Recall strategies for patients found to have a nodule in cirrhosis: is there still a role for CEUS?

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Abstract
Development of liver tumors and their evolution to hepatocellular carcinoma (HCC) is a multi-step process in which different HCC-etiologies induce continuous rounds of hepatocyte damage and regeneration. Over an extended time, this triggers cirrhosis which is a pathological state of the liver in which lesions can progress to become dysplastic nodules. Later, these nodules may evolve into HCC and occasionally generate metastatic events. To provide optimal care, patients with liver cancer should be managed using a multidisciplinary approach in specialized centers in which all the diagnostic and therapeutic resources are available. Among the different imaging modalities the introduction on contrast agents for ultrasound use has opened new further applications in different clinical settings. In fact, contrast enhanced ultrasound (CEUS) has been applied for more than ten years and plays increasingly important roles in the management of HCC. Since early 2000, international societies including the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL), the Asian Pacific association for the Study of the Liver (APASL), the Japanese society of Hepatology (JSH), the Italian society for the study of the liver (AISF), the World Federation for Ultrasound in Medicine and Biology (WFUMB), and the European Federation of Societies for Ultrasound in Medicine and Biology (EFUSMB) have discussed the important role of CEUS in the diagnosis of HCC. In the present review an update of the literature and a detailed discussion of the present Guidelines regarding the role of CEUS in the evaluation of nodules in cirrhotic patients is offered.

Keywords: hepatocellular carcinoma, contrast-enhanced ultrasound, CT, MRI, cirrhosis guidelines

Liver cirrhosis is defined as the histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury such as alcohol, infections, autoimmune, vascular and metabolic dis-

eases, biliary obstruction, or cryptogenic forms. It is a pathological state of the liver in which regenerative nodules can progress to become dysplastic nodules. Later, these nodules may evolve into hepatocellular carcinoma (HCC) and occasionally generate metastases [1].

HCC is the sixth most common malignant tumor in the world and the third cause of cancer-related death. In Western countries it arises in a cirrhotic liver in the large majority of cases (90%) although it may occur in some patients with chronic hepatitis B (HBV) or chronic hepatitis C (HCV) infection, non alcoholic fatty liver disease, or alcohol abuse. The risk of HCC is higher when the nodule size increases. Nodules < 1 cm are rarely malignant. In nodules > 1 cm the rate of HCC is 66%, in
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Vito Cantisani et al

Maneuvers such as evaluation of lesions in cirrhotic patients are an effective imaging modality to characterize liver lesions in the late and post-vascular phases. However, when dealing with lesions in cirrhosis such patterns are not more relevant, but rather the arterial phase becomes of greater significance. The primary feature to be searched in order to characterize lesions in cirrhosis is the hyperenhancement in the arterial phase although the detection of subsequent hypoenhancement during portal or late phase is requested to definitively establish the diagnosis of HCC.

Hyperenhancement in the arterial phase is usually homogeneous and intense in HCC but it may be inhomogeneous, especially in larger nodules (>5 cm), because of areas of necrosis. The rates of arterial hyperenhancement are variable, increasing with size: in lesions ≤ 2.0 cm, and 3.0 cm are between 40-70% respectively [2,3]. Hypoenhancement in the late phase is observed overall in about half of the cases of HCC but more rarely in small nodules (20%-30% in those 1-2 cm) [3]. It tends to start later in HCC, usually not before 60 s after injection of the contrast agent and in about 25% of cases appears only after 180 s; therefore, it is important to prolong the observation of nodules in cirrhosis up to 4 minutes. By applying these features, several authors have shown that CEUS is an effective imaging modality to characterize liver lesions in cirrhosis. According to those results, AASLD included CEUS in the practical guidelines of HCC management in 2005 [10]. In details, they provided the following recommendations: nodules less than 1 cm should be followed with US every 3-6 months until 2 years and when
no growth had been observed, routine surveillance may be advised; nodules between 1-2 cm found on US should be investigated further with two dynamic studies, either CT scan, CEUS, or MRI with contrast. If they show typical characteristics of HCC in two techniques the lesions should be treated as HCC, while in the doubtful case, the lesion should be biopsied. If the nodule is larger than 2 cm and has the typical features of HCC on a dynamic imaging technique or AFP is >200 ng/mL, a biopsy is not necessary. However, in a doubtful case or if the nodule is detected in a non-cirrhotic liver, a biopsy is needed. If the biopsy is negative for HCC, patients should be followed by US or CT scanning at 3-6 monthly intervals until the nodule disappears, enlarges, or displays diagnostic characteristics of HCC.

However, a few years later, Vilana et al reported that intrahepatic cholangiocellular carcinoma (ICC) in cirrhotic liver may not be clearly distinguishable from HCC at CEUS [20]. A total of 21 patients were evaluated. The median nodule size was 32 mm. All nodules showed contrast enhancement in the arterial phase; in 10 cases it was homogeneous and in 11 cases peripheral (rim-like). All nodules displayed washout during the venous phases. In 5 of the 11 nodules showing homogeneous arterial hyper-enhancement, wash out had already taken place already during the portal phase and it appeared no earlier than in the late phase in the remaining 6 cases. These 10 nodules (five larger than 2 cm) displayed the pattern considered diagnostic for HCC, namely homogeneous contrast uptake followed by washout according to the AASLD criteria. However, none of these lesions displayed wash-out in the venous phase on MRI, leading therefore to a non diagnostic pattern at MRI and hence to biopsy. They concluded that CEUS should not be used as the sole imaging technique for conclusive hepatocellular carcinoma diagnosis and, if the MRI does not confirm the diagnostic vascular pattern in the venous phase, a biopsy is recommended. Following this report, CEUS was dropped from the diagnostic techniques in the latest AASLD Guidelines, as it may offer a false positive HCC diagnosis in patients with ICC [10], and also because CEUS for non-cardiac indications is not available in the USA, so CEUS liver scanning is not applicable for the North American population [21].

However, Barreiros et al also commented that CEUS may be important to identify arterial hypervascularity in presence of a typical pattern of HCC. Accordingly, the diagnosis of HCC should be questioned only when either the wash-out is atypical for HCC (very rapid and/or very marked) or the pattern at CT/MRI for staging is atypical. In fact, rejecting CEUS as a diagnostic technique would lead to more biopsies including the respective risk and less benefit. In addition, ICCs are relatively rare in cirrhotic livers (1-2% of all new nodules) and CEUS can even show differences in the vascularization patterns between HCC and ICC [22]. HCC shows an arterial global hyperenhancement and delayed contrast wash-out in the late phase. ICCs are characterized by an arterial contrast enhancement at the tumor periphery with early contrast wash-out of the vascularized parts of the lesions in the portal and late phases [23]. In addition, since the evaluation of cirrhotic patients is performed by applying multimodality imaging strategy, CT and MRI have to be performed. As reported by D’Onofrio et al, the behavior of ICC at CEUS is different from the one in CT. During the late phase, ICC appears hypervascular at CT, because of desmoplastic reaction due to fibrotic component, while at CEUS it appears hypovascular [22]. In these cases CEUS should not be used as the sole imaging technique for conclusive hepatocellular carcinoma diagnosis and if the MRI does not display the diagnostic vascular pattern, a confirmatory biopsy is mandatory [20]. More recently, de Sio et al enrolled 282 cirrhotic patients who underwent CEUS and subsequent biopsy with histological evaluation as the gold standard for correct classification of FLLs. They calculated the best ‘time to wash-out’ cut-off values to characterize FLLs. Histological diagnosis of liver lesions was as follows: 34 benign and 248 malignant lesions (223 well-to-moderately differentiated HCCs; 7 poorly-differentiated HCCs; 5 ICCs; 5 primary non-Hodgkin B-cell lymphomas (NHBLs); and 8 metastatic liver tumors). A wash-out time >55s identified patients with HCC with the highest level of accuracy (92.7%). Similarly, a wash-out time ≤55s correctly identified the vast majority of the non-HCC malignancies (100% sensitivity, 98.2% specificity and diagnostic accuracy of 98.3%). They concluded that CEUS is an accurate and safe procedure for discriminating FLLs in cirrhotic patients, especially when a cut-off wash-out time of 55s is chosen as a reference value. Very similar timing for the occurrence of wash-out in ICC (median time around 50 secs) were reported also by another recent Chinese study, which addressed the issue of ICC in cirrhosis [24].

Sporea et al reported their experience based on a total number of 356 cases in which CEUS had 85.7% sensitivity, 85.9% specificity, 91.6% positive predictive value, 77.1% negative predictive value, and 85.8% accuracy for differentiation between malignant and benign liver lesions. In particular, they showed that the majority of HCC presented wash-in and later wash-out, while ICC peripheral wash-in and earlier washout. The CEUS accuracy for differentiation between malignant and benign liver lesions was similar in tumors ≤2cm and those >2cm. In this study the reference methods were CT, MRI, or biopsy. These results were in concordance with...
the DEGUM and STIC studies [25]. However, more recently other international guidelines have been published such as WFUMB-EFSUMB and AISF, especially the former includes input from the other professional bodies [15]. These guidelines underline the fact that CEUS is increasingly accepted for clinical diagnostic imaging in focal liver lesions in cirrhosis (FLLs) playing an important role for characterization and post-ablation evaluation. In fact, several studies demonstrated a high sensitivity and specificity in the evaluation of ablation treatments of liver tumors [26,27]. The guidelines point out that CEUS cannot be used to detect – as opposed to characterize – small HCC, since the CEUS identification of small HCC relies on the detection of the hypervascularisation in the arterial vascular phase which is too fast and too transient for the evaluation of the whole liver in the very short arterial enhancement phase. It is recommended that the detection of small HCC must be first carried out using baseline US. These respected guidelines are held in high esteem by many experts who describe in detail the presentation of HCC at CEUS in non-cirrhotic and cirrhotic liver and in variable clinical settings. They report “that CEUS is extremely useful, especially when performed immediately after nodule detection, to make a rapid diagnosis. However, CT or MRI are needed (unless contraindicated) to stage the disease before the treatment strategy is decided”. In 2012 an expert panel nominated by the Italian Association for the Study of the Liver (AISF) issued guidelines for a multidisciplinary clinical approach to HCC, with the scope of developing practical recommendations on the multidisciplinary management for the diagnosis of HCC, providing the most appropriate way to define the staging and treatment according to the patient’s status and tumor stage at diagnosis. They provided recommendations for an effective diagnostic and staging work-up, followed by recommendations for the best patient-tailored treatment choice. The AISF Expert Panel is based on the 2010 updated AASLD guidelines for HCC. The AISF guidelines state that patients at risk of HCC development should be enrolled in surveillance programs that in most cases consist of bi-annual liver ultrasound. In other cases, i.e. in the presence of conditions clearly limiting the accuracy of ultrasound, CT or MRI may be proposed as a supplementary imaging technique. CEUS is discussed for the recall and characterization of a focal liver lesion detected at US surveillance. The recall strategy for lesions ≥1 cm is based on contrast-enhanced imaging techniques with the use of vascular contrast media. However, more emphasis was put on either CT or MRI. The recommendations state that “the lesion should be assessed prior to and after contrast injection in the arterial, portal and venous phases (dynamic contrast imaging) at either CT or MRI”. Diagnosis depends on the vascular pattern of the lesion during contrast media injection in the arterial, portal and venous phases and CEUS is a reliable technique to detect tumor vascularity. The recommendations continue with considerations on the use of CEUS. In the updated AASLD algorithm, CEUS is not included among the imaging techniques for the diagnosis of HCC in a lesion detected during surveillance as it was in the past [16,28]. However, the AISF experts recognize the validity of CEUS since scientific evidence of a number of studies shows that a CEUS wash-in and wash-out pattern typical for HCC has a positive predictive value >95% [16,30]. AISF experts discuss evidence in the right perspective and they report that ICC accounts for only 1–2% of all new nodules detected in a cirrhotic liver [3,29] and, among them, only half show the typical HCC pattern at CEUS [28]. Conversely, the AISF expert panel considers the available scientific evidence as insufficient to remove CEUS from the diagnostic tools since a CEUS pattern typical for HCC has a high positive predictive value. The wash-in/wash-out pattern at CEUS of a nodule in cirrhosis should be considered specific for malignancy and, unless discordant findings with MRI or CT are obtained, it should be considered suggestive of HCC, without the need for biopsy. However, due to the need for CT or MRI for tumor staging, the use of CEUS as a first line approach, despite being possible, is not considered the most cost-effective imaging modality [20]. However, MRI is the gold standard for the characterization of small nodules in cirrhotic liver. The AISF and EFSUMB professional guidelines have not removed CEUS from the management of HCC. While CEUS alone is not recommended for staging, it is still recommended for the evaluation prior to trans-arterial chemoembolization (TACE) or ablation procedures.

Alaboudy et al [30] reported that CEUS combined with CT or MRI improved the sensitivity and specificity of HCC diagnosis. Few articles have focused on the role of preoperative CEUS combined with CE-CT or MRI for staging of HCC in surgical patients, in surgical decision-making, or on the correlation between CEUS and intraoperative ultrasound. Even more recently, Zhang et al, evaluated the clinical role of CEUS combined with CE-CT or MRI with the aim to improve the preoperative staging of HCC. Sixty-nine patients who underwent liver resection for HCC were prospectively submitted to CEUS and CE-CT/MRI before surgery and then to intraoperative ultrasound (IOUS). One hundred and twenty-seven nodules, comprising 94 HCCs confirmed by histopathology and 33 benign lesions confirmed by histopathology and follow-up, were identified. The overall diagnostic sensitivity rates of CE-CT/MRI, CEUS, IOUS and CEUS + CE-CT/
MRI were 78.7%, 89.4%, 89.4%, and 89.4%, respectively. CEUS combined with CT or MRI significantly increased the diagnostic specificity of CT/MRI, CEUS, and IOUS, alone (100%, 72.7%, 97.0%, and 69.7%, p=0.004, p=0.002, p=0.002, respectively). The diagnostic accuracy was significantly higher for CEUS + CT/MRI compared with CT/MRI (92.1% vs 77.2%, p=0.001). Indeed, the authors concluded that CEUS combined with CT or MRI improved the accuracy of preoperative staging for hepatocellular carcinoma and may help to guide individualized treatment for patients with HCC [31].

As showed above, the role of CEUS for the diagnosis of HCC has been a controversial issue, so the technique is continually being evaluated. More recently, a meta-analysis on previous studies to determine the diagnostic accuracy of CEUS for diagnosis of small (≤2 cm in diameter) HCC was published [32]. A comprehensive literature search of PubMed, Embase, Web of Science, and China BioMedicine databases was conducted on articles published before 1 March 2013; 15 studies were included with a total of 908 cirrhotic patients with 1,032 small hepatic nodules. All lesions were histologically confirmed through liver biopsies after CEUS. The pooled sensitivity was 0.81 (95% CI=0.78-0.85), the pooled specificity was 0.86 (95% CI=0.82-0.89), the pooled positive LR was 5.90 (95% CI=3.90-8.94), the pooled negative LR was 0.20 (95% CI=0.14-0.29), and the pooled DOR was 37.07 (95% CI=24.79-55.44). According to this meta-analysis, CEUS is a useful diagnostic tool with high sensitivity and specificity for identifying small HCC [32].

Therefore, it is generally accepted that CEUS is a cost-effective second line imaging modality once the liver focal lesion is detected at US although MRI is the gold standard for the characterization of small nodules at high-risk for HCC in cirrhotic liver. However, CEUS as recently reported by Jang et al [33], has some advantages over CT and MRI such as: the more sensitive depiction of arterial hypervascularity of HCC, the better demonstration of rapid wash-out for non-HCC malignancy, as well as of very late wash-out of HCC. Visualization of early vascular filling patterns for benign hypervascular lesions is of indisputable value. A frequently unaccounted benefit of CEUS includes the value of its performance following nodule detection at ultrasound surveillance, including one-stop exclusion of typical benignancy, preclusion of arterial pseudolesions shown on CT/MR, and the avoidance of miscarrelation of a nodule on surveillance and subsequent diagnostic imaging. Therefore, CEUS can effectively be used in the diagnostic algorithm for new liver nodules detected during HCC surveillance.

In conclusion there has been a lot of controversy regarding the role of CEUS for the diagnosis of HCC, and the technique is continually being evaluated. In our opinion, the role of CEUS in HCC management will be re-considered as technology (e.g. quantitative perfusion) continues to evolve and as its use spreads not only among expert operators and referral centers but also among everyday ultrasound personnel involved in HCC surveillance [34].

Conflict of interest: We want to mention that Vito Cantisani, lectured for Bracco SpA Milan, Samsung, Toshiba, and Siemens, Franca Meloni for Bracco, Fabio Piscaglia was a speaker and advisory board member for Bayer, a speaker for Bracco and Siemens and he is on the Advisory board for GE and has a research contract with Esaote. All the aforementioned activities do not represent potential conflict of interest.

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