensitive in the recognition of malignancy and 16.1% more specific in the exclusion of malignancy and overall 22.9% more accurate. Also in our study, CEUS proved to be a very useful method that allowed the differentiation between benign or malignant FLL, with only 10% of unsuccessful examinations.

In a study performed in 11 centers in China [8], a group of 148 patients, with 164 lesions, was evaluated. The final diagnosis in malignant lesions was based on the gold standard, liver biopsy, in 129/164 cases. The evaluation of CEUS diagnostic performance versus the gold standard, showed that CEUS accuracy (88%) was markedly higher than that of fundamental ultrasound (41%) ($p<0.01$).

The same good results were obtained in the Chinese study regarding lesion type characterization. Among benign lesions, the concordance of fundamental ultrasound with the gold standards for hemangiomas was 43%, while after CEUS it increased to 93%. Among malignant lesions, the concordance in the diagnosis of HCC increased from 48% with fundamental ultrasound to 95% after SonoVue® administration. For metastases, the concordance improved from 50% with unenhanced ultrasound to 91% with contrast US.

In a large study, that included 452 patients with 452 undetermined lesions by baseline US, Quaia *et al* [10] reported that the diagnostic accuracy for FLL characterization increased from 49% at baseline US examination to 85% after CEUS. After contrast, the sensitivity and specificity increased from 53% and 41% to 83% and 95%, respectively.

In another study [11] on 126 lesions in 124 patients with FLL detected by baseline US, CEUS examination was able to improve the sensitivity from 78% to 100% and the specificity from 23% to 92%.

All these studies are clearly in favor of CEUS as compared to standard US for the characterization of FLL, increasing the sensitivity and specificity of the ultrasound method. On the other hand, other studies, such as the one performed by Trillaud *et al* [9], showed that CEUS is the best imaging method for the characterization of FLL.

But CEUS has some limitations: the acoustic window for liver visualization must be very good (sometimes the examination of the cirrhotic liver can be very difficult or impossible); also, the hepatic lesion must be well seen in standard US in order to be able to perform CEUS evaluation. On the other hand, if more than one lesion is present in the liver, a new injection of contrast agent is needed for their characterization in every vascular phase (especially on a cirrhotic liver). Thus, we must underline that in real life not all FLL can be evaluated by CEUS, only those that are well seen by standard ultrasound. In daily practice, especially in Europe, FLL are usually discovered at baseline US and evaluated at a later time by means of CEUS.

The real value of CEUS for FLL characterization was demonstrated in well known multicentre studies performed in Germany and France, each one including more than 1000 lesions. The German study [3] included 1,349 patients with FLL discovered in standard US that could not be characterized by standard US alone, and in which CEUS was compared with a diagnostic "gold standard": biopsy in more than 75% of the lesions, spiral contrast CT or contrast MRI in the rest of the cases. In this study, the diagnostic accuracy of CEUS for the diagnosis of FLL was 90.3%. CEUS correctly characterized 723/755 of the malignant lesions and 476/573 of the benign lesions, with 95.8% sensitivity and 83.1% specificity with 95.4% PPV and 95.9% NPV for differentiating benign vs. malignant lesions. Regarding the ability of CEUS in diagnosing different types of lesions, CEUS correctly diagnosed 82.2% of the hemangiomas, 87.1% of the focal nodular hyperplasias (FNHs), 57.9% of the adenomas, 84.9% of the HCCs and 91.4% of the metastases. Thus CEUS proved to be a sensitive method for the diagnosis of liver metastases and HCCs, but less sensitive for the diagnosis of adenoma.

Another study based on the DEGUM multicentre

study assessed the value of tumor-specific vascularization pattern [12] such as: a wheel-spoke pattern and arterial hyperenhancement followed by isoenhancement in the late phase in FNH, or a nodular peripheral enhancement and partial or complete fill-in pattern in hemangiomas, or late phase hypoenhancement in metastases. The tumor-specific vascularization pattern could be assessed in the majority of cases, but not in all, so that the diagnostic accuracy of CEUS was 83.1 % for all benign lesions, 95.8 % for all malignant lesions and 91.4 % for liver metastases and 84.9 % for hepatocellular carcinomas.

Another very well known study, the multicentre French study (STIC) [4] included 874 patients with 1034 FLL. CEUS was compared to contrast spiral CT, contrast MRI or liver biopsy, considered to be the "gold standard". Standard US correctly diagnosed 62.4% of the cases, while CEUS increased the diagnostic performance to 86.1%. The diagnostic concordance between CEUS and the gold standard method was 73% (kappa=0.67), better for FLL on non-cirrhotic liver (73.5%, kappa=0.66), than in nodules on cirrhotic liver (71.8%, kappa=0.42). For differentiating between benign vs. malignant, CEUS had 79% sensitivity and 88% specificity.

In a study [5] on a subgroup of patients from the DEGUM multicentre study, CEUS was compared to standardized spiral-CT (SCT). From the 267 patients, histological findings were available in 158 subjects. In this subgroup assessment of tumor differentiation with CEUS and SCT was concordant in 124 cases and discordant in 30 cases (CEUS/SCT: sensitivity 94/90.7%, specificity 83/81.5%, PPV 91.6/91.5%, NPV 87.5/80%, accuracy 90.3/87.8%). A statistically significant difference could not be established. The analysis of particular tumor specification showed a statistically non significant slight advantage in tumor differentiation for CEUS in the case of hemangioma, FNH, HCC and metastases. But we must bear in mind that CT is a method that exposes subjects to radiation and that CEUS is a very safe method (a study retrospectively analyzed 23,188 abdominal CEUS studies and reported only 29 adverse events, of which only two were graded as serious; the overall reporting rate of serious adverse events was 0.0086%, with no fatal outcome) [13].

In a recently published study [14], also on a subgroup of patients from the DEGUM multicentre study, CEUS was compared to contrast MRI. The study included 262 patients with FLL. In this study, there were no statistically proven differences between the results in CEUS and MRI evaluation.

The task of our study was to show the real value of CEUS in daily practice, concerning the final diagnosis of a FLL (when typical CEUS aspect is obtained), and this was obtained in 82% of cases. On the other hand we found that the results can differ significantly between centers (77.1% vs 92.8%; $p<0.0001$), and this may be due to the different protocols used for diagnosis, to the quality of the ultrasound machine and possibly, to the experience of the center or of the examiner [15]. The same significant differences were found between the performances of these two centers for the differentiation between benign and malignant FLL (88.7% vs. 95.5%; $p=0.0032$).

Regarding the financial analysis of the use of CEUS as the first step for the evaluation of a new FLL discovered by US, there are some published data that showed that CEUS is also a cost-effective method. In the French multicentre study [16], the cost for CEUS evaluation was 155.2 Euros, for multislice contrast CT it was 191.65 Euros and for contrast MRI it was 322.3 Euros, one of the conclusions of this study being that MRI investigation doubles the cost of a FLL evaluation. Also, an Italian multicentre study [17], that included 485 subjects with 575 lesions, compared the costs of a classic patient work-up (which included baseline US followed by contrast CT or MRI) to a new scheme in which, following the baseline US, a CEUS examination was performed, in which the total savings were 162 Euros/patient. A study published by Giesl [18] who conducted a cost-minimization analysis of CEUS as compared to multi-phase computed tomography (M-CT) as the diagnostic standard for diagnosing incidental liver lesions, concluded that CEUS was the more cost-effective method in all scenarios in which CEUS examinations were performed at specialized centers (122.18-186.53 Euros) as compared to M-CT (223.19 Euros).

Conclusion

In our study, CEUS was conclusive for the diagnosis in 82% of the FLL and the benign or malignant character of a lesion was demonstrated in approximately 91% of cases. Thus, when faced with an uncharacteristic FLL on standard ultrasound examination, our local strategy is to perform CEUS as a first-line investigation (thus avoiding other expensive examinations) and only in unclear cases to perform contrast enhanced CT or MRI (or liver biopsy). CEUS is an adequate method for the characterization of FLL. As compared to contrast CT and MRI, CEUS has the advantage of being safe (extremely rare allergic side effects, no radiation), well tolerated by the patient, less expensive and sometimes, available at the time of the initial ultrasound detection of FLL.

Conflict of interest: none

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