

How Useful is Contrast Enhanced Ultrasonography for the Characterization of Focal Liver Lesions?

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Abstract

Aim: Focal liver lesions (FLLs) are quite frequently discovered in daily practice at routine ultrasound. The aim of our study is to present a single centre experience concerning the use of contrast enhanced ultrasound (CEUS) in the characterization of FLL and to find when one can avoid using other expensive imaging modalities such as contrast enhanced CT or MRI. **Method:** We performed a prospective, single centre study during September 2009 - April 2010, and we evaluated 379 FLLs. A CEUS examination was considered conclusive if the FLL had a typical enhancement pattern according to the EFSUMB guidelines. **Results:** From the 379 cases with FLL, 198 (52.2%) were patients without known liver disease and 181 (47.8%) with known chronic liver disease (156 had cirrhosis, 25 chronic hepatitis); in 296/379 cases (78.1%) CEUS was conclusive. CEUS allowed the positive diagnosis of benign vs. malignant lesion in 261/294 (88.8%) de novo FLLs (CEUS performed for the first time), while in 33 (11.2%) cases it was inconclusive and could not differentiate between benign or malignant lesions. The CEUS results included 129 (49.4%) benign lesions and 132 (50.6%) malignant. **Conclusion:** CEUS was conclusive in approximately 80% of the FLLs and the benign or malignant character of a lesion was demonstrated in about 90% 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.

Key words

Contrast enhanced ultrasound – focal liver lesions
– contrast agent – liver cirrhosis.

Introduction

Focal Liver Lesions (FLLs) 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 programs for patients with liver cirrhosis, FLLs are discovered 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 US (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 imaging method (contrast CT or MRI). On the other hand, this increases the medical costs in these patients, since both contrast CT and MRI are expensive imaging methods – the local prices in Timisoara for CT and MRI are 70 and 155 Euros, respectively, while for CEUS, the price calculated as the cost of 1/2 vial of SonoVue + the cost of abdominal US is about 45 Euros. Another advantage of CEUS evaluation of FLL is that it can be performed immediately after the standard abdominal US, so that in about 5 minutes (the total duration of this investigation) a confident diagnosis can be obtained.

The European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) issued the first Guidelines regarding the use of CEUS in 2004 [1], revised in 2008 [2], presenting the main indications of this method. 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] compared CEUS to the liver biopsy, and the second, performed by the French Society of Ultrasound, compared CEUS to contrast CT or MRI and/or liver biopsy considered to be the “gold standard” [4].

Considering all these data, the questions that arise are how useful is CEUS in daily practice for the evaluation of FLL, and if, by using this method, we can decrease the

Received: 13.06.2010 Accepted: 16.09.2010

J Gastrointest Liver Dis

December 2010 Vol.19 No 4, 393-398

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medical costs for the diagnosis, knowing also that CT scan exposes the patients to possibly harmful radiation.

The aim of our study is to present a single centre experience regarding the use of CEUS for the characterization of FLL, and to find when we can avoid using more expensive diagnostic methods such as contrast enhanced CT or MRI for their diagnosis.

Material and method

We performed a prospective, single centre study during a seven month period (September 2009 - April 2010). All the patients with FLL evaluated in the Ultrasound Laboratory from the Department of Gastroenterology and Hepatology, University of Medicine and Pharmacy Timișoara (a tertiary centre with experience in the diagnosis and percutaneous treatment of hepatocellular carcinoma - HCC) were included in the study. In all the cases in which standard US was not sufficient for diagnosis, we performed CEUS according to the EFSUMB Guidelines [2]. Following CEUS, we divided the patients in two groups: one in whom CEUS evaluation was conclusive and no other diagnostic methods were required; and another one in which CEUS was inconclusive and other diagnostic methods were performed (contrast CT or MRI, or biopsy of the lesions). We also divided our patients into patients without diffuse hepatic disease (excluded using clinical, biological, US and elastographic criteria - transient elastography - TE) and patients with chronic hepatopathy (liver cirrhosis or chronic hepatitis).

Exclusion criteria for performing CEUS were: pregnant women and subjects with acute cardiac infarction, with class III/IV cardiac failure or arrhythmias. 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, for four hours after the procedure. The clinical status, blood pressure and heart rate were followed-up.

Four experienced ultrasonographers, who were aware of the patients' clinical histories, performed US scanning by means of a Siemens Acuson S2000TM Ultrasound System with a 3.5 MHz convex array probe. A baseline survey examination, including a color/power Doppler analysis, was performed. Once set, the US scan parameters - such as focal zone and time gain compensation - were not changed throughout the study. A low frame rate (5 Hz) and a very low mechanical index (MI), < 0.08, were used for real-time imaging. Cadence™ Contrast Pulse Sequencing Technology was used for the contrast study, software versions 1.5A and 1.6B. One focus was positioned below the level of the lesion. Each examination lasted about 5 min after bolus injection. The US contrast agent used in the present study was SonoVue® (Bracco, Italy), a perfluoro gas containing agent, provided as a sterile, lyophilized powder contained in a septum-sealed vial. A white, milky suspension of sulphur hexafluoride (SF₆) microbubbles was obtained by adding 5 ml of physiological saline (0.9% sodium chloride) to the powder (25 mg), followed by hand agitation. Each patient received an i.v. bolus of SonoVue® for each lesion to be

characterized (usually 2.4 ml) via a 20-gauge i.v. catheter placed in the ante-cubital vein, 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 (hypo-, hyper-, iso-enhancing), as compared with the adjacent liver parenchyma during the arterial, portal venous and late phases were evaluated. The spatio-temporal pattern of the lesions' filling was also assessed in the arterial phase.

Ultrasound diagnosis, in terms of the nature (malignant or benign) and type of the lesion (hemangiomas, focal nodular hyperplasia - FNH, HCC or metastases) was based on SonoVue® enhanced US. The number, location, size and characteristics of the lesions were recorded. Two experienced physicians (level II or III in the EFSUMB classification: www.efsumb.org) evaluated all the SonoVue® enhanced images, formulating a final diagnosis.

A CEUS examination was considered conclusive if, following contrast administration, the FLL had a typical enhancement pattern according to the EFSUMB guidelines [2], and inconclusive if the enhancement pattern of the lesions was not in concordance with this guide.

Results

During the study period, 379 FLLs were evaluated: 198 (52.2%) in patients without known hepatic disease and 181 FLL (47.7%) in patients with known chronic hepatic diseases (156 with liver cirrhosis and 25 with chronic hepatitis). CEUS was conclusive in 157/198 cases (79.3%) without liver disease and in 139/181 (76.8%) patients with chronic hepatopathies. Overall, CEUS was conclusive in 296/379 (78.1%) cases, and inconclusive in 83 (21.9%) cases.

From the 379 evaluations, in 294 cases CEUS was performed for de novo FLL (141 women - 48% and 153 men - 52%, mean age 57.4, ranges 23 to 86 years). Out of the 294 cases, in 214 (72.8%) CEUS established a positive diagnosis, while for the rest of 80 cases (27.2%) the examination was not conclusive. In 261 cases (88.8%), CEUS allowed the differential diagnosis of benign vs. malignant, while in 33 (12.2%) cases it was not conclusive (Fig. 1). The conclusive results of CEUS included 129 (49.4%) benign and 132 (50.6%) malignant lesions.

The final diagnosis obtained by CEUS in noncirrhotic patients was: metastasis - 70 cases; hemangiomas in 46 cases (Fig. 1abc); focal nodular hyperplasia in 9 cases; fatty liver alterations in 21 patients (focal fatty infiltration in 3 cases and fatty-free areas - 18 cases); complex biliary cysts - 10 cases; complex hydatid cysts - 5 cases; adenomas - 6 cases; abscess - 1 case; hematoma - 1 case (Fig. 2).

Out of the 156 FLLs evaluated in cirrhotic patients, 102 were de novo lesions, the rest detected during the follow-up of percutaneously treated HCCs. Out of the de novo

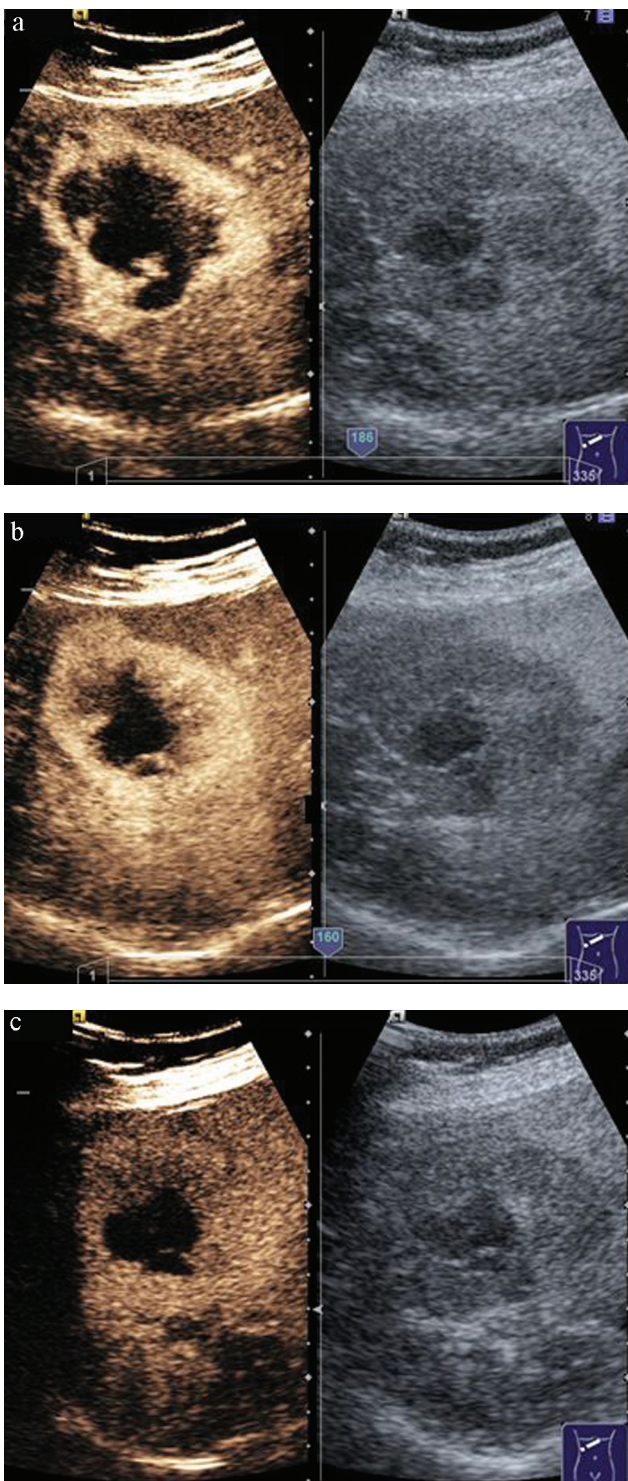


Fig 1. CEUS enhancement pattern of a hemangioma: a) arterial phase - peripheral, nodular enhancement; b) portal phase – peripheral, nodular hyperenhancement with a non-enhanced central area due to necrosis; c) late phase - peripheral, nodular hyperenhancement with a non-enhanced central area due to necrosis.

FLLs in cirrhotic patients, 82 were HCCs (Fig. 3 abc); 9 were regenerative nodules; 5 were metastases; 3 were hemangiomas; 2 were focal fatty infiltration and one was a liver abscess.

From the 83 inconclusive CEUS cases, the final diagnosis

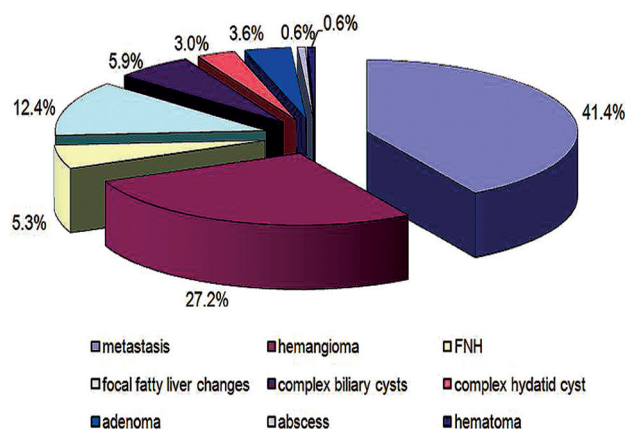


Fig 2. The final diagnoses obtained by CEUS in noncirrhotic patients.

was made by means of contrast CT in 26 cases, contrast MRI in 42 cases and biopsy in 2 cases, 13 cases being lost to follow-up (Fig.4).

Discussion

The place of CEUS in the diagnostic algorithm of FLL is not very well established. The EFSUMB Guidelines [1, 2] formulated some indications regarding the use of this method, but several studies [3-7] demonstrated the real practical value of this method. On the other hand, despite the effervescence of this method in Europe (and partially in Asia and Canada), there are some regions (such as the USA) in which second generation US contrast agents are not yet licensed.

We made this prospective single centre study in order to evaluate the relevance of this method for daily practice in Romania. In our study, for patients with new FLL discovered by US we could perform immediately CEUS, in the same session, and we were able to obtain the diagnosis in about 80% of cases. Thus, only 1/5 of the patients required a second line imaging technique evaluation (multislice contrast enhanced CT or contrast enhanced MRI). On the other hand, using the same US machine (Siemens Acuson S2000), we had the opportunity to immediately perform real time Acoustic Radiation Force Impulse Elastography (ARFI), thus assessing the severity of liver fibrosis. This could be useful for the differential diagnosis, because solid liver lesions in cirrhosis have a high probability for being HCCs, and ARFI has been proved to be a very good non-invasive method for the prediction of severe fibrosis and cirrhosis [8-10].

In our study, we divided the patients in: patients without chronic hepatopathies - in whom CEUS provided a conclusive diagnosis in 79.3% cases - and patients with liver cirrhosis / advanced fibrosis - in whom we obtained conclusive CEUS diagnosis in 76.8% of cases. In both categories we had some difficult cases. In those without hepatopathies, it is sometimes difficult to formulate a correct diagnosis of hepatic adenoma (differential diagnosis with focal nodular hyperplasia - FNH) [11]. On the other hand,

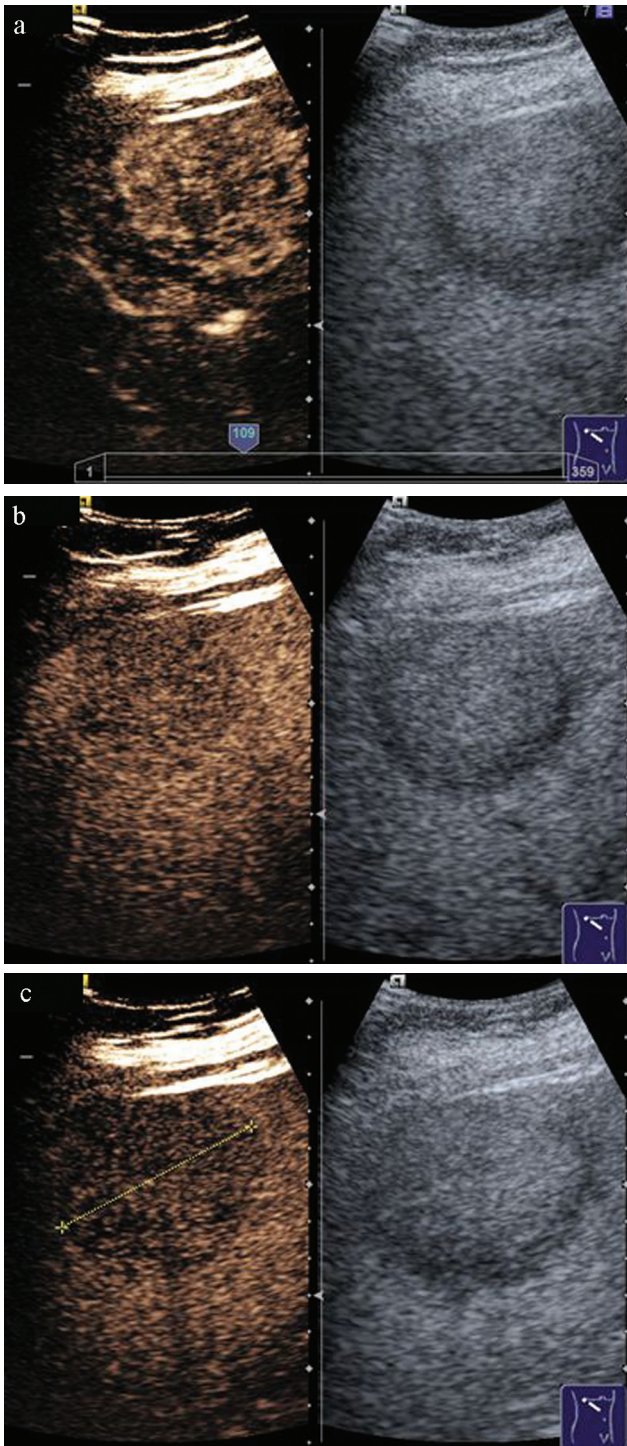


Fig 3. CEUS enhancement pattern in HCC: a) arterial phase – hyperenhancing; b) portal phase – wash-out; c) hypoenhancing in the late phase.

it was shown that the sensitivity and specificity 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% [11]. Also, the sensitivity and specificity of CEUS for the diagnosis of FNH and hemangioma were 100% and 87%, resulting in an accuracy of 94.5% [12].

In patients with liver cirrhosis or advanced fibrosis,

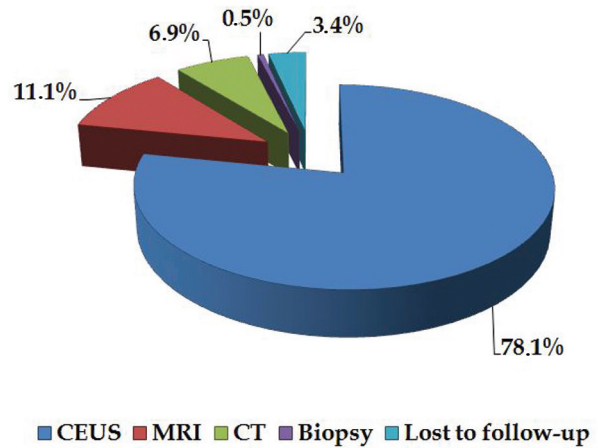


Fig 4. Method by which the final diagnosis was established in our series.

we had difficulties in the CEUS diagnosis for some HCCs (usually small or undifferentiated), as well as for the diagnosis of cholangiocarcinoma. Published studies showed that the accuracy of CEUS for the characterization of cholangiocarcinoma was only 57% [11].

A very recently published multinational study [12] included 134 patients with one FLL detected by baseline US. Second line imaging methods included CEUS (n=134), contrast-enhanced CT (n=115) and/or dynamic contrast-enhanced MRI (n=70). In comparison with CT and/or dynamic MRI, CEUS for characterization of FLL was with 30.2% more sensitive in the recognition of malignancy and 16.1% more specific in the exclusion of malignancy, overall with 22.9% more accurate. In our study, CEUS also allowed the differentiation between benign or malignant FLL, with only 10% unsuccessful examinations.

In a study performed in 11 centers from China [11], 148 patients with 164 lesions were evaluated. The final diagnosis of malignant lesions was based on the gold standard, i.e. liver biopsy (129/164). The evaluation of CEUS diagnostic performance versus the gold standard showed that CEUS accuracy (88%) was markedly higher than that of the fundamental method (41%) (p<0.01). The specificity and sensitivity of SonoVue® were also higher than those of the fundamental method (p<0.01). Good results were obtained for lesion type characterization. Among benign lesions, the concordance of standard imaging with the gold standard 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 standard imaging to 95% after SonoVue® administration. For metastases, the concordance improved from 50% with unenhanced imaging to 91% with CEUS.

In a very large study that included 452 patients with 452 undetermined lesions by baseline US, Quaia et al [13] reported that the diagnostic accuracy for FLLs characterization increased from 49% at baseline US to 85% after CEUS. After contrast, the sensitivity and specificity increased from 53% and 41% to 83% and 95%, respectively.

In another study [14] on 126 lesions detected by baseline US in 124 patients, 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 in comparison with standard US for the characterization of FLL, increasing the sensitivity and specificity of the US method. Other studies showed that CEUS is the best imaging method for FLL characterization [12].

However, 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 a 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 time (especially in a cirrhotic liver).

The real value of CEUS for FLL characterization was demonstrated in multicentre studies performed in Germany and France, each one including more than 1,000 lesions. The German study [3] included 1,349 patients with FLLs discovered in standard US that could not be characterized by standard US alone, and in whom 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 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. CEUS correctly diagnosed 82.2% of the hemangiomas, 87.1% of the 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 of the DEGUM assessed the value of the tumor-specific vascularization pattern [15]: a wheel-spoke pattern and arterial hyper-enhancement followed by iso-enhancement 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 most, but not in all cases, so that the diagnostic accuracy of CEUS was 83.1% for benign lesions, 95.8% for malignant lesions 91.4% for liver metastases and 84.9% for HCCs.

The multicentre French study (STIC) [4] included 874 patients with 1,034 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 FLLs in non-cirrhotic liver (73.5%, $\kappa=0.66$), than for nodules in cirrhotic liver (71.8%, $\kappa=0.42$). For

differentiating between benign and malignant lesions, CEUS had 79% sensitivity and 88% specificity.

In a subgroup of 267 patients from the DEGUM multicentre study [5], histological findings were available in 158 subjects. In this subgroup assessment of tumor differentiation with CEUS and spiral CT was concordant in 124 cases and discordant in 30 cases (CEUS/spiral CT: sensitivity 94/90.7%, specificity 83/81.5%, PPV 91.6/91.5%, NPV 87.5/80%, accuracy 90.3/87.8%). A significant difference could not be established. The analysis of particular tumor specification showed a non significant slight advantage in tumor differentiation for CEUS in the case of hemangioma, FNH, HCC and metastases.

In another subgroup of patients from the DEGUM study [16], CEUS was compared to contrast MRI. The final diagnosis in typical liver hemangioma and FNH was based on the MRI as the “diagnostic gold standard”, on clinical evidence and additional follow-up (180 patients) or on histology (82 patients). Tumor differentiation was concordant in 56 (68.3%) and tumor entity in 44 cases (53.7%). There were no statistical differences between CEUS and MRI.

Some financial analyses of the CEUS use as the first step for the evaluation of a new FLL discovered by US showed that CEUS is also a cost-effective method. In the French study [17], in which the diagnosis costs of 149 nodules with liver biopsy as the gold standard for diagnosis were evaluated, the total savings were 128 Euros/nodule (the mean CEUS cost 155 Euros, multi-slice contrast CT 192 Euros, contrast MRI 322 Euros). Also, an Italian multicentre study [18] compared the costs of a classic patient work-up (baseline US followed by contrast CT or MRI with a total cost of 135 Euros) to a new scheme in which, following the baseline US, a CEUS examination was performed (total cost was 56 Euros). The savings were 79 Euros/patient. A cost-minimization analysis of CEUS as compared to multi-phase computed tomography (M-CT) as the diagnostic standard for diagnosing incidental liver lesions [19] concluded that CEUS was the more cost-effective method in all scenarios in which CEUS examinations were performed at specialized centers as compared to M-CT.

Regarding the safety profile of SonoVue®, retrospective analysis of 23,188 abdominal CEUS examinations reported 29 adverse events (AEs), of which only two were graded as serious. The overall reporting rate of serious AEs was 0.0086% with no fatal events [20]. A Dutch study reviewed 352 consecutive cardiac SonoVue studies, and revealed that 2.0% of the patients experienced AEs, mild allergic reactions in 1.1% of the cases and severe allergic reaction resulting in nonfatal shock in 0.9% of the cases [21], higher incidence than that reported in the post-marketing surveillance studies, in which 19 non-fatal severe (0.01%) and 3 fatal (0.002%) complications were reported in 157,838 patients. In our study no AE were encountered following the injection of SonoVue®.

Our study had some advantages: it was a single centre one (homogeneous examining team); we wanted to see if CEUS

was conclusive or not for the diagnosis by using only well established CEUS patterns for different types of lesions, and we found out that CEUS was conclusive in 80% of cases (irrespective if the patient did or did not have cirrhosis); and we also demonstrated that CEUS can differentiate between benign vs. malignant lesions in 90% of the cases.

Conclusion

Contrast Enhanced US is an adequate method for the characterization of FLL. As compared to contrast CT and MRI, CEUS has the advantage of being safe, well tolerated by the patient, less expensive and, sometimes, available at the time of the initial detection of FLL. In our study, CEUS was conclusive in 80% of the FLLs and was able to differentiate between benign or malignant lesions in approximately 90% of the cases. Therefore, our local strategy when faced with a newly discovered FLL, not characteristic in standard US, is to use CEUS as the first line investigation thus avoiding other expensive examinations. In non conclusive CEUS evaluations, further imaging or morphological examination are required for the final diagnosis.

Conflicts of interest

None to declare.

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