

Review

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# Contrast-enhanced ultrasound with sulphur-hexafluoride in diagnosis of early HCC in cirrhosis

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## Abstract

Contrast-enhanced ultrasound (CEUS) with pure blood stream contrast agents allow the study of blood supply of focal liver lesions and especially of hepatocellular carcinoma (HCC) in cirrhosis. Its sensitivity and specificity in diagnosis of small tumors is very high. This review summarizes the recent results on CEUS with SonoVue, which is one of the second generation contrast agents, in the diagnosis of early HCC in cirrhosis emphasizing its increasing role in routine clinical practice.

**Keywords:** Hepatocellular carcinoma, contrast-enhanced ultrasound, cirrhosis, early hepatocellular carcinoma

## INTRODUCTION

Today the use of dynamic imaging modalities allows the study of liver vasculature and in particular the study of the blood supply of the focal liver lesions. Focal liver lesions can be non-invasively differentiated and characterized in benign or malignant on the basis of their vascular support, so to avoid the need of biopsy. This revolution was provided non-invasively by the dynamic study of liver vasculature using contrast-enhanced CT (CECT), contrast-enhanced MRI (CEMRI) and, lastly, Contrast-enhanced ultrasound (CEUS). These new dynamic imaging techniques have had a strong impact especially in the field of diagnosis of hepatocellular carcinoma (HCC) in cirrhosis, and have achieved considerable importance in the management



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of this kind of tumor. HCC is the most frequent primary epithelial malignant tumor of the liver<sup>[1]</sup>. The main feature of this tumor is that it arises mainly in patients with cirrhosis through the transformation of normal regenerating nodules in dysplastic nodules and finally overt HCC<sup>[1-5]</sup>. For non cirrhosis HBV patients, it is via HBV-DNA integration into the host genome, which occurs at early steps of clonal tumor expansion and induces both genomic instability and direct insertional mutagenesis. Therefore, patients with cirrhosis represent a high risk population for developing HCC and should undergo a 6 months surveillance with ultrasound (US) to allow the detection of the tumor at an early stage<sup>[6-13]</sup>. In clinical practice, CECT and CEMRI are not recommended in the surveillance programs. Viceversa, when US examination shows a new nodule, CECT and/or CEMRI are recommended for the staging of the disease.

## **VASCULAR CHANGES IN HEPATOCARCINOGENESIS AND CEUS**

It is well known that in the case of HCC arising on cirrhosis the normal vascular support is reversed: while in normal subjects the vascular support of the liver is provided by the portal venous system up to 75%, in HCC the blood supply of the nodule is only arterial.

The process of hepatocarcinogenesis in cirrhosis includes the progression from Low Grade Dysplastic nodule to High Grade Dysplastic nodule (HGDN) and overt HCC. During this process, unpaired arteries progressively substitute tumoral portal tracts so that overt HCC blood supply is only arterial. This pathological phenomenon explains the arterial hyperenhancement of typical HCC nodules on dynamic imaging modalities such as CECT, CEMRI and CEUS<sup>[14,15]</sup>.

In recent years, CEUS has gained significant popularity in the characterization of focal liver lesions. CEUS has shown to have a great capability in distinguishing between benign or malignant hepatic nodules on the basis of characteristic patterns of blood supply of the lesions<sup>[16]</sup>. The 2nd generation contrast agent SonoVue is a pure blood stream agent formed by micro bubbles with inert gas sulphur- hexafluoride and a palmitic acid shell. After Intra venam injection of 2.4 mL of SonoVue, in real time and second by second, the arterial phase appearance of contrast agent distribution within the nodule's vessels (duration 10-30 s after contrast injection) can be studied and recorded, followed by the portal phase (30-60 s after injection ) and the late or sinusoidal phase (60-240 s)<sup>[16,17]</sup>. The typical CEUS pattern of HCC in cirrhosis is reported in [Figures 1-5](#)<sup>[18,19]</sup>.

## **HCC DIAGNOSIS IN CIRRHOSIS AND ROLE OF CEUS**

### **US surveillance of HCC in cirrhosis and CEUS**

It is well known that conventional US, although a unique tool for surveillance, has a great sensitivity but a very low specificity in the characterization of HCC in cirrhosis<sup>[16]</sup>. CEUS has shown to significantly improve US accuracy<sup>[16,20]</sup>. CEUS using SonoVue easily show the characteristics of liver nodules blood supply and therefore allow the characterization of malignant nodules<sup>[17]</sup>.

CEUS has determined a real revolution by eliminating the low specificity of conventional US in diagnosing and managing HCC after recognition of a new nodule in a cirrhotic liver: this is due to the immediate and real time visualization of its vascular supply<sup>[16]</sup>. Other advantages of CEUS are the absence of ionizing radiation, the low cost, repeatability, safety and, more important, the possibility to be performed in patients with renal insufficiency<sup>[16,21]</sup>. Moreover, it has been reported that CEUS add significant diagnostic information in the characterization of atypical or indistinctive lesions on conventional US<sup>[21,22]</sup>.

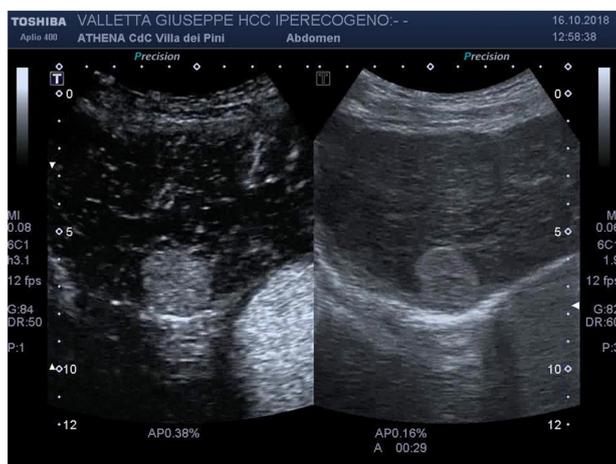
The main limitation of CEUS using pure blood stream contrast agents is based on the fact that only one lesion at a time can be studied and characterized, due to the very short duration of the arterial phase (see later). Consequently, CECT and/or CEMRI are the only dynamic imaging modalities to be used for the staging of the tumor. For the same reasons, CEUS with pure blood stream agents such as sulphur hexafluoride cannot be used for surveillance, unlike Sonazoid which is a new US contrast agent using perflubutane (see later).



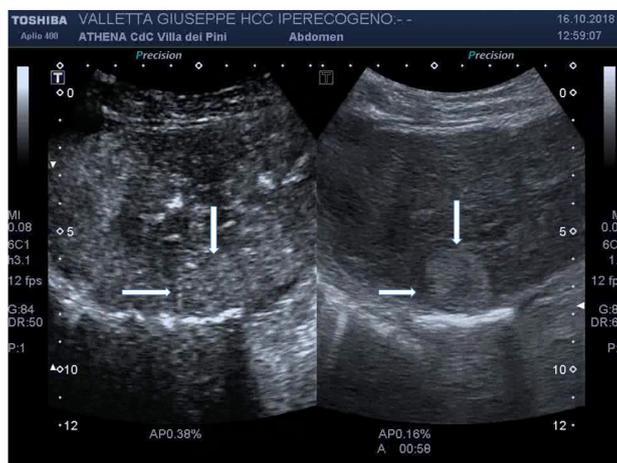
**Figure 1.** A 75-year old man with HCV related cirrhosis, successfully treated one year before with DAAs and presenting with a small 2 cm angioma-like hyperchoic nodule in the 7th segment of the liver, not present during the surveillance in the previous ultrasound (US) exam 6 months before



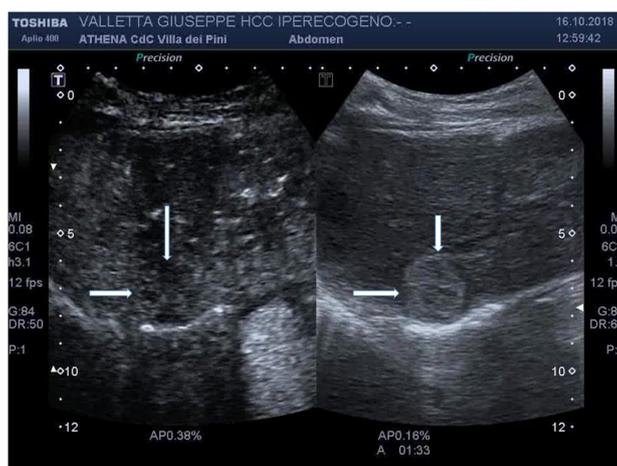
**Figure 2.** A very small hypochoic round portion (white arrow) is seen within the hyperchoic nodule ( nodule in nodule)



**Figure 3.** CEUS appearance: in the arterial phase, the nodule becomes homogeneously hyperechoic (hyperehanced) (left of the figure)



**Figure 4.** At the end of the portal phase (59 s) the nodule (white arrows) appears iso-enhanced



**Figure 5.** Only at 1.33 min in the late phase, the nodule (white arrows) becomes slightly hypoechoic (hypo-enhanced)

### CEUS patterns of small HCC in cirrhosis and international guidelines

Nowadays, all practice guidelines on the management of HCC in cirrhosis have endorsed CEUS as a dynamic imaging modality capable of diagnosing HCC in cirrhosis per lesion<sup>[8-13]</sup>. The Italian Society for the Study of the Liver, in cooperation with the Italian Societies of Oncology, Radiology, Surgery, Hepatobiliary Surgery and Organs Transplant, published a position paper stating that CEUS can diagnose non-invasively as HCC a hepatic nodule when the characteristics of arterial hyperenhancement and wash out are present, like CECT and CEMRI<sup>[12]</sup>. The guidelines of CEUS hepatic applications of EFSUMB and WFUMB date back to 2012<sup>[13]</sup>.

The recent EASL guidelines for the management of HCC recognized that “CEUS can be effectively utilized to characterise lesions in cirrhosis” although CT and MRI are panoramic technique useful for the staging of the tumor, since the rapid CEUS arterial enhancement does not allow the detection of eventual multiple nodules scattered in the liver<sup>[10]</sup>. In fact, CEUS “can be utilised to characterise one or few nodules detected on conventional US surveillance”. Nonetheless, EASL does not recommend CEUS as first line tool, but only in cases where CT/MRI are contraindicated or inconclusive<sup>[10]</sup>.

2017 Chinese guidelines stated that in HBV/HCV chronic hepatitis or cirrhosis patients diagnosis of HCC > 2 cm can be made with only one dynamic imaging tool (CECT, CEMRI or CEUS) when the typical findings are present. If the nodule has a diameter < 2 cm, two dynamic imaging techniques are needed<sup>[23]</sup>.

The new 2017 Japanese guidelines on management of HCC stated that CEUS sensitivity is similar to dynamic CT or dynamic MRI in diagnosis of HCC and therefore CEUS is able to characterize nodules detected on sonography. The US contrast agent indicated in these guidelines is Sonazoid, which is a US contrast agent phagocytized by Kupffer cells<sup>[24]</sup>. In the past, controversies arose over the possibility of misdiagnosis between small (< 3 cm) Intrahepatic Cholangiocarcinoma (ICC) arising in cirrhosis and HCC. In such cases, CEUS was considered unable to distinguish between these two entities in cirrhotic livers because, in the experience of Spanish authors, CEUS washout patterns of ICC can mimic those of HCC<sup>[25]</sup>. As of today, it is well established that the differential diagnosis between small < 3 cm ICC in cirrhosis and small HCC is no longer a problem. It is well known that, at CEUS, small ICC can present an intense (as HCC) arterial phase hyperenhancement, but a more rapid and marked washout in the portal phase (always < 42 s), differently from the mild and very late wash-out (> 60 s) of HCC in the sinusoidal phase, avoiding any pitfalls<sup>[26,27]</sup>. Therefore, the old diatribe that for several years has labelled CEUS not able to distinguish between small HCC and ICC nodules arisen in a cirrhotic liver is now to be considered surpassed<sup>[25-31]</sup>. Nevertheless, we should consider that small HCC nodules (< 2 cm) can present with hyperenhancement in the arterial phase followed by isovascularity in the portal and sinusoidal phases in more than 50% of cases (as is shown in [Figure 4](#) and Giorgio's 2011 results .as reported below.

### CEUS LI-RADS and HCC

A so-called CEUS LI-RADS was proposed by the American College of Radiology based on the Liver Imaging Reporting and Data System (LI-RADS) using CECT and CEMRI patterns for HCC in cirrhotic livers. LI-RADS was originally developed for CECT and CEMRI, but expanded to include CEUS. Based on CEUS features, focal liver lesions ("observations" in radiologic terminology) detected in a cirrhotic liver can be classified in 5 major classes ranging from "definitely benign" (LR-1) to "definitely HCC" (LR-5)<sup>[32]</sup>. Sonovue is included in the CEUS LI-RADS version 2017<sup>[32]</sup>. The 5 major categories (LR-1-LR-5) are classified according to the diameter of the lesions and their contrast enhancement patterns.

The CEUS pattern characterized by the presence of rapid, intense and homogeneous hyperenhancement in the arterial phase (APHE) followed by mild and late (> 60 s) wash-out is termed as CEUS LI-R 5. When a hepatic nodule discovered in a cirrhotic liver presents with the CEUS LR-5 pattern, the nodule can managed as HCC and there is no need for biopsy. This classification is applied to nodules > 10 mm<sup>[32-35]</sup>.

Very recently, Terzi *et al.*<sup>[36]</sup> reported very interesting data that strongly influenced the last 2018 EASL guidelines in diagnosis of HCC. In a multicentre retrospective study, these authors evaluated CEUS patterns of 1,006 nodules in 848 patients with chronic liver disease at risk for HCC. Median size of nodules was small: 2 cm. Five hundred twenty one (52%) out of all nodules showed APHE and a mild, late wash-out. The 17% of nodules showed APHE and isoechogenicity in the portal and late phase, while 16% of nodules were iso-enhancing in the arterial and portal-late phases. The most important data was that 512 (98.5%) of all nodules classified as CEUS LR-5 were HCC. When authors included in their analysis 3 other CEUS LR-5 cases that were judged underdiagnosed and that resulted HGDN at biopsy, the rate of HCC diagnosis became 99%. In their study, Terzi *et al.*<sup>[36]</sup> did not report any case of misdiagnosis with ICC.

Moreover, studies on inter-observer agreement suggest that the classification of small hepatic nodules (< 2 cm) with LI-RADS-CEUS is reproducible with good consistency in patients with chronic liver disease<sup>[37-39]</sup>.

### CEUS arterial hyper enhancement and early HCC

Some authors studied the interobserver agreement for CEUS-based standardized algorithms in diagnosis of HCC in high-risk patients. The interobserver agreement was good for arterial phase hyper enhancement, which is the key diagnostic feature for HCC nodules in a cirrhotic liver<sup>[39]</sup>. For what has been said so far, although it is evident that HCC diagnosis on CEUS relies also on the washout findings (type and time),

arterial hyper-enhancement remains the main element for the visualization of the HCC nodule when pure blood stream contrast agents are used.

This feature was also studied by Giorgio *et al.*<sup>[40]</sup> who reported a considerable effectiveness of CEUS in detection of arterial hyperenhancement in small nodules (7-20 mm) discovered in cirrhotic patients during surveillance, so to shorten the diagnostic work-up for the management of HCC.

In Giorgio's experience, CEUS showed arterial hyperenhancement in 95.5% of HCC nodules, with a sensitivity of 94.48%, a specificity of 100% and 100% PPV. In this study, CEMRI showed 97% sensitivity, 80% specificity and 97% PPV. The authors concluded that CEUS has a great capability in detection of arterial hypervascularity in < 2 cm HCC. In Giorgio *et al.*<sup>[40]</sup>'s experience, only 4.5% of new nodules escaped the demonstration of arterial hypervascularity. Therefore authors concluded that "CEUS must be performed immediately after conventional US to contrast the malignant fate of small lesions arising in a cirrhotic liver". Moreover, "CEUS should be included in the diagnostic management of HCC in order to avoid a late diagnosis, enable an early treatment and improve survival".

It was shown that CEUS vascular patterns of HCC lesions are related to size and histologic differentiation of the tumor. Ling *et al.*<sup>[41]</sup> reported that < 3 cm HCC nodules show more homogeneous hyperenhancement compared to > 3 cm lesions<sup>[41]</sup>. Moreover, heterogeneous arterial enhancement of HCC nodules > 3 cm were followed by faster washout compared to < 3 cm nodules. The portal and late phase washout was faster in poorly differentiated HCC compared to well-differentiated lesions.

Italian authors also reported that CEUS has high capability in the differential diagnosis of dysplastic nodules (DN), early hepatocellular carcinoma and progressed HCC<sup>[42]</sup>. According to this study, DN, early HCC and progressed HCC have different and characteristic CEUS patterns. Progressed HCC is characterized by rapid, intense and homogeneous arterial hyperenhancement, while early HCC displays the so called "reticular pattern". This pattern is characterized by inhomogeneous enhancement during arterial phase and complete enhancement in the late phase. In the experience of the authors, the "reticular pattern" identified early HCC nodules with a sensitivity of 85.7% and a specificity of 96.1%<sup>[42]</sup>.

### **Comparison among CEUS, enhanced CT and enhanced MRI in diagnosis of small (2-3 cm) HCC nodules in cirrhosis**

Many authors studied the diagnostic capability of CECT, CEMRI and CEUS alone or in combination for the diagnosis of small HCC on cirrhosis. Aubé *et al.*<sup>[43]</sup> carried out a large multicentre study in a large number of cirrhotic patients (544 nodules in 381 patients). Authors aimed at evaluating the accuracy of CECT, CEMRI and CEUS alone and in combination, in diagnosing small (10-30 mm) HCC nodules. The best combination for the 10-20 mm nodules was CEMRI -CECT. They found that, when a first imaging tool was inconclusive and CEUS was used as second dynamic technique, this combination allowed the highest specificity with only a slight drop of sensitivity for 10-20 mm nodules and the highest sensitivity and specificity for 20-30 mm nodules. The authors concluded that in diagnosis of small HCC nodules the best combination is CEMRI followed by CEUS<sup>[43]</sup>.

Moudgil *et al.*<sup>[44]</sup> compared the role of CEUS and CECT in diagnosis of HCC. In their experience, CEUS and CECT were similar in demonstrating the arterial hypervascularity of HCC nodules. Vice versa, they found a better capability of CEUS in the demonstration of washout pattern and the presence of the capsule of the nodules, when present .

Finally, Intraoperative Contrast-Enhanced Ultrasound (CEUS/IOCEUS) is routinely performed during surgical resection of HCC in cirrhosis. It has been shown that such technique allows the detection of

additional liver lesions. This advantage was demonstrated when IOCEUS was compared to preoperative MRI, as well as to preoperative CEUS. According to results of Huf *et al.*<sup>[45]</sup>, in 27% of their cases IOCEUS allowed the detection of further liver lesions not detected preoperatively. Such detection of further lesions modified the treatment planning and resection was extended if necessary.

## CONCLUSION

Today, CEUS plays an essential role in the clinical recognition of small nodules arising *de novo* or recurrent in cirrhotic livers at risk for HCC. The advantages of CEUS over CT/MRI are unique and are represented by: the high sensitivity in depiction of arterial hypervascularity of HCC; the better demonstration of rapid washout for non-HCC malignant nodules; the very late washout of HCC.

In 2016, SonoVue was approved for the first time in the United States for the diagnostic imaging of liver tumors in adults and children. It is undisputable that this approval represents a milestone for CEUS<sup>[46]</sup>. In clinical practice, CEUS demands are constantly increasing in Europe, Asia and Canada (and we are hoping also in USA after the FDA approval) in the Hepatology Units and not only (see Gastroenterology Units, Infectious disease Units, Internal Medicine Units and Surgical Units).

It is undoubtable that the most important benefit of CEUS is based on the fact that physicians can perform CEUS soon after the detection on conventional US of a new nodule during surveillance of cirrhotic patients. Thanks to this technique, physicians can immediately exclude typical benignancy, non-HCC malignant nodules such as ICC and, mainly, in case of CEUS recognition of early HCC, physicians can define a rapid therapeutic work-up choosing among liver transplantation, resection or ablation.

## DECLARATIONS

### Authors' contributions

Design of the work, data analysis and interpretation: Giorgio A

Data acquisition, material support: Giorgio A, Gatti P, Matteucci P, Giorgio V

Wrote the manuscript: Giorgio A, Giorgio V

### Availability of data and materials

Not applicable.

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None.

### Conflicts of interest

All authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

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