Is Contrast Enhanced Ultrasound (CEUS) ready for use in daily practice for evaluation of Focal Liver Lesions?

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Abstract

Abdominal ultrasound is one of the most popular imaging methods due to its feasibility, low cost and accessibility. Contrast Enhanced Ultrasound (CEUS) with second generation contrast agents became in the last years a useful tool for the characterization of focal liver lesions (FLL) so that EFSUMB issued guidelines for its use in clinical practice. Several large studies proved that CEUS has similar performance to more expensive imaging methods such as contrast enhanced CT and contrast enhanced MRI for the characterization of FLL. Also, several studies proved that CEUS is cost-effective as a first-line imaging method. Considering all these data, we think that CEUS is ready to be used in daily practice for the evaluation of FLL.

Keywords: contrast enhanced ultrasound, focal liver lesions, clinical practice, cost-effective

Abdominal ultrasound became the most popular imaging method due to its feasibility, low cost and accessibility. Ultrasound machines are better every day, a lot of image improvements becoming available in most devices (color Doppler, Power Doppler, or THI). Regarding the individuals who should perform ultrasound, they can be either radiologists (practice more common in Anglo-Saxon countries), or clinicians (gastroenterologists, urologists, internal medicine specialists, etc). Clinical ultrasound or “point of care” ultrasound [1] is a common practice for a long time in a part of Europe (Germany, Italy or Romania) and was recently “rediscovered” in the United States [2].

Since such a huge number of abdominal ultrasound examinations are performed in daily practice (either by clinicians or by radiologists), during which the liver structure should always be evaluated, a large number of focal liver lesions (FLL) are discovered. Some of them are the so called “incidentalomas” (incidental discovered lesions in asymptomatic subjects); others are lesions in patients known with chronic diseases (liver cirrhosis or oncologic patients). But, even if standard (grey scale) ultrasound is a sensitive method for the visualization of such lesions, it has low accuracy for their characterization.

In the last period, the use of Contrast Enhanced Ultrasound (CEUS) with second generation contrast agents (“bubbles”) became a useful tool for the characterization of FLL. The evaluation time with CEUS is 4-5 minutes, and the conclusion can be drawn immediately after the examination. In 2004 the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) issued the first Guidelines concerning the use of contrast agents for the evaluation of FLL [3], which were updated in 2008 [4] and in 2012 [5]. The latest EFSUMB Guidelines [5], reflect a common point of view with the World Federation of Ultrasound in Medicine and Biology (WFUMB) (with the exception of USA, where second generation contrast agents are not approved by FDA).

Considering that CEUS has been proven to be an accurate method for FLL evaluation [and in the same time

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To assess the usefulness of CEUS for FLL characterization. The first two meta-analyses originated from Germany (DEGUM study) and France (STIC study), each one including more than 1000 lesions.

The German study [6] included 1,349 patients with FLL that could not be characterized by standard US alone. For each FLL analyzed, a diagnostic “gold standard” was available: biopsy in more than 75% of the lesions, CE-CT or CE-MRI in the rest of the cases. There were 575 malignant tumors; 62.3% of them incidentally discovered lesions, 17.3% discovered during the follow-up of patients with known liver cirrhosis and 27.0% in the follow-up of patients with known hepatocellular tumor. The overall accuracy of CEUS for the diagnosis of FLL was 90.3%. CEUS had 95.8% sensitivity and 83.1% specificity, with 95.4% positive predictive value (PPV) and 95.9% negative predictive value (NPV) for differentiating benign vs. malignant lesions.

Regarding the ability of CEUS to characterize 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 hepatocellular carcinomas (HCCs) and 91.4% of the metastases.

The French multicentre study (STIC) [7] included 874 patients with 1034 FLL. In this study also, CEUS was compared to a reference method: CE-CT, CE-MRI or live biopsy. 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 reference method was 73% (kappa=0.67), better for FLL on non-cirrhotic liver (75.3%, kappa=0.66), than in nodules on cirrhotic liver (71.8%, kappa=0.42). CEUS had 79% accuracy for differentiating between benign vs. malignant FLLs. The diagnostic concordance between the most frequent FLL (hemangioma, FNH, metastases and HCC), the sensitivities were 85.4%, 82.5%, 79% and 94.7% respectively.

Sub-analyses were performed starting from the DEGUM study, considering some important and interesting issues. In such a study [8], the accuracy of CEUS was compared to CE-CT considering live biopsy as the reference method. The tumor assessment of differentiation between benign and CEUS was concordant in 124/158 cases (78.8%) with sensitivity 90.7%, specificity 98%, PPV 95.7% and NPV 90.5%, and for CE-CT: sensitivity 94.0/90,7%, specificity 83.0/81.5%, PPV 91.6/91.5%, NPV 87.5/80.0%, accuracy 90.3/87.8%. A statistically significant difference regarding the accuracy of CEUS vs. CE-CT could not be established. If specific tumors such as hemangiomas, FNH, HCC and metastases were analyzed, a statistically non significant slight advantage in tumor differentiation was found for CEUS.

In another sub-analysis [9] on a subgroup of patients from these NGU multicentre studies, national data were compared to contrast MRI in 262 patients, in which the reference method was considered to be either CE-MRI for typical hemangioma and FNH, or clinical evidence and additional follow-up (180 patients) or histology (82 patients). The subgroup in which biopsy was performed included mainly malignant lesions (55 cases), with 8 hemangiomas and 5 FNHs. Tumor differentiation was concor-dance in 56 cases and tumor entity in 44 cases (53.7%). Again there were no statistically significant differences between CEUS and MRI.

An advantage of CEUS is the possibility to dynamically evaluate the vascular pattern during the arterial, venous and late phases, thus allowing an accurate diagnosis in typical FLLs. Another study derived from the DEGUM multicentre study assessed the value of specific vascularization pattern in CEUS [10]. The patterns evaluated were: a: spoke-wheel filling and arterial hyperen- hancement followed by isoenhancement in the late phase in FNH; b: portal peripheral enhancement and partial or complete fill-in pattern in hemangiomas; portal and late phase hyperenhancement in metastases. Considering these typical vascular patterns, the diagnostic accuracy of CEUS was 83.1% for all benign lesions, 95.8% for all malignant ones, 91.4% for liver metastases and 84.9% for hepatocellular carcinomas.

In Romania we have one of the largest experiences regarding CEUS (data in press). In a prospective study performed in 14 centers from Romania, between Feb-ruary 2011 and June 2012, patients diagnosed with one to three de novo FLLs on B-mode ultrasound were evaluated with CEUS and FNH, HCC. A reference method was available: CE-CT, CE-MRI or biopsy. FLLs were characterized during CEUS according to the EFSUMB Guidelines. For statistical analysis, indeterminate FLLs were considered as false classifications. A total num-ber of 536 cases were included in the final analysis, 344 malignant (64.2%) and 192 benign lesions (35.8%). The reference method was: CE-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% cases and inconclusive in 10.7%. To differenti-ate between malignant and benign metastases, CEUS had 85.7% sensitivity, 95.6 specificity, 95.7% PPV and 85.8% accuracy. In this study, CEUS accuracy for differentiation between malignant and benign liver lesions was similar in tumors smaller than 2 cm vs. those with the diameter larger than 2 cm. The conclusion of this study was that, in clinical practice, CEUS is highly useful as a first line method for differentiating between malignant and benign metastases, in concordance with the previous multicenter studies: DEGUM (Germany) and STIC (France) [6,7].

Our answer is most certainly yes, and as an argument we present a few large studies that proved the usefulness of CEUS for FLL characterization. The first two meta-analyses included mainly malignant lesions (55 cases), with 8 hemangiomas and 5 FNHs. Tumor differentiation was concordant in 56 cases and tumor entity in 44 cases (53.7%). Again there were no statistically significant differences between CEUS and MRI.

The total savings were 128.5 Euros/nodule (considering as the mean cost CEUS 152.5 Euros; CE-CT 191.65 Euros; and of CE-MRI 322.3 Euros). In a German study [11] a cost-minimization analysis of CEUS as compared to CE-CT as the diagnostic standard for diagnosing incidental FLLs was conducted. The conclusion was that CEUS was more cost-effective method in all scenarios in which CEUS were performed at specialized centers (122.18-186.53 Euros) as compared to CE-CT (223.19 Euros). In an Italian multicentre study [15] that included 485 subjects with 573 lesions, the total savings were 78,902 Euros, or 162 Euros/patient, if the classic patient work-up (baseline US followed by CE-CT or CE-MRI) was replaced by a new strategy in which baseline US was performed by CEUS. Data from a Romanian study also demonstrated that CEUS as the first line of diagnosis for FLL was the most cost-effective, with total savings of approximately 4,000 Euros as compared to CE-CT and approximately 24,900 Euros as compared to CE-MRI as first line imaging method for the characterization of 316 FLL [16].

Recently, a recently published systematic review [17] concluded that CEUS is a cost-effective replacement for CE-MRI also. CEUS was considered cost-effective as compared to CE-CT in the surveillance of cirrhosis and for the characterization of incidentally detected FLLs with similar costs and effects for the detection of liver metastases secondary to colorectal carcinoma. Another important conclusion of this study was that CEUS had similar performance to CE-CT and CE-MRI for FLLs characterization.

Thus, considering the results of multicenter national experiences, of a large monocentric experience and of two recent meta-analyses (of CEUS as compared with other sectional imaging methods), we can conclude that in this moment CEUS is ready to be used in daily practice as a first line diagnostic method for incidentally discovered FLLs in standard abdominal ultrasound. In inconclusive cases, CE-CT/ MRI or echoguided biopsy should be used for the final diagnosis.
References