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Poor contrast enhanced ultrasonography! There is no limit to its decline in the diagnosis of hepatocellular carcinoma on cirrhosis!

To the Editor

We have read with great interest the article by Forner and co-workers, who described the use of contrast-enhanced ultrasound (CEUS) to define the priority for diagnostic work-up of hepatocellular carcinoma (HCC) nodules <2 cm arising in cirrhotic livers during ultrasound (US) surveillance [1].

Nevertheless we would like to make some criticism

In their prospective study carried out from 2003 to 2011, the authors state that fine needle biopsy (FNB) result was considered the gold standard for diagnosis of HCC, but that after 2007, they considered only enhanced MRI result as gold standard, as priory validated. Our question to the authors is why did they not continue to perform FNB to diagnose HCC nodules? It seems to us methodologically incorrect to change the diagnostic method during the study. Maybe MRI has 100% specificity in diagnosing HCC? As far as we know, in a recent meta-analysis comparing CEUS and enhanced MRI for diagnosis of HCC [2], including only patients diagnosed with percutaneous biopsy [3,4], CEUS showed a statistically better specificity than MRI in the pair-wise comparisons (0.86 *vs.* 0.78; $p = 0.014$), and a statistically better sensitivity than computed tomography [(CT) 0.88 *vs.* 0.78; $p = 0.030$] [2]. In addition, in a recent work, the specificity of CEUS plus CT and/or MRI was significantly higher than the specificity of CT and/or MRI, CEUS, or intraoperative ultrasound [(IOUS) $p = 0.004$, $p = 0.002$, and $p = 0.002$, respectively]. The diagnostic accuracy of CEUS plus CT/MRI was higher than that of CT/MRI ($p = 0.001$) [5].

Furthermore, in a specific section, the authors state that FNB was performed using a 20 G spinal needle, and state that, when "technically feasible because of location and accessibility, a core biopsy was performed using a 18 G needle biopsy". From histology, there were 3 intrahepatic cholangiocarcinomas (ICCs) and 35 regenerating nodules or dysplastic nodules and 1 neuroendocrine tumor. It is evident that diagnosis of ICC and dysplastic nodules can be made only using histology. Another question arises: were all ICCs and dysplastic nodules and metastasis of endocrine tumors located in a "feasible and accessible location" in the liver? It seems improbable to us. Moreover, it is probably incorrect to use the term FNB when two different needles are used for performing biopsies, since the 18 G needle is not definable as "fine", as it is >1 mm.

In addition, 3% of cases (5 cases) of US detected nodules were not evaluable with CEUS examination. Four out of 5 of them were HCC. This is quite interesting, and it would be useful to know if all nodules were located in a deep position, since they had been normally detected with conventional US. It would be also interesting to know if any MRI resulted unfeasible in the study.

Finally, in the results section, authors reported that 10/18 (55.6%) CEUS un-enhanced patients with final diagnosis of HCC, experienced tumor recurrence after treatment (4 resections and 14 ablations), "confirming their overt malignant profile": how

can authors state that recurrence is due to the "malignant profile" if nodules had been resected or ablated and "classified as necrotic"? Is it not possible that distant recurrences were due to the well-known hepatocarcinogenesis of HCC on cirrhosis?

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Reply to: "Poor contrast enhanced ultrasonography! There is no limit to its decline in the diagnosis of hepatocellular carcinoma on cirrhosis!"

To the Editor:

We would like to thank Giorgio *et al.* for their interest in our recent study about the role of contrast-enhanced ultrasound (CEUS) in the diagnostic process of small nodules detected during screening US [1]. In this study, the main conclusion was that the absence of contrast hyperenhancement during the arterial phase at CEUS does not predict a less malignant profile and thus, priority for diagnostic work-up and treatment should not differ according to contrast profile at CEUS. The letter by Giorgio *et al.* criticised some methodological aspects of our study and they claim that CEUS still has an important role in the diagnostic recall strategy upon the detection of a nodule by screening US. The first concern raised in the letter was the use of the non-invasive diagnostic criteria by MRI after 2007 as gold standard for HCC conclusive diagnosis. Since the non-invasive HCC diagnosis by imaging has been extensively and prospectively validated, and fully accepted by the main scientific societies [2,3] and the Spanish guidelines for HCC management [4], Giorgio *et al.* will surely agree with us that delaying the HCC diagnosis and treatment until histological confirmation is ethically questionable. In addition, we would like to highlight that in only 14 out of 119 (11.7%) HCC lesions the final diagnosis was based only on imaging criteria, and all 18 HCC lesions with absence of arterial contrast hyperenhancement detection at CEUS were histologically confirmed. Moreover, Giorgio *et al.* summarize some studies aimed to evaluate the diagnostic accuracy of CEUS alone or associated to CT/MRI for HCC diagnosis, emphasizing that CEUS showed the best diagnostic accuracy. This is not surprising since the combination of imaging techniques is always associated with better specificity than when just only one imaging technique, whatever one is used. Furthermore, Giorgio *et al.* questioned the feasibility of cytology for diagnosing intrahepatic cholangiocarcinoma and dysplastic nodules. However, the samples were processed in cell-block; this allows the assessment of cyto-histological findings and the use of immunohistochemistry markers, which permits the diagnosis of both entities [5,6].

Regarding the feasibility of CEUS, in the 5 cases (3%) mentioned the nodule was deeply located with a poor sonographic window and despite that the nodule was previously visualized by US, a reliable CEUS was not possible. This is not surprising since our study was prospective and the inclusion criteria was the identification of a solitary nodule smaller than 2 cm by screening US and not by CEUS exploration, and expert radiologists will agree that not all US visible nodules can be explored by CEUS.

Giorgio *et al.* also claim data regarding the diagnostic accuracy of MRI. We would like to stress that our study is not aimed to assess the diagnostic accuracy of MRI, or compared it with CEUS, since this information has been previously reported [7,8]. As requested, in our cohort of patients, MRI did not identify the target nodule in 25 out of 168 patients (14.8%), but only 3 of these