Contrast-enhanced ultrasound of hepatocellular carcinoma: where do we stand?

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Contrast-enhanced ultrasound (CEUS) represents a significant breakthrough in ultrasonography (US), and it is being increasingly used for the evaluation of focal liver lesions (FLLs). CEUS is unique in that it allows non-invasive assessment of liver perfusion in real time throughout the vascular phase, which has led to dramatic improvements in the diagnostic accuracy of US in the detection and characterization of FLLs, the choice of therapeutic procedures, and the evaluation of response. Currently, CEUS is included as a part of the suggested diagnostic work-up of FLLs, including in cirrhotic patients with hepatocellular carcinoma, resulting in better patient management and cost-effective delivery of therapy.

Keywords: Contrast-enhanced ultrasonography; Hepatocellular carcinoma; Ultrasound contrast media; Liver; Ultrasonography; Liver cirrhosis

Introduction

Hepatocellular Carcinoma: The Burden

Hepatocellular carcinoma (HCC) is the sixth most common tumor worldwide and the fourth most common cause of cancer-related death [1]. Hepatitis B virus and/or hepatitis C virus infection, alcohol, and nonalcoholic fatty liver disease are the most predominant risk factors for HCC worldwide [2]. Patients with cirrhosis are considered a particularly high-risk group for developing HCC, prompting several international scientific societies to publish guidelines recommending surveillance of adults with cirrhosis based on evidence of improved overall survival [3–12]. The suggested surveillance tool for early detection of HCC is ultrasonography (US), usually performed every 6 months, with or without an α-fetoprotein serum assay.

Once HCC is suspected in a patient with cirrhosis, diagnostic imaging is recommended for confirmatory diagnosis and radiological staging. In particular, many international guidelines recommend a diagnostic evaluation for HCC using either multiphasic computed tomography (CT) or multiphasic magnetic resonance imaging (MRI) because both modalities show similar diagnostic performance [3]. Regardless of the particular strengths and shortcomings of each technique, both CT and MRI require contrast agents, the use of which can be problematic in patients with severely impaired renal function [13,14].
Contrast-Enhanced Ultrasound

Despite technical advances in both spatial and contrast resolution, gray-scale US is still considered a non-specific technique for the diagnosis of focal liver lesions (FLLs) [15]. Doppler examination may provide some clues to the diagnosis; for example, a spoke-wheel pattern associated with the arterial waveform in a pulsed Doppler evaluation may be highly suggestive, although not pathognomonic, of focal nodular hyperplasia in otherwise healthy young women taking oral contraceptives [16]. Nevertheless, Doppler examinations can only assess large vessels (i.e., >100 μm), and Doppler US is prone to motion artifacts.

In the late 1990s, the introduction of microbubble-based contrast agents, along with contrast-specific gray-scale US techniques, led to a better depiction of microcirculation (i.e., vessels as thin as 40 μm). Contrast-enhanced ultrasound (CEUS) enabled an accurate depiction of both macrocirculation and microcirculation, which was immediately exploited for the detection and characterization of FLLs, with reported sensitivity and specificity values approaching those of CT and MRI [17,18].

CEUS is a real-time dynamic imaging technique, which enables the use of US to assess the contrast-enhancement patterns of FLLs in real time, without ionizing radiation and with a much higher temporal resolution than is possible with CT and MRI [19]. The examination is performed by injecting intravenously microbubble-based contrast agents (USCAs) consisting of gas bubbles with a radius ranging from 1 to 10 μm, presenting flexible shells (e.g., phospholipids) that are filled with low-solubility gases (e.g., perfluoropropane, perfluorocarbon, or sulfur hexafluoride) [20]. When injected intravenously, microbubble-based contrast agents pass through the pulmonary filter and remain within the liver.
intravascular space (blood-pool agents), where they act as purely vascular tracers (blood markers).

Some USCAs also present a post-vascular phase in the liver and spleen, where they can be trapped in the liver sinusoids or may be selectively taken up by phagocytic cells of the reticuloendothelial system [21]. USCAs are completely eliminated within 5 to 20 minutes after injection; the gas diffuses into the blood and is then exhaled via the lungs, while the shell components are metabolized by the liver or filtered by the kidney [22].

USCAs are generally safe and well tolerated. They are not nephrotoxic and may be used even in patients with renal failure, renal obstruction, or chronic obstructive pulmonary disease. It is not recommended to perform laboratory tests of renal function before administering them. In a multicenter study of 23,188 patients who had been examined for liver lesions, a serious adverse event rate of 0.0086% was reported, with no deaths and a life-threatening anaphylactoid reaction rate of less than 0.002% [23]. By comparison, the incidence of serious adverse events is about 0.02%–0.1% after administration of non-ionic X-ray contrast agents and 0.005%–0.2% after administration of gadolinium chelates for MRI [24].

Currently, CEUS is included as a part of the suggested diagnostic work-up of liver FLLs, resulting in better patient management and cost-effective delivery of therapy [25]. The use of CEUS for this purpose is supported by a recent meta-analysis confirming that CEUS had excellent diagnostic capability for differentiating malignant from benign FLLs. In that study, the pooled sensitivity, specificity, diagnostic odds ratio, positive likelihood ratio, negative likelihood ratio, and area under the curve for CEUS in the characterization of FLLs were 92%, 87%, 104.20, 7.38, 0.09, and 0.0086%.
Fig. 3. Hepatocellular carcinoma in a 53-year-old man.
A. A magnetic resonance image obtained during the hepatic arterial phase reveals a substantially unenhancing lesion in the fifth segment, measuring 1.5 cm (arrow). B, C. On magnetic resonance images obtained at same level during the portal venous (B) and the hepatocellular-specific (C) phases, the lesion appears hypointense (arrows). D–F. On contrast-enhanced ultrasonography, the same lesion is hypervascular on the image acquired during the arterial phase (arrow), is not evident during the extended portal-venous phase, but shows clear-cut washout (arrow) 300 seconds after sulfur hexafluoride injection (F).
The US technique used in the cases illustrated in this article consisted of continuous scanning performed by means of various ultrasound equipment: RS80A and RS85A with Prestige (Samsung Medison, Co. Ltd., Seoul, Korea), an iU22 unit (Philips Ultrasound, Bothell, WA, USA), and MyLab Twice (Esaote, Genova, Italy). All of these units are provided with multifrequency convex array probes and contrast-specific imaging software. A baseline survey examination, including a color/power and pulsed Doppler analysis, was always performed in order to choose the best acoustic window and plane to image the lesion. Once set, the US scan parameters—such as focal zone and time gain compensation—were not changed throughout the study. The US contrast agent used was a sulfur hexafluoride-filled microbubble-based contrast agent (SonoVue, Bracco, Milan, Italy), which was injected intravenously as a 2.4-mL bolus (equivalent to 0.003 mL/kg for 70 kg of body weight) followed by 5–10 mL of normal saline flush using a 20- or 22-gauge peripheral intravenous cannula. In order to minimize microbubble disruption, a low frame-rate (5 Hz) and a low mechanical index (MI), ranging from 0.05 to 0.08, were used for real-time imaging. One focus was positioned below the level of the lesion. Each examination lasted roughly 5 minutes after the bolus injection.

Digital cineloops were registered both during baseline and post-contrast US scanning in the arterial (i.e., 10–35 seconds from the start of the contrast agent bolus injection), portal venous (i.e., 55–80 seconds from the start of the injection), and late (i.e., 235–260 seconds from the start of the injection) phases. The baseline echogenicity and the dynamic enhancement pattern of each lesion in the arterial, portal-venous, and late phases in comparison with adjacent liver parenchyma were evaluated.

HCC: CEUS Findings

Through exploiting the progressive changes in the intranodular blood supply during the process of hepatocarcinogenesis, unlike...
what occurs in the development of many other solid tumors, the diagnosis of HCC can be non-invasively established by imaging without histopathologic confirmation [26].

Hepatocarcinogenesis is usually the result of a complex multistep process characterized by several key alterations at molecular, cellular, and histologic levels, including peculiar hemodynamic changes. Notably, during the step-wise progression from cirrhotic nodules through dysplastic nodules and early HCC to advanced HCC, portal tracts (which contain portal veins and nontumoral hepatic arteries) progressively diminish, whereas newly formed unpaired (nontriadal) arteries develop. Eventually, HCC is supplied mostly by the abnormal hepatic artery system [27].

As a consequence, cirrhotic nodules, also known as regenerative nodules (RNs), have a similar blood supply to the normal liver, and dysplastic nodules (DNs) are usually non-hypervascular. The vast majority of RNs and DNs are isoechocic to adjacent liver parenchyma during all phases on CEUS (Fig. 1) [28]. In contrast, HCC nodules are typically hyperenhanced in the arterial phase and show washout in the portal venous and delayed phases on contrast-enhanced multiphasic CT and MRI [29]. In this setting, CEUS is perfectly able

Fig. 5. Intrahepatic cholangiocarcinoma in a 73-year-old man.
A. An oblique ascending right subcostal baseline image reveals a highly heterogenous lesion with ill-defined margins measuring 6.5 cm in the eighth hepatic segment (arrow). B, C. During the arterial phase, the mass appears heterogeneously vascularized (arrow) (B) with rapid (43 seconds after sulfur hexafluoride injection) washout (arrow) (C). D. Arterial phase contrast-enhanced computed tomography shows a hypoattenuating subcapsular mass (white arrow) associated with moderate bile duct dilatation in the context (black arrow). E, F. The lesion shows progressive enhancement during the portal-venous (E) and the late (F) phases (arrows).
to depict the typical contrast-enhancement pattern of arterial-phase hypervascularity and later washout of HCC, with reported inherent superior sensitivity to microbubbles compared to the sensitivity of CT or MRI to iodinated or gadolinium-based agents (Fig. 2) [30]. Furthermore, the real-time nature of CEUS imaging allows the demonstration of enhancement, whereas CT/MRI may fail to show enhancement because of inappropriate arterial-phase timing (Fig. 3) [31]. Not surprisingly, the sensitivity of CEUS in the detection of arterial hypervascularity from nodules in liver cirrhosis has been reported to be significantly higher than that of CT/MRI [32-34].

Interestingly enough, the enhancement patterns of HCC on CEUS are related to its pathology. In a study by Jang and colleagues on 112 HCCs, hypervascularity was more frequently seen in moderately differentiated HCCs than in well or poorly differentiated HCCs [35]. Hence, the imaging findings on CEUS may overlap between DNs and well-differentiated HCCs due to the variable blood supply (Fig. 4) [28].

Furthermore, washout time was reported to be significantly shorter in moderately and poorly differentiated HCCs than in well-differentiated tumors [35]. This finding is of clinical relevance considering that washout in HCC tends to be late and often begins later than 90 seconds after injection, whereas metastases or intrahepatic cholangiocarcinomas usually show arterial-phase hypervascularity followed by rapid washout (<60 seconds) (Fig. 5) [36]. Hence, when performing CEUS, a long observation period (up to ~5 minutes, or as long as enhancement lasts) is essential to avoid missing the late (>1 minute), weak washout typical of HCC (Fig. 2).

Furthermore, size may be a factor influencing arterial contrast-enhancement patterns: in a study by Tada et al. [37], 63 of 68 (92.6%) small HCCs (<3 cm in size) showed a mainly diffuse homogeneous arterial-phase enhancement pattern, and 66 of 68 (97%) small HCCs showed regular tumor margins on CEUS. In large HCCs, a heterogeneous arterial-phase enhancement pattern can often be observed due to non-enhancing areas related to fibrosis, necrosis, or internal hemorrhage (Fig. 6).

Wash-in Issues: Differentiating HCC from Other Arterial-Enhancing Lesions
It is well documented that up to 93% of small hypervascular foci seen on CT/MRI in the arterial phase only represent non-neoplastic

**Fig. 6. Hepatocellular carcinoma in a 70-year-old man with hepatitis C-related cirrhosis.**

A, B. An oblique ascending right subcostal baseline image reveals a markedly inhomogeneous lesion measuring 9.7 cm in the seventh hepatic segment (calipers) (A) with a vascular signal in its context (B). C. During the arterial phase, the mass is highly hypervascular (arrow). D. During the extended portal-venous phase, a slight hyperechoic peripheral rim is evident, suggesting a pseudocapsule (white arrow) with necrotic areas inside the mass (black arrow). E. The lesion shows a washout sign, appearing hypoechoic with respect to the surrounding liver parenchyma 5 minutes after the start of the hexafluoride injection (arrow).
pseudolesions, especially arteriportal shunts, even in patients with pathologically proven HCC [38,39].

Furthermore, thanks to its high temporal resolution and real-time nature, CEUS is able to overcome the fugacity of the arterial phase, allowing a precise assessment of early vascular filling patterns, often crucial for differentiating small, rapidly enhancing, benign hypervascular lesions from well-differentiated HCC not showing washout. Hence, CEUS can easily characterize flash-filling hemangiomas and focal nodular hyperplasia by demonstrating early peripheral nodular enhancement, followed by centripetal fill-in and a spoke-wheel pattern with centrifugal progression, respectively (Fig. 7) [40–44].

Additionally, small cholangiocarcinomas usually show arterial phase enhancement on CEUS, with either a rim-like or diffuse pattern, the latter of which can be homogeneous or heterogeneous, followed by rapid washout (Fig. 5) [45–47]. Usually, MRI should be performed when these unusual enhancement patterns for HCC are observed on CEUS, and eventually biopsy sampling whenever necessary.

CEUS-specific image processing techniques, such as real-time maximum intensity processing, may further clarify arterial-phase contrast-enhancement patterns, thus improving the characterization of liver nodules [48].

Washout Issues: Differentiating HCC from Other Washing-out Lesions
The extracellular contrast agents used with CT or MRI can progressively leak into the tumor interstitium, whereas the microbubbles in CEUS are purely intravascular. This characteristic explains why, regardless of the arterial contrast-enhancement

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**Fig. 7.** Liver hemangioma in a 48-year-old woman with hepatitis C-related cirrhosis. A. Baseline image shows a homogeneously hyperechoic lesion measuring 1.7 cm in the seventh hepatic segment (arrow). B. In the arterial phase, peripheral globular enhancement is evident (arrow); C, D. The lesion presents progressive centripetal fill-in in the extended portal-venous phase (arrow), complete 3 minutes after the start of the sulfur hexafluoride injection.
pattern, all types of malignant liver lesions show washout on CEUS, whereas CT or MRI may not show washout in malignant tumors with high vascular permeability and large extracellular interstitial space (Fig. 5). The main implication of this feature is that, in patients with cirrhosis, the observation of washout is only suggestive of malignancy, but not sufficient to differentiate HCC from non-HCC malignancies. For this purpose, a careful characterization of the timing and degree of washout may allow a correct diagnosis. Early (i.e., <60 seconds) and marked or punched-out washout is characteristic of non-HCC lesions, whereas late (>60 seconds) and mild washout is characteristic of HCC lesions, such as intrahepatic cholangiocarcinoma (ICC) or metastases [49–51]. On the other hand, early but mild washout or late but marked washout are suggestive of malignancy in general and not specific of any particular malignancy. These lesions should be further investigated by means of MRI or biopsy [52].

HCC: CEUS in Clinical Practice

Despite its inherent advantages, the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL)/European Organization for Research and Treatment of Cancer guidelines on HCC updated in 2011 and 2012, respectively, did not include the use of CEUS in the diagnostic imaging workup, mainly due to the lack of reported specificity in the differentiation between HCC and ICC, the latter of which occurs at a rate of 2%–5% of all new nodules in cirrhosis [47,53]. Nevertheless, the above-discussed differences in arterial contrast enhancement and in the timing and degree of washout occurring in ICC lesions has enabled to it to be better differentiated from HCC. The former often shows rim-like arterial contrast enhancement followed by early (i.e., <60 seconds) and marked washout, whereas the latter usually shows non-rim-like arterial contrast enhancement followed by late (i.e., >60 seconds) and mild washout [45,50,54–57]. This refinement in CEUS capability in the characterization of ICC has led various scientific societies, including Italian, German and British scientific organizations, to develop specific LI-RADS codes for such lesions [45,50,54–57].

![Fig. 8. Contrast Enhanced Ultrasound Liver Imaging Reporting and Data System (CEUS LI-RADS) algorithm. CEUS LI-RADS v2017 Core (2017) with permission of American College of Radiology [59].](image)

![Fig. 9. Complete response after radiofrequency ablation of hepatocellular carcinoma in a 58-year-old woman. A, B. An oblique ascending right subcostal baseline ultrasound image shows a 1.4-cm-sized inhomogeneous, mainly hyperechoic area in the sixth segment (calipers) (A) with no vascular signal on color Doppler (B). C. On contrast-enhanced ultrasonography in the arterial phase (30 seconds after sulfur hexafluoride injection), the lesion shows a lack of contrast enhancement (arrow).](image)
societies, to suggest the use of CEUS in the diagnostic algorithm of HCC in their guidelines (http://www.webaisf.org, http://www.drg.de, and http://www.nice.org.uk, respectively). In the latest version of EASL guidelines on the management of HCC, CEUS is considered a diagnostic tool for HCC, as well as CT and MRI [58].

The American College of Radiology (ACR) has also endorsed the use of CEUS in the diagnostic work-up of HCC. The ACR released in 2016, and then updated in 2017, a dedicated freely-available Contrast Enhanced Ultrasound Liver Imaging Reporting and Data System (CEUS LI-RADS) which uses the size of a lesion, the type and degree of arterial phase enhancement, the presence of washout, and the timing and degree of washout as the major features for categorization of FLLs in patients at high risk for HCC development (Fig. 8) [59]. CEUS LI-RADS is expected to improve the role of CEUS as a major imaging tool, as well as CT and MRI, and facilitate its incorporation into a multimodality imaging approach for liver studies in patients at risk for HCC [60]. The CEUS LI-RADS algorithm has been reported to be highly specific for HCC, while at the same time avoiding the misdiagnosis of ICC [61]. In particular, a study reported that CEUS showed high specificity (92.9%), but limited sensitivity (39.6%), in the diagnosis of HCC, thus suggesting that CEUS may play a role both in the characterization of nodules detected.

Fig. 10. Residual tumor after radiofrequency ablation of hepatocellular carcinoma. A. An axial baseline image in a 54-year-old woman shows a 1.6-cm-sized slightly hyperechoic area in the fifth segment (arrow). B. Contrast-enhanced ultrasonography in the arterial phase (17 seconds after sulfur hexafluoride injection) shows a clear-cut area of eccentrically located hypervascular tissue around the treated area (arrow). C. Three-dimensional i-Slice reconstruction better depicts the same finding in each slice (arrows).
HCC: CEUS in the Assessment of Therapeutic Response

Over the past decade, locoregional therapies (LRTs) have emerged as a valid alternative to conventional surgery in patients with HCC [63,64]. LRTs are usually delivered under US guidance, but correct targeting of the tumor may be inaccurate or even impossible for small HCC nodules, which are poorly defined on US. In this setting, CEUS may facilitate radiofrequency ablation (RFA) electrode placement in hypervascular HCC, which is poorly depicted by B-mode US [65,66]. Newly developed techniques, such as fusion imaging between US and CT/MRI datasets, can further improve the conspicuity of HCCs and the feasibility of percutaneous RFA of HCCs not visible on conventional US, including even subcentimeter HCCs, thus increasing the success rate of percutaneous ablation therapy for HCC [67–69]. Furthermore, an accurate assessment of therapeutic response is of crucial importance, considering that complete tumor ablation significantly increases the likelihood of patient survival, whereas the presence of residual unablated tumor calls for additional treatment [70,71]. Similarly, CEUS suggests that a procedure has been successful when a previously enhancing, hypervascularized HCC nodule shows a lack of contrast enhancement after treatment, whereas still viable tumoral tissue is typically depicted as an arterial-enhancing focus with portal-venous washout (Fig. 9) [72,73]. More recently, 3-dimensional CEUS has been reported to improve the study of tumor vascularity, thereby enabling the response to RFA to be evaluated in the three orthogonal planes (Fig. 10) [74,75].

CEUS: Portal Vein Thrombosis Assessment

Abnormal venous drainage evolves during hepatocarcinogenesis
from the hepatic veins to portal vessels, explaining the predilection of HCC to invade into and disseminate via the portal vein, instead of the hepatic veins [27]. The detection of malignant portal or hepatic vein thrombosis is crucial for proper clinical management. However, benign thrombosis can be found, even without malignant disease, in 4.5%–26% of patients with chronic liver disease [76]. Raza et al. [77] reported that CEUS was able to differentiate malignant and benign venous thrombosis associated with HCC with high diagnostic accuracy, by showing arterial enhancement of the malignant thrombus (Fig. 11).

**CEUS: Limitations**
CEUS shares many limitations with conventional US. Large body habitus, intervening bowel gas, a poor acoustic window, movement artifacts, or even poor clinical conditions may prevent obtaining an optimal CEUS scan. Furthermore, tiny lesions deeply located in the liver parenchyma may be difficult to explore with CEUS, especially at a depth more than 12 cm and in livers with diffuse fibro-fatty changes [78].

Multiple injections of contrast agent are required to investigate different lesions in the same liver and, sometimes, to properly evaluate even a single lesion. Overlapping findings between malignant and benign lesions may exist. In those patients, other imaging modalities, such as multidetector CT or MRI, should be performed for staging or characterization purposes.

Adequate training and knowledge is required to perform an optimal CEUS study; consequently, teaching issues should be considered in order to achieve a reasonable and widespread diagnostic quality. Intravenous administration of a contrast agent must be performed under medical control, which requires additional time, as does the off-line visualization of multiple video clips for the accurate evaluation of all phases of contrast enhancement, affecting the throughput of already busy US departments.

**HCC and CEUS: Final Considerations**
Almost 20 years after its commercial introduction, CEUS is increasingly being recognized as a safe and robust imaging modality, which enables real-time, adequate depictions of the contrast-enhancement patterns of FLLs, including HCC. This unique feature of CEUS has dramatically improved the accuracy of US in the detection and characterization of HCC, as well as in the guidance and evaluation of response to therapeutic procedures [79–81].

Currently, CEUS is increasingly being performed on a routine basis and, in the appropriate clinical setting, is included as a part of the suggested diagnostic work-up of HCC, resulting in better patient management and cost-effective delivery of therapy [82,83].

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