Review Article

Current Role of Contrast-Enhanced Ultrasound in the Diagnosis of Hepatocellular Carcinoma

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Abstract

The routine use of microbubble ultrasound contrast agents for studies of the liver has overcome several limitations of conventional B-mode and Doppler ultrasound techniques. Contrast-enhanced patterns of liver lesions can be studied during all vascular phases (arterial, portal venous, late phases), as in contrast-enhanced computed tomography (CT) and contrast-enhanced magnetic resonance imaging (MRI). Furthermore, the use of contrast-enhanced ultrasound (CEUS) to characterize focal lesions in cirrhosis has recently been recommended in the clinical practice guidelines issued by the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB). CEUS is a well-known, non-invasive technique that can be used to diagnose hepatocellular carcinoma (HCC) and can be performed in real time and under complete control of the ultrasound operator.

In this review article, we summarize the basic concepts and techniques of CEUS, focusing on hepatic applications for the diagnosis of HCC. We also report the main guidelines regarding CEUS in the diagnosis of HCC, which have recently questioned its front-line role in clinical practice.

Introduction to Contrast-Enhanced Ultrasound

The routine use of microbubble ultrasound contrast agents has overcome some of the limitations of conventional B-mode and Doppler ultrasound techniques for the study of different organs, particularly the liver. Indeed, the contrast-enhanced patterns of liver lesions can be analyzed during all vascular phases (arterial, portal venous, late phases), as in contrast-enhanced computed tomography (CT) and contrast-enhanced magnetic resonance imaging (MRI). The clinical practice guidelines issued by the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) have also recently recommended the use of contrast-enhanced ultrasound (CEUS) to characterize focal lesions in the cirrhotic liver [1]. This well-known, non-invasive technique is able to diagnose hepatocellular carcinoma (HCC) with the advantage of being performed in real time and with the complete control of the ultrasound operator.

Basics of contrast-enhanced ultrasound (CEUS)

The first studies on the use of an ultrasound (US) contrast agent, Levovist®, were published in 2000 [2,3]. However, the use of a hydrosaline solution to better visualize the aortic arc was reported as early as 1968.

US contrast agents consist of stabilized gaseous microbubbles (equal to or smaller than red blood cells, with a diameter of less than 7 μm). Based on their characteristics, US contrast agents are divided into first-generation contrast agents, which contain bubbles of air, and second-

generation contrast agents, which are prepared from other gases. Gaseous microbubbles are stabilized inside a shell. Technological progress has revealed that US contrast agents produce a harmonic (non-linear) signal that has a double frequency with respect to the surrounding tissue, and second-generation contrast agents have considerably improved imaging due to their major stabilization and favourable performance compared to air at low acoustic pressure [4].

Currently, three US contrast agents are commonly used for liver studies:

SonoVue® (sulfur hexafluoride with a phospholipid shell), Bracco SpA, Milan, Italy, introduced in 2001. Licensed in Europe, China, India, Korea, Hong Kong, New Zealand, Singapore and Brazil;

Definity®/Luminity® (octafluoropropane [perflutren] with a lipid shell), Lantheus Medical, Billerica, MA, USA, introduced in 2001. Licensed in Canada and Australia;

Sonazoid® (perfluorobutane with a phospholipid shell: hydrogenated egg phosphatidyl serine), Daiichi-Sankyo, GE Tokyo, Japan, introduced in 2007. Licensed in Japan and South Korea.

The pharmacokinetics of US contrast agents are different from the contrast agents used for CT and MRI imaging: for US, the microbubbles are confined to the vascular space (blood pool enhancer), whereas the majority of contrast agents for CT and MRI are rapidly removed from the blood into the extravascular space. In the liver, the dual blood supply from the portal vein (70-75%) and the hepatic artery (25-30%) results in three vascular phases in CEUS studies:

Arterial phase: usually beginning within 20 s after injection and continuing for 30-45 s, depending on the patient's circulatory status; this phase provides information about arterial vascular supply;

Portal venous phase: generally beginning within 30-45 s after contrast agent injection and lasting for 2-3 min;

Late phase: usually continuing until the clearance of the US contrast agent from the circulation and limited to 4-6 min.

A new contrast agent, Sonazoid®, has an additional post-vascular (Kupffer cell or parenchymal) phase, with the contrast agent being retained in the liver and spleen [5] due to the phagocytosis of the contrast agent by Kupffer cells. The post-vascular phase begins 10 min after injection and lasts for an hour or more; to avoid an overlap with the late phase, this phase imaging should not be performed sooner than 10 min after injection.

Late and post-vascular phase enhancement provides important information about the features of lesions: the majority of malignant lesions are hypo-enhancing, whereas most solid benign lesions are iso- or hyper-enhancing [6-12].

US contrast agents are generally safe, with a low incidence of side effects: serious adverse events are reported at a rate of 0.0086% after abdominal use [13]. The good tolerance and safety profiles of US contrast agents permit their repeated administration, even in the same session if needed. Furthermore, because of the absence of cardio-, hepato- or nephro-toxic effects, it is not necessary to perform laboratory tests to assess liver or kidney function before the administration of these agents. Additionally, the incidence of severe hypersensitivity is lower than with iodinate contrast agents and is comparable to that found with MRI contrast agents. Life-threatening anaphylactic reactions in abdominal applications have been reported at a rate of 0.001%, with no deaths among the larger number of patients who have undergone this procedure [13]; nonetheless, ultrasound providers should be trained in resuscitation manoeuvres. Data regarding the use of US contrast agents during pregnancy and breast-feeding or in paediatric patients are limited [14]; therefore, their use in these contexts is off-label and requires informed consent. Although data regarding adverse reactions to US contrast agents in cardiac disorders are inconclusive [15-17], current EFSUMB guidelines suggest caution in the use of US contrast agents in patients with severe coronary artery disease [1].

The contrast-enhanced ultrasound (CEUS) procedure

Every CEUS investigation should start with a conventional B-mode evaluation to analyse the size, site, and echogenicity of the lesion and its relationship with other hepatic structures. The second step involves Doppler evaluation focusing on the vascular pattern: the presence of peripheral or central lesion vessels. The last step is CEUS evaluation. When a target lesion is identified, it may be selected in a contrast-specific imaging mode at a low mechanical index. Technological advancements now permit the simultaneous viewing of dual screens, one with a contrast-specific display and the other with conventional B-mode imaging. The US contrast agent is administered with a bolus injection (1-5 ml), followed by a flush of saline solution (5-10 ml); to avoid destruction of the microbubbles during injection, the needle calibre should not be smaller than 20 gauge. Real-time CEUS can be recorded in the form of video clips. A typical CEUS examination lasts for 5 min, though it may be necessary to continue for a longer time period because of a delayed wash-out. If a second contrast bolus is required, it is necessary to wait for the disruption of the previously injected microbubbles from the first contrast bolus (approximately 6-10 min) or to use multiple high mechanical index flashes. In the case of difficulty in the visualization of small lesions, patient cooperation is essential. Despite the use of a low mechanical index, the target lesion should be scanned intermittently after the arterial phase to avoid microbubble disruption [1].

Clinical hepatic applications of CEUS

The majority of clinical applications of CEUS in the abdomen are for the liver. In 2012, EFSUMB published its revised guidelines and recommendations for the use of CEUS in liver diseases [1]. Clearly the principal aim of CEUS in the liver is the characterization of focal liver lesions (FLLs). Although US without contrast can characterize only simple cysts and typical haemangiomas, the use of US contrast agents unfortunately may not overcome these well-known limitations due to a patient's habitus, intestinal gas and poor compliance. Moreover, if B-mode imaging is unsatisfactory, a CEUS study will be unsatisfactory as well.

Some of the most important limitations of CEUS in the liver are as follows:

Because of the resolution limit of CEUS, the smallest recognizable lesions generally have a diameter of 3-5 mm, especially under specific scanning conditions [18];

There is a possibility of overlooking very small FLLs;

It is impossible to analyse sub-diaphragmatic lesions, especially those in segment VIII, though an intercostal approach or a left lateral decubitus position can be useful;

Limited visualization of deep-seated lesions in case of steatosis, for which a left lateral decubitus position can be useful;

The falciform ligament and surrounding fat can cause an enhancement defect that may be erroneously interpreted as an FLL [1].

Hepatocellular Carcinoma: A Brief Summary

Epidemiology and aetiology

Liver cancer is the sixth most commonly diagnosed cancer and the third most common cause of cancer-related death, amounting to 7% of all cancers [19], and the most common primary malignancy of the liver in adults is HCC, representing more than 90% of primary liver cancers. In 2008, the incidence rates were 65,000 and 21,000 cases and the mortality rates were 60,240 and 18,400 cases in Europe and the United States of America, respectively [19]. Because of the growing incidence of HCC, it is estimated that by 2020, the number of cases will be 78,000 in Europe and 27,000 in the USA. This increase in HCC incidence reflects the number of hepatitis C virus (HCV)-infected patients in Europe during the 1940-60 period and ten years later in the USA. HCC is more frequent in males, with a male to female ratio of 2.4, and its incidence increases progressively with age [19].

Based on the current epidemiologic data, it is clear that HCC is a major worldwide public health problem.

Approximately 90% of HCC risk factors are known. Chronic viral hepatitis (types B and C), alcohol intake and aflatoxin exposure represent the most frequent risk factors. Among viral infections, hepatitis B is the primary cause of HCC in Africa and East Asia, whereas hepatitis C is the major risk factor in the Western world [20].

In particular, 31% of cases of HCC are due to chronic hepatitis C infection, which affects 170 million people worldwide. Furthermore, cirrhosis is a well-known risk factor for HCC: approximately one-third of cirrhotic patients will develop HCC during their lifetime [21]. All aetiologies of cirrhosis can result in HCC, including chronic viral infection, alcohol intake, non-alcoholic fatty liver disease, hemochromatosis and alpha-1-antitrypsin deficiency, but the risk is higher with viral infections. The annual rate of patients with cirrhosis that develop HCC is 2% with HBV infection and 3-8% with HCV infection [22]. Additionally, HCV genotype 1b appears to increase the oncogenic risk [23].

Detection of HCC

Early HCC detection is crucial for decreasing tumour-related mortality; thus, surveillance programmes are recommended for patients at a high risk of developing HCC. Table 1 reports the categories of patients who should be involved in surveillance programmes [24]. US is the most widely used imaging technique in HCC surveillance, and HCC typically appears as a hypo-echoic lesion compared to the surrounding parenchyma, but it may also appear as iso-echoic, hyper-echoic, mixed or with a characteristic pattern of nodule in nodule. Approximately 50% of HCC cases show a hypo-echoic halo (Figure 1).

Cirrhotic patients at CP stage A, B
Cirrhotic patients at CP stage C awaiting OLT
Non-cirrhotic HBV carriers with active hepatitis or family history of HCC
Non-cirrhotic patients with chronic hepatitis C and advanced liver fibrosis F3

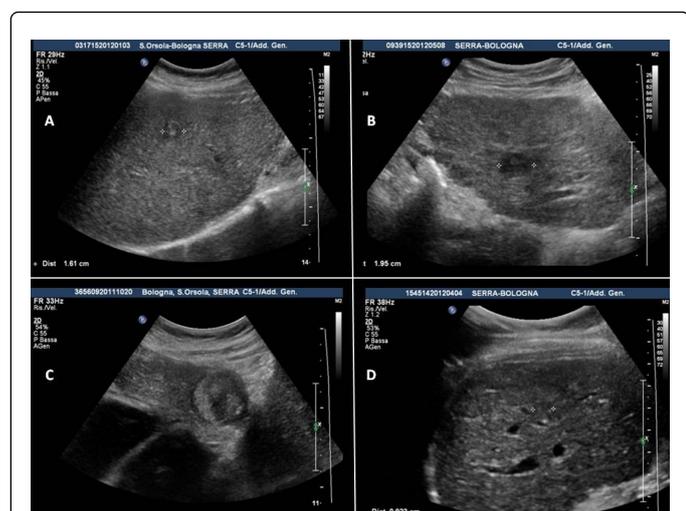**Table 1:** Categories of patients involved in surveillance programmes.

Figure 1: Different patterns of HCC. A: Small hyper-echoic HCC with hypo-echoic halo. B: Typical hypo-echoic HCC. C: Dishomogeneous HCC with hypo-echoic halo and a nodule-in-nodule pattern. D: Iso-echoic HCC.

The major advantages of US include its non-invasiveness, good acceptance by patients and moderate costs, together with its diagnostic accuracy as a surveillance test, with a sensitivity of 58-89% and a specificity of more than 90% [25,26]. Recent data show a very high overall sensitivity (94%), which is lower (63%) in early HCC [27]. In fact, HCC detection can be difficult due to the inhomogeneous eco-coarse pattern of the cirrhotic liver (Figure 2), which is characterized by fibrous septa and regenerative nodules, and US contrast agents do not increase the ability of US to detect small HCCs [28]. Because of these limitations, it is recommended that surveillance programmes involving US should be performed by experienced operators using good-quality equipment and with specific training. Unfortunately, CEUS does not have a role in the detection of HCC but is implemented only in the characterization of a B-mode-detected lesion. In fact, compared to contrast-enhanced CT and MRI, scanning of the entire liver is not possible during the arterial phase of CEUS. In conclusion, CEUS is not currently indicated for increasing the detection rate of HCC in the course of surveillance [28].
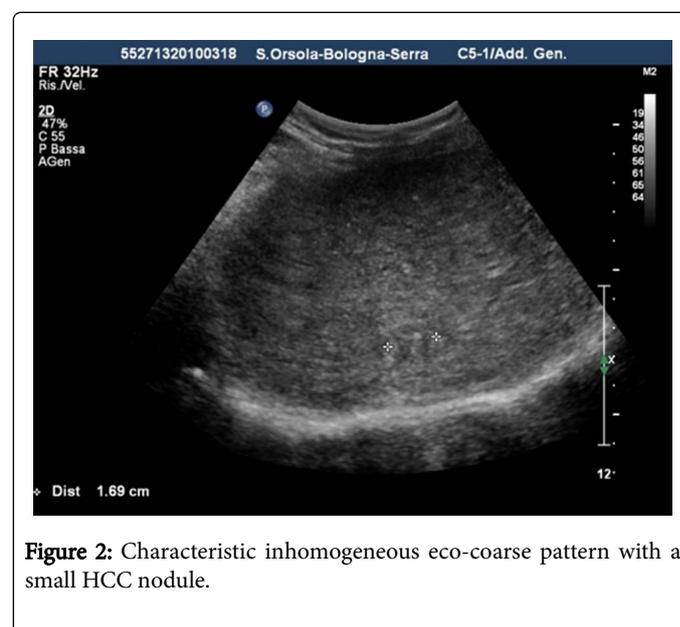

Figure 2: Characteristic inhomogeneous eco-coarse pattern with a small HCC nodule.

According to the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD), US without Alpha-Fetoprotein (AFP) is considered the most appropriate test for surveillance [24,29]. AFP lacks adequate sensitivity and specificity for diagnosis and surveillance [27,30], and AFP levels can increase during infection flares and rarely increase in early-stage tumours. Overall, combination with AFP is not recommended because it increases the detection rate by only 6–8%, generates false-positive results, and consequently results in a significant increase in cost [27,31].

Based on the HCC volume doubling time and on meta-analysis and cost-effectiveness studies [27,32], AASLD and EASL-EORTC guidelines suggest a surveillance interval of 6 months as the preferable choice with a good cost-effectiveness ratio. Because of extensive inter-patient variability, Japanese guidelines have proposed a shorter 3-month interval [33,34].

The probability of HCC increases with nodule size. Nodules <1 cm are rarely malignant, and ultrasound follow-up (at 3-4-month intervals) is sufficient in these cases [24,29]. Conversely, nodules >1 cm have a higher probability of being malignant: the percentage of HCC is 66% for nodules 1–2 cm in size, 80% for nodules 2–3 cm in size, and 92–95% for nodules with a diameter larger than 3 cm. Consequently,

additional investigations are needed when the nodule is more than 1 cm in diameter [35-37].

Role of CEUS

Diagnosis and characterization of HCC

In approximately 90% of cases, carcinogenesis is a multistep pathway in cirrhosis (International Consensus Group for Hepatocellular Neoplasia 2009) [38] and presents the following steps:

Large regenerative nodule;

Low- or high-grade dysplastic nodule;

Dysplastic nodule with a focus of HCC;

Well-differentiated HCC;

Moderate to poorly differentiated HCC

Cytological and architectural modifications occur during this process. Among the architectural modifications, a decrease in both normal arterial and portal blood flows and a progressive increase in arterial flow from newly formed tumour vessels (neo-angiogenesis), termed non-triadal arteries, is common. This arterial neo-angiogenesis is the hallmark of HCC that permits diagnosis [39-42].

The Doppler pattern of HCC is characterized by a rich arterial vascularization that is called the basket pattern due to the fine blood flow surrounding the nodule with a high frequency (>1 kHz) and elevated resistive index (>0.71) [43,44]. An artero-portal fistula can occasionally be observed. In contrast, macro-regenerative and dysplastic nodules either do not present vascularization or may exhibit arterial vessels with a low frequency and a normal resistive index [45]. Unfortunately, these Doppler signals can be visualized only in 50% of small HCCs [45].

Although macro-regenerative and dysplastic nodules generally do not present early contrast uptake, resembling liver parenchymal behaviour, the typical CEUS pattern of HCC in liver cirrhosis is hyper-enhancement in the arterial phase, followed by wash-out in the late phase [29]. This pattern corresponds to HCC in more than 97% of cases [46,47] but has also been reported in peripheral CCC and hepatic lymphoma in 1–3% of cases. Arterial hyper-enhancement is generally strong and homogeneous in HCC but can be inhomogeneous in larger nodules with a diameter greater than 5 cm because of the presence of necrotic regions. Unfortunately, it is well known that high-grade dysplastic nodules and hyper-enhancing haemangiomas may also present arterial hyper-vascularization [48]. Based on these findings, to increase the specificity of CEUS, the demonstration of wash-out is decisive; overall, wash-out is observed in approximately half of HCC cases, less often compared with CT or MRI due to their different contrast pharmacokinetics [49]. The presence of wash-out in HCC also depends on the nodule dimensions: wash-out is described only in 20–30% of nodules with a diameter of 1–2 cm but in 40–60% of nodules with a diameter of 2–3 cm [18,35]. Furthermore, wash-out characterizes HCC with poorer grades of differentiation, whereas well-differentiated HCC tends to be iso-enhanced with respect to the parenchyma in the portal venous or late phase [50-53]. In addition, wash-out tends to start later in HCC, generally not before 60 s after injection, and in one-fourth of cases appears only after 180 s [54] (Figure 3). For this reason, it is mandatory to observe nodules in cirrhosis (>4 min) for a longer time period to increase the sensitivity of the diagnosis of HCC. The presence of early wash-out (<60 s) has been

described in poorly differentiated HCCs and in cases of non-hepatocellular cancers, for example, in peripheral CCC [51,53,54]. The fibrolamellar variant of HCC also shows a rapid wash-out as well as rapid hyper-enhancement with a heterogeneous pattern [1,55]. These findings led the authors of AASLD and EASL to remove CEUS as the front-line detection method for HCC [24,29].

Figure 3: Iso-echoic HCC. A: US appearance. B: CEUS appearance: hyper-enhancement during the arterial phase. B: CEUS appearance: wash out in the late phase.

In cases of arterial hyper-enhancement not followed by wash-out, the lesion is highly suspicious for well-differentiated HCC; however, this type of pattern is not conclusive [36,46,51]. According to EFSUMB recommendations, if the CEUS pattern is not definitive, CT or MRI should be performed, and if those techniques are also inconclusive, biopsy is necessary [1]. In the case of negative biopsy, it is mandatory to follow-up on the nodule every 3 months at least for the first 2 years, as the diagnosis of small, well-differentiated HCCs remains a challenge [1].

Staging

Because of the propensity of HCCs to form satellite lesions, accurate intrahepatic staging is mandatory to guide clinical management. During the short duration of the arterial phase, CEUS is not able to assess the entire liver parenchyma to detect small tumour foci [24,29]. Thus, contrast-enhanced CT or MRI is essential to stage patients with HCC. The additional post-vascular (or Kupffer) phase for Sonazoid® may improve staging of the disease [1].

Biopsy

US is the imaging technique most commonly used worldwide to guide liver biopsy when a pathological diagnosis is necessary. CEUS can guide focal biopsy by increasing accuracy and decreasing false-negative rates, especially for larger focal liver lesions. By revealing vascularized and necrotic regions, CEUS can locate the correct site for biopsy [56]. Furthermore, CEUS can localize occult lesions on non-enhanced US [57].

Portal vein thrombosis

Portal vein thrombosis involves the development of solid material in the portal vein, which can completely or partially occupy the vascular lumen; it may be a simple clot or a neoplastic thrombosis. Malignant thrombosis influences the prognosis and management of the patient. In B-mode ultrasonography, the thrombus usually appears as echoic material in the vascular lumen. Doppler imaging shows no flow signal into the vein, and in Doppler spectral study, the presence of intra-thrombus arterial signals has a high specificity and moderate sensitivity for malignant tumours. CEUS permits characterization of the thrombus: an appositional thrombus is avascular during all phases (Figure 4), whereas a neoplastic thrombosis shows tumour-like characteristics, including arterial hyper-enhancement and rapid wash-out [58,59] (Figure 5).
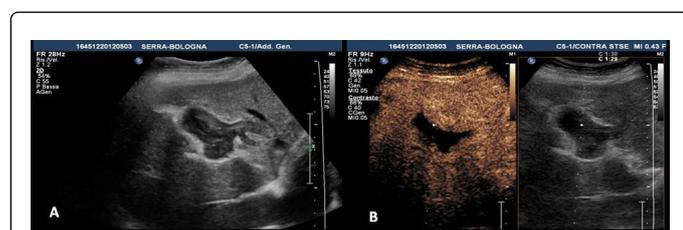

Figure 4: Non-neoplastic portal vein thrombus. A: US appearance. B: CEUS appearance: the thrombus is avascular during all vascular phases
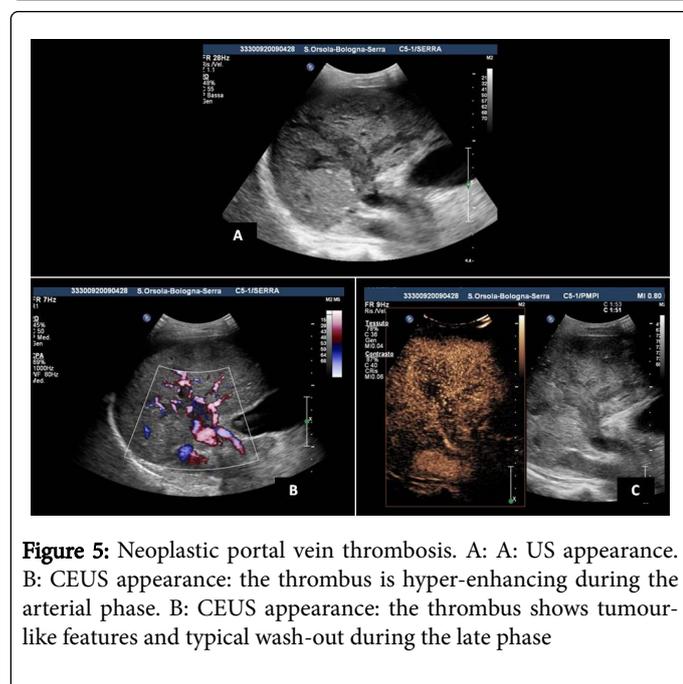

Figure 5: Neoplastic portal vein thrombosis. A: A: US appearance. B: CEUS appearance: the thrombus is hyper-enhancing during the arterial phase. B: CEUS appearance: the thrombus shows tumour-like features and typical wash-out during the late phase

CEUS has a significant function in thrombus biopsy guidance through region enhancement [60].

CEUS in loco-regional treatment

Loco-regional treatments play a key role in the management of HCC patients. In general, unenhanced US guides ablation, and CEUS is fundamental for comparisons of enhancing patterns before and after treatment and can facilitate needle positioning in case of unclearly delineated lesions. Early evaluation of treatment effect after ablation can allow the immediate re-treatment of a residual tumour, decreasing the rate of incomplete ablation from 16% to 6% [61].

Intra-operative CEUS

Intra-operative (IO) US is considered the gold standard for the surgical management of patients with HCC or colorectal liver metastasis undergoing resection [62,63]. Recently, IO-CEUS has been proposed for patients undergoing tumour resection because of its high sensitivity, specificity and accuracy compared with IO-US, CT or MRI. The shorter contrast enhancement duration with respect to percutaneous CEUS can limit this technique, and repeated injections may be required [64-66].

Discussion

The non-invasive diagnosis of HCC is relatively recent in clinical practice. Until 2000, HCC diagnosis was based on biopsy, and histological diagnosis had some limitations related to feasibility and diagnostic accuracy. A biopsy can be contraindicated, as in the case of difficult sites or altered coagulative parameters [67]. Furthermore, differential diagnosis between high-grade dysplastic nodules and early HCCs can be very difficult, with the most important criterion being stromal invasion [68].

In 2001, for the first time, non-invasive criteria for HCC diagnosis were reported by an EASL Panel of Experts on HCC in Barcelona [69]. HCC diagnosis required only one dynamic behaviour: the up-take of a contrast agent during the arterial phase by CT, MRI angiography or US. Nodular lesions with a diameter of more than 2 cm in cirrhosis were considered HCCs if they presented this contrast behaviour in two imaging techniques or presented contrast enhancement in a unique imaging technique with AFP levels above 400 ng/ml. In all other cases, biopsy was needed [69].

In 2005, EASL and AASLD reported a new radiological hallmark, i.e., contrast uptake in the arterial phase and wash-out in the venous/delayed phase [70]. Non-invasive HCC diagnosis was based on the presence of the typical radiological hallmark in a unique imaging technique if the nodules were larger than 2 cm and in two imaging techniques (CT, MRI and CEUS) if the nodules measured between 1-2 cm. AFP was eliminated from the diagnostic algorithm due to its previously reported limitations [70].

Although CEUS has a role as the first line of investigation in the diagnosis of HCC, it is currently variably accepted in national and international guidelines. At present, CEUS is recommended by EFSUMB and is part of the Japanese guidelines on HCC [1,71,72] but has been removed from the American and EASL guidelines [24,29]. The primary reason for the removal of CEUS is the risk of misdiagnosing Intrahepatic Cholangiocellular Carcinoma (ICC) for HCC using CEUS alone [47,73]. In contrast, MRI is very specific for the diagnosis of ICC because of the absence of wash-out in the venous and late phases [73]. In clinical practice, the probability of misdiagnosis is minimal when CEUS is performed by a trained physician [74]. Moreover, this exclusion from AASLD guidelines is also correlated with the fact that ultrasound contrast agents are not licensed for the liver in the USA, and CEUS is consequently not available. It has to be emphasized that in the EFSUMB guidelines, the typical pattern of ICC is a peripheral rim enhancement, with non-enhancement as a variation, and hypo/non-enhancement in the portal and late phases with rapid wash-out (<60 s). Regardless, significant variability has been

described over the past several years, resulting in the use of CEUS remaining controversial [74].

In 2010, AASLD recommended that nodules larger than 1 cm should be investigated with a single imaging modality: 4-phase multidetector CT scan or dynamic contrast-enhanced MRI [29]. If the typical radiological hallmark is present, HCC diagnosis is made; however, if the nodule's behavior is not characteristic, a second imaging technique or a nodule biopsy is mandatory [29]. This change in procedure is based on different studies, with some showing that the use of a single contrast-enhanced technique causes a reduction in the positive predictive value, which remains above 90% [18,35]; other reports evidence high specificity of the typical radiological hallmark, permitting a single contrast-enhanced modality [49,75]. AASLD guidelines suggest the necessity of strict adherence to imaging protocols and the execution of non-invasive diagnosis of HCC in expert centres [29].

Recent EASL guidelines, similar to AASLD, suggest the use of latest generation CT and MRI for the non-invasive diagnosis of HCC [24]. For nodules between 1 and 2 cm, EASL guidelines recommend one imaging modality only in centres of excellence with high-end radiological equipment and two imaging techniques in suboptimal settings. This prudent behaviour is due to the evidence of equivocal data regarding the non-invasive diagnosis of 1-2-cm nodules [35,49,76,77].

For cirrhotic patients, both AASLD and EASL guidelines recommend US follow-up every 3-4 months for nodules less than 1 cm and a single contrast-enhanced technique for lesions greater than 2 cm in diameter [24,29].

The key role suggested for CEUS in the EFSUMB guidelines is very different.

Because of the great difference in the range of tumour types between cirrhotic and non-cirrhotic livers, EFSUMB guidelines separately describe the characterization of FLLs for these 2 subgroups of patients, with and without cirrhosis [1].

Characterization of FLLs in the non-cirrhotic liver

For the characterization of FLLs in non-cirrhotic patients, the most important aim is to distinguish between benign and malignant lesions. Malignancies are characterized by hypo-enhancement in the late and post-vascular phases, corresponding to the wash-out phenomenon. Rare exceptions are some metastases and atypical HCCs.

The EFSUMB indications for CEUS with regard to FLL characterization in non-cirrhotic patients are as follows:

Incidental findings on routine ultrasound;

Lesion or suspected lesion(s) detected by US in patients with a known history of a malignancy as an alternative to CT or MRI;

The need for a contrast study when CT and MRI contrast analyses are contraindicated;

Inconclusive CT and MRI;

Inconclusive cytology/histology results [1].

Characterization of FLLs in the cirrhotic liver

The case of FLLs in the cirrhotic liver is very different. The more frequent FLLs that occur in the cirrhotic liver are hepatocellular lesions (>95% of cases), peripheral cholangiocellular carcinomas (CCCs), lymphomas and haemangiomas. Benign lesions are possible and may be considered but for unknown reasons are very rare. Accordingly, any lesion in the cirrhotic liver should be considered HCC until proven otherwise [1].

The EFSUMB indications for CEUS with regard to FLL characterization in cirrhotic patients are as follows:

Characterization of all nodules found on surveillance and routine US;

characterization of nodules in cirrhosis and establishment of a diagnosis of HCC, and it is extremely useful, especially when performed immediately after nodule detection, to make a rapid diagnosis, though disease staging with CT or MRI is needed (unless contraindicated) before deciding a treatment strategy;

Characterization of nodules when CT or MRI is inconclusive, especially in nodules not suitable for biopsy;

Contributing to the selection of nodule(s) for biopsy when they are multiple or have different contrast patterns;

Follow-up of nodules not diagnostic for HCC, monitoring changes in size and enhancement patterns over time;

Characterization of nodules after inconclusive histology [1]

Conclusions

CEUS is a method that is non-invasive, rapid, cost-efficient, less stressful and less invasive for patients that is also accurate, repeatable and useful for the diagnosis and management of HCC; there is no radiation exposure, and CEUS is non-nephrotoxic and non-allergenic. The early detection of HCC with US screening has permitted tumour diagnosis when effective treatment can be initiated. When nodular lesions are checked in the cirrhotic liver, CEUS permits a rapid characterization with a good accuracy when performed by a trained physician [74]. The early diagnosis of small, well-differentiated HCCs is nevertheless still a challenge. As previously reported, lesions of 1-2 cm in diameter frequently show inconclusive behaviour [77]. In these situations, following inconclusive CT, MRI, and histology, CEUS can play a key role. Furthermore, CEUS has an important function in guiding focal liver lesion biopsy and in guiding and monitoring loco-regional treatments.

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