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High frame-rate contrast enhanced ultrasound (HIFR-CEUS) in the characterization of small hepatic lesions in cirrhotic patients

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Abstract

Background To show the effectiveness of plane wave HighFrame-Rate CEUS (HiFR-CEUS) compared with "conventional" (plane wave) CEUS (C-CEUS) in the characterization of small (< 2 cm) focal liver lesions (FLLs) not easily detected by CT in cirrhotic patients. HiFR-CEUS exploit an ultra-wideband nonlinear process to combine fundamental, second and higher-order harmonic signals generated by ultrasound contrast agents to increase the frame rate. C-CEUS is limited by the transmission principle, and its frame-rate is around 10 FPS. With HiFR-CEUS (Shenzhen Mindray Bio-Medical Electronics Co., China), the frame-rate reached 60 FPS.

Material and methods Ultrasound detected small FLLs (< 2 cm) in 63 cirrhotic patients during follow-up (June 2019–February 2020); (7 nodules < 1 cm and were not evaluable by spiral CT). Final diagnosis was obtained with MRI (47) or fine needle aspiration (16 cases) C-CEUS was performed and HiFR-CEUS was repeated after 5 min; 0.8–1.2 ml of contrast media (SonoVue, Bracco, Italy) was used. 57 nodules were better evaluable with HiFR-CEUS; 6 nodules were equally evaluable by both techniques; final diagnosis was: 44 benign lesions (29 hemangiomas, 1 amartoma, 2 hepatic cysts; 2 focal nodular hyperplasias, 3 regenerative macronodules, 3 AV-shunts, 3 hepatic sparing areas and 1 focal steatosis) and 19 malignant one (17 HCCs, 1 cholangioca, 1 metastasis); statistical evaluation for better diagnosis with X^2 test (SPSS vers. 26); we used LI-RADS classification for evaluating sensitivity, specificity PPV, NPV and diagnostic accuracy of C- and HFR-CEUS. Corrispective AU-ROC were calculated.

Results C-CEUS and HiFR-CEUS reached the same diagnosis in 29 nodules (13 nodules > 1 < 1.5 cm; 16 nodules > 1.5 < 2 cm); HiFR-CEUS reached a correct diagnosis in 32 nodules where C-CEUS was not diagnostic (6 nodules < 1 cm; 17 nodules > 1 < 1.5 cm; 9 nodules > 1.5 < 2 cm); C-CEUS was better in 2 nodules (1 < 1 cm and 1 > 1 < 1.5 cm). Some patient's (sex, BMI, age) and nodule's characteristics (liver segment, type of diagnosis, nodule's dimensions ($p = 0.65$)) were not correlated with better diagnosis (p ns); only better visualization (p 0.004) was correlated; C-CEUS obtained the following LI-RADS: type-1: 18 Nodules, type-2: 21; type-3: 7, type-4: 7; type-5: 8; type-M: 2; HiFR-CEUS: type-1: 38 Nodules, type-2: 2; type-3:4, type-4: 2; type-5: 15; type-M: 2; In comparison with final diagnosis: C-CEUS: TP: 17; TN: 39; FP: 5; FN:2; HIFR-CEUS: TP: 18; TN: 41; FP: 3; FN:1; C-CEUS: sens: 89.5%; Spec: 88.6%, PPV: 77.3%; NPV: 95.1%; Diagn Acc: 88.6% (AU-ROC: 0.994 ± SE_{AUC}: 0.127; CI: 0.969–1.019); HiHFR CEUS: sens: 94.7%; Spec: 93.2%, PPV: 85.7%; NPV: 97.6%; Diagn Acc: 93.2% (AU-ROC: 0.9958 ± SE_{AUC}: 0.106; CI: 0.975–1.017) FLL vascularization in the arterial phase was more visible with HiFR-CEUS than with C-CEUS, capturing the perfusion details in the arterial phase due to a better temporal resolution. With a better temporal resolution, the late phase could be evaluated longer with HiFR-CEUS (4 min C-CEUS vs. 5 min HiFR-CEUS).

Conclusion Both C-CEUS and HIFR-CEUS are good non invasive imaging system for the characterization of small lesions detected during follow up of cirrhotic patients. HiFR-CEUS allowed better FLL characterization in cirrhotic patients with better temporal and spatial resolution capturing the perfusion details that cannot be easily observed with C-CEUS.

Keywords Contrast enhanced Ultrasound · Plane wave technology · Sonovue · Cirrhosis · Hepatocellular carcinoma · Nodule characterization

Extended author information available on the last page of the article

Introduction

Cirrhosis is a risk condition for development of hepatocellular carcinoma [1]; In the United States, HCC related to hepatitis C has recently become the fastest rising cause of cancer-related death, and during the past two decades, the incidence of HCC has tripled while the 5-years survival rate has remained below 12% [2]; In Europe annual incidence is actually about 10% [3]; the main (American -AASLD- [4], European -EASL- [5], Asian -APASL- [6, 7]) guidelines recommend surveillance for patients with cirrhosis because of their high risk of developing HCC. The APASL and EASL guidelines extend surveillance to certain non-cirrhotic high-risk groups, while the AASLD guidelines do not address the issue of HCC in non-cirrhotic livers [8].

Compared to the previous guidelines, there have been changes in the diagnostic tests and in the decision algorithm. For example, the 2018 updated guidelines from AASLD [4] and EASL [5] now include gadoxetic acid-enhanced MRI as a diagnostic test, while the new EASL [5], Asian -APASL- [6, 7] and Korean (KLCA) [9] guidelines now include CEUS as a second-line diagnostic test.

Regarding the surveillance mode, all guidelines agree on the use of ultrasound but differ concerning the utilization of alpha-fetoprotein (AFP).

The role of contrast-enhanced ultrasonography in the detection of small nodules in cirrhotic patients is not considered because this technique is not "panoramic" of the whole liver in arterial phase [10]; instead it's use in the diagnosis is controversial: AASLD does not recommend contrast enhanced ultrasonography (CEUS), APASL considers it to be as sensitive as CT or MRI, and EASL considers it to be sufficient for the diagnosis of nodules ≥ 1 cm in size in cirrhotic patients. In general, several studies have confirmed the utility of CEUS for diagnosing HCC [11–13]. However, some have cautioned against using just CEUS to diagnose HCC, because intrahepatic Cholangiocellular carcinoma (iCC) might display the same vascular pattern as HCC [14, 15]. Subsequent studies have demonstrated that the washout in iCC begins earlier (less than 60 s) after contrast injection than in HCC [16–19], which has led to a slightly modified definition of the typical hallmark of HCC at CEUS, i.e. arterial phase hyperenhancement followed by late (> 60 s) washout of mild degree [20, 21]. Recent large multicentre study [22] confirmed in daily practice the high specificity of CT, MRI and CEUS imaging techniques for HCC between 20 and 30 mm, and therefore authors validated the EASL-AASLD recommendations for these lesions, but they found a drop in specificity using CT or MRI in 10–20 mm HCC and they don't recommend systematic combined imaging at first as sensitivity would be very low. This explains the sequential strategy used in the EASL/EORTC and AASLD guidelines allowing HCC diagnosis in cirrhosis based on a single technique (CT or MRI). A recent review [23] discusses the emerging role of hepatobiliary magnetic resonance contrast media and contrast-enhanced ultrasound for noninvasive diagnosis of Hepatocellular Carcinoma: the best sequential approach combined MRI and CEUS. The explanation of the phenomenon is that there are several distinctive features of CEUS, in comparison to CT/MRI, that reflect the dissimilarities in their underlying methods of image acquisition and types of contrast agent used [23]. First, CEUS allows real-time evaluation of the enhancement of a nodule, resulting in more sensitive detection of arterial phase hyperenhancement (APHE) than CT or MRI which may fail to demonstrate transient APHE in the early arterial phase. Therefore, CEUS can be considered to be an alternative imaging option for nodules categorized in CT or MRI as LR-3 or LR-4 due to the absence of APHE, because some of these nodules potentially could be upgraded to LR-5 if APHE is shown on CEUS [24]. Second, there are no vascular pseudolesions on CEUS [23].

Nevertheless, MRI and CT are the first methods of choice for diagnosing HCC, because they enable examination of the liver as a whole [25].

Even if CEUS has no detection power [25], it still rises to characterize well even small nodules (< 2 cm) detected during ultrasound surveillance [26]. This technique serves as a one-stop diagnostic test for 80.8% of the patients, reducing the need for CT-MR scans and providing savings in terms of radiation exposure, time, and money [27]. The use of contrast agents may improve the ability of US to distinguish between liver cancer and benign abnormalities and, because it can be performed at the same appointment as unenhanced US, more rapid diagnoses may be possible and some CT and MRI examinations may be avoided [12].

Conventional (baseline and contrast-enhanced) ultrasonography is based technically on Delay And Sum (DAS) technique [28]; the DAS technique uses several transmissions of US signals focused in one or more regions to scan the entire area to be analyzed and to form the scan lines that will be used to reconstruct the final image. This process is time-consuming and limits the frame rate to approximately 30–40 frames per second.

In recent years, new conventional and contrastographic ultrasound technology has developed: the so called "Plane-Wave Imaging" (PWI), that works with the simultaneous excitation of all available elements in a certain transducer. This technology transmits a single "plane wave" to insonate the entire region of interest and collect the same ultrasonic signals reflected and refracted in a single impulse; this means a global reduction of number of insonations (per second) to obtain the ultrasonographic image with a consequent increase in the number of images obtainable.

PWI has been applied to most fields in medical ultrasound [29] yielding framerates as high as several thousands of images per second. The simultaneous excitation of all available elements in a certain transducer to transmit and collect ultrasonic signals is necessary; At first this increase in framerate was obtained at the expense of reduced contrast and resolution. However, this drawback was skillfully addressed by Coherent Plane-Wave Compounding (CPWC) [30, 31], that, using a significantly smaller number of insonations (at least ten times lower), is able to reach an image quality comparable to conventional B-mode [32] and contrast enhanced ultrasonography [33]. Furthermore, this technology, by spreading the spatial peak acoustic intensity over more pulses, reduces the peak pressure and, hence, preserves the microbubbles [33].

Other studies have demonstrated that CPWC technology is more sensible to detect the contrast agent in comparison to conventional CEUS [34], and consequently offers an improvement in the CPWC-contrast imaging in comparison to the conventional one [35].

Recently, Schiefler [36] demonstrated that the acquisition of multiple frames and the angulation, used to excite the transducer elements, tends to compensate the information lost by the use of sparse conditions, improving the lateral and axial resolutions besides the contrast.

This new technology was implemented for transient elastography [32], for the study of flow inside the vessels [37, 38] and for echocardiography [39], which introduced a trade-off between framerate and image quality;

The CPWC contrast enhanced ultrasound (C-CEUS) has a limited frame-rate (around 10 FPS); recently a new CPWC with high frame rate (about 60 FPS) has been developed (HiFR-CEUS) (Shenzhen Mindray Bio-Medical Electronics Co., China); the higher frame rate technology may be able to give better details of small lesions, less contrast agent destruction and consequently its longer persistence in late phase [40].

Aim of this prospective study is to show the effectiveness of High Frame-Rate CEUS (HiFR-CEUS) compared with conventional CEUS (C-CEUS) in the characterization of small (< 2 cm) focal liver lesions (FLLs) not easily detected by CT in cirrhotic patients.

Material and methods

Materials

63 cirrhotic patients in child A, during ultrasonographic semiannual surveillance from 1st June 2019 to 29th February 2020 demonstrated a new hepatic lesion ≤ 2 cm; these patients have been submitted to C-CEUS and thereafter HiFR-CEUS in the same examination session.

Equipment

A commercially available ultrasound machine, equipped with Plane wave technology, was used for this study (Resona series, Shenzhen Mindray Bio-Medical Electronics Co., China), that works with a new ultrasound technology called zone sonography [41, 42] and based on Plane-Wave Imaging (PWI) [43] with Pixel compounding [44].

Conventional (baseline and contrast-enhanced) ultrasonography is based technically on Delay and Sum (DAS) technique [28]; the DAS technique uses several transmissions of US signals focused in one or more regions to scan the entire area to be analyzed and to form the scan lines that will be used to reconstruct the final image. This process is

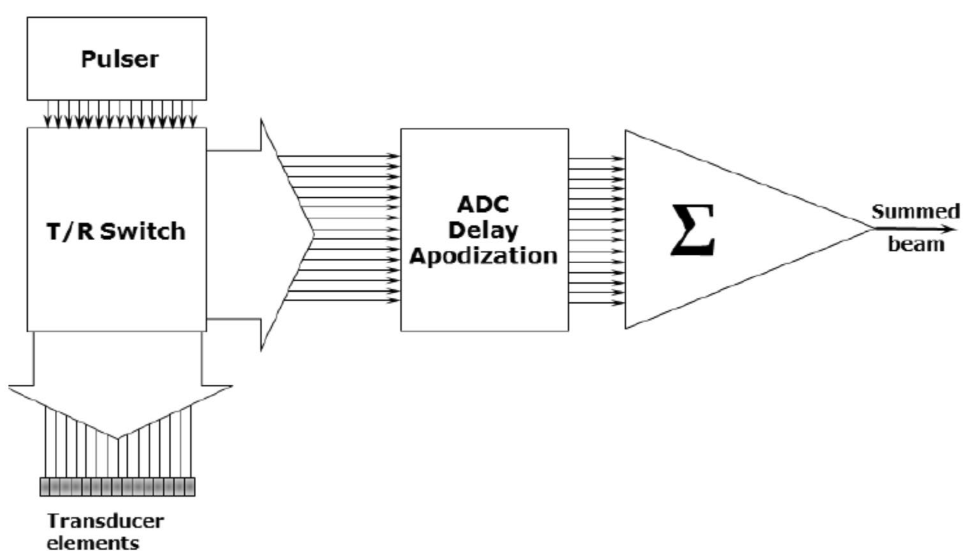

Fig. 1 Block diagram of a typical beamformer. It includes a transmit/receive switching network, analog-to-digital converters (ADC), delay circuits required for focusing and beam steering, apodization generation required for side lobe suppression, and finally a summing circuit which sums the echoes from individual transducer elements into a single beam (from: [41])

time-consuming and limits the frame rate to approximately 30 to 40 frames per second (Fig. 1).

Zone sonography yields framerates as high as several thousands of images per second with a low frame rate (around 10 FPS). The system works with the simultaneous excitation of all available elements in a certain transducer to transmit and collect ultrasonic signals (Fig. 2); At first this increase in framerate was obtained at the expense of reduced contrast and resolution. However, this drawback was skillfully addressed by Coherent Plane-Wave Compounding (CPWC) for very high frame rate ultrasonography and transient elastography [32], for the study of flow inside the vessels [37, 38] and for echocardiography [39], which introduced a trade-off between framerate and image quality; coherent plane-wave compounding has many advantages because it provides an image of a full region of interest for each ultrasonic transmission using all array elements [32].

Study protocol: First, grayscale US was used to scan the whole liver and locate the lesion. The blood flow of the target lesion was evaluated using color Doppler flow imaging (CDFI). Second, C-CEUS scanning was performed. Third, HIFR-CEUS was performed after no less than 10 min, when the microbubbles from the previous injection had disappeared. 0.8–1.2 ml of contrast media (SonoVue, Bracco, Italy) was used. Both C-CEUS and HIFR-CEUS used the same scanning protocol. For the arterial and portal venous phase, scanning of the FLL was continuous, while late phase scanning of the FLL was intermittent to avoid the destruction of contrast agents. Both the C-CEUS and HIFR-CEUS scanning lasted for at least 5 min after the injection of contrast agent. All imaging data were recorded. Diagnostic gold standard techniques were or radiological with MRI (according to recent literature [22]) or with biopsy 57 nodules were better evaluable with HiFR-CEUS; 6 nodules were equally evaluable by both techniques; Spiral Ct and MRI were performed in all patients; 7 nodules < 1 cm were not evaluable by spiral CT. Final diagnosis was obtained with MRI [47] and/or fine needle aspiration (16 cases).

Final diagnosis was: 45 benign lesions (27 hemangiomas, 1 hamartoma, 3 hepatic cysts; 2 focal nodular hyperplasia, 5 regenerative macronodules, 3 AV-shunts, 3 hepatic sparing areas and 1 focal steatosis) and 18 malignant one (15 HCCs, 1 cholangioca, 2 metastases); statistical evaluation was performed with SPSS vers. 26.

The American College of Radiology (ACR) [45] issued classification criteria for the characterization of hepatocellular carcinoma (li-rads); The contrast-enhanced US Liver Imaging Reporting and Data System (CEUS LI-RADS) algorithm was an effective tool for characterization of small (< 20 mm) liver nodules in patients at risk for hepatocellular carcinoma [21, 46] (Fig. 3).

Statistical analysis

Conspicuity score: Subjective measures included image quality, lesion conspicuity, and reader confidence. Reader agreement was measured with kappa statistic; correlation with truth by Pearson coefficient, CNR with repeated mANOVA; subjective quality measures utilized Tukey-Cramer corrections for multiple testing, $p < 0.05$ considered significant. Sensitivity (Sens), Specificity (Spec), Overall Diagnostic Accuracy (ODA), Positive Predictive values (PPV) and Negative predictive Values (NPV) were evaluated in comparison to final diagnosis; Receiver Operating Characteristic (ROC) curves were evaluated; Fischer X2

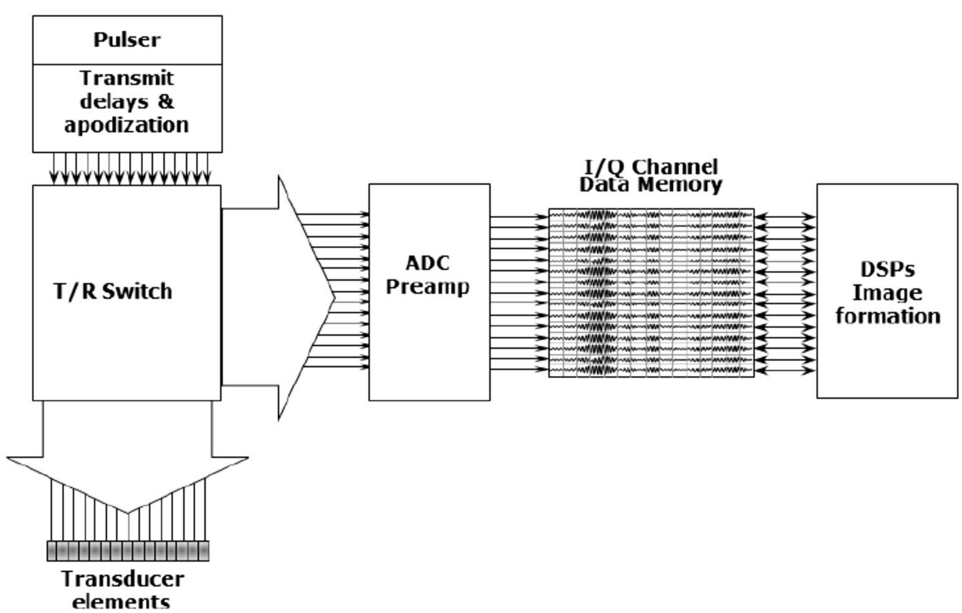

Fig. 2 Simplified block diagram of a ZONE Sonography system. All echoes received by each transducer element are stored in Channel Domain Memory forming a complete acoustic data set for each image frame. This memory is then accessed by Digital Signal Processors (DSP's) to retrospectively analyze the data and form an image from a complete acoustic data set and not from individual beams. Note that the classic beamformer does not exist in the ZONE Sonography architecture as it has been replaced by software (from: [41])

exact test was performed for differences between the two types of CEUS.

Results

The population consists of 63 cirrhotic patients (mean age ±, with six-monthly ultrasound follow-up. 25 men (mean age ± standard deviation: 69 ± 12.46) and 38 women (mean age + standard deviation), all HCV positive.

final diagnosis was: 44 benign lesions (29 hemangiomas, 1 amartoma, 2 hepatic cysts; 2 focal nodular hyperplasias, 3 regenerative macronodules, 3 AV-shunts, 3 hepatic sparing areas and 1 focal steatosis) and 19 malignant one.

LI-RADS score obtained by C-CEUS and HiFR-CEUS are described in Table 1; C-CEUS and HiFR-CEUS reached the same diagnosis in 29 nodules (13 nodules > 1 < 1.5 cm; 16 nodules > 1.5 < 2 cm); HiFR-CEUS reached a correct diagnosis in 32 nodules where C-CEUS was not diagnostic (6 nodules < 1 cm; 17 nodules > 1 < 1.5 cm; 9 nodules > 1.5 < 2 cm); C-CEUS was better in 2 nodules (1 < 1 cm and 1 > 1 < 1.5 cm). Some patient's (sex, BMI, age) and nodule's characteristics (liver segment, type of diagnosis, nodule's dimensions ($p = 0.65$)) were not correlated with better diagnosis (p ns); only better visualization (p 0.004) was correlated;

In comparison with final diagnosis (Table 2) C-CEUS obtained 17 true malignant nodules; 39 true "non malignant" nodules; 5 nodules, incorrectly considered malignant, and 2 incorrectly considered benign; HIFR-CEUS revealed obtained 18 true malignant nodules; 41 true "non malignant" nodules; 3 nodules, incorrectly considered malignant, and 1 incorrectly considered benign.

C-CEUS reached the following corresponding values: sensitivity: 89.5%; Specificity: 88.6%, PPV: 77.3%; NPV: 95.1%; Diagn Acc: 88.6% (AU-ROC: 0.9940 ± SEAUC: 0.127; CI: 0.969–1.019); HiHFR CEUS reached the following corresponding values: sens: 94.7%; Spec: 93.2%, PPV: 85.7%; NPV: 97.6%; Diagn Acc: 93.2% (AU-ROC: 0.9958 ± SEAUC: 0.106; CI: 0.975–1.017). Differences in AUC are small but remarkable in comparison to diagnostic accuracy [47].

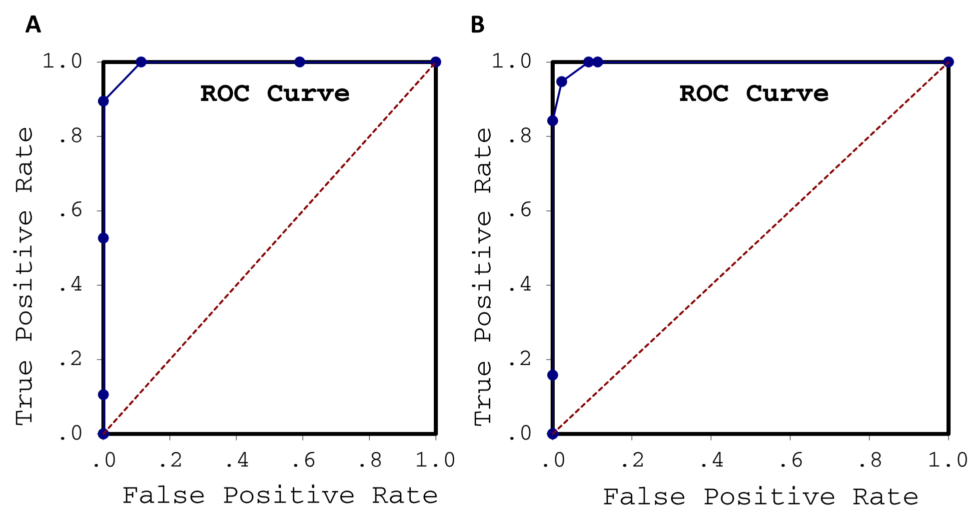

Fig. 3 **A** Area Under the Curve of "conventional" CEUS (using plane wave) reveals a diagnostic accuracy equal to 88.3%; **B** Area Under the Curve of "High Frame Rate" CEUS (using plane wave) reveals a diagnostic accuracy equal to 93.2%

Table 1 Vascular behaviour of small liver nodules according to CEUS LI-RADS

	LR-1	LR-2	LR-3	LR-4	LR-5	LR-M
C-CEUS	18	21	7	7	8	2
HIFR-CEUS	38	2	4	2	15	2

Table 2 True Positives (TP) and Negatives (TN), False Positives (FP) and False Negatives (FN) and corresponding values of sensitivity (SENS), Specificity (Spec), Positive Predictive Values (PPV) and Negative Predictive Values (NPV), and Overall Diagnostic Accuracy (DIAGN ACC.)

	TP	TN	FP	FN	SENS (%)	SPEC (%)	PPV (%)	NPV (%)	DIAGN ACC. (%)
C-CEUS	17	39	5	2	89,5	88,6	77,3	95,1	88,6
HiFR-CEUS	18	41	3	1	94,7	93,2	85,7	97,6	93,2

Differences

FLL vascularization in the arterial phase was more visible with HiFR-CEUS than with C-CEUS, capturing the perfusion details in the arterial phase due to a better temporal resolution. With a better temporal resolution, the late phase could be evaluated longer with HiFR-CEUS (4 min C-CEUS vs. 5 min HiFR-CEUS).

Discussion

Hepatocellular carcinoma is the fastest increasing cause of cancer-related death over the past decade in the United States and the third leading cause of cancer- related death worldwide [48]. The detection of a tumor, amenable to surgical resection, thermal ablation, or liver transplantation could improve the prognosis, which is severe, in absence of indications to radical treatment. Being the third leading cause of death from cancer worldwide, accurate tests are needed to diagnose hepatocellular carcinoma. The HCC diagnosis and staging in people with chronic liver disease needs Computed tomography (CT) and/or MRI. CT/MRI are currently the second step after ultrasound and alpha-foetoprotein (or their combination). As an ideal diagnostic test, CT/MRI should ensure a low proportion of false-negative results because people with undetected hepatocellular carcinoma cannot receive proper treatment. People with false-positive results are exposed to unnecessary further diagnostic workup and possible invasive treatment. The estimated pooled sensitivity and specificity derived from one recent analysis suggest that 22.5% of people with hepatocellular carcinoma would be missed, and 8.7% of people would be unnecessarily treated [49].

Furthermore, spiral CT and MRI are not able to correctly characterize small nodules sometimes because they aren't able to detect the entire pattern of vascularization, even if they have a panoramic view (not available for ultrasound). On the opposite, Contrast-enhanced Ultrasound (CEUS) is able to evaluate frame-by frame the microvascularization of a single nodule but has not panoramic view.

CEUS has several advantages over CT or MRI: firstly, microbubbles can be safely injected in patients with renal failure as there is no renal excretion of the contrast. CEUS is therefore a useful problem-solving method for characterizing liver masses when CT or MRI is contraindicated due to renal failure. There is no need of blood test for renal function before contrast injection. Secondly, CEUS allows real-time assessment of arterial- phase enhancement, eliminating the issue of appropriate arterial-phase timing. CEUS often detects arterial-phase hypervascularity when CT or MRI fails to show it because of incorrect arterial-phase timing. Thirdly, washout phenomenon (negative enhancement of liver lesion relative to the liver in the late phase) in malignant liver lesions is more consistently seen on CEUS than CT/MRI [50].

The meta-analysis performed by Niu [11] on CEUS for the diagnosis of small HCC (< 2 cm) showed a pooled sensitivity of 0.84 (95% CI 0.77, 0.90) and pooled specificity of 0.89 (95% CI 0.81, 0.94) for SonoVue. These results provide strong support for the use of CEUS as a useful diagnostic tool with high sensitivity and specificity for the identification of small HCC.

CEUS is now recognized as a useful imaging modality for non-invasive diagnosis of small (1–2 cm) newly detected liver nodules during HCC surveillance. However, in those small nodules related to cirrhosis, there is a considerable overlap in the imaging findings between benign and malignant nodules, requiring biopsy or close follow-up [51].

Forner et al. [52] demonstrated that absence of contrast hyperenhancement on CEUS during the arterial phase in nodules < 2 cm in a cirrhotic liver does not predict a less malignant profile. According to authors, priority for diagnostic work-up and treatment should not differ according to contrast profiles on CEUS.

A first meta-analysis [53] demonstrated an overall CEUS high sensitivity (81%), specificity (86%) with AUC equal to 0.92; a second meta-analysis [54] confirmed the same data and compared CEUS and CT, concluding that CEUS showed a diagnostic ability comparable to that of CECT in characterizing small HCC.

A third meta-analysis [55] analyzed the accuracy of contrast-enhanced ultrasound (CEUS) in differentiating malignant from benign focal liver lesions evaluating also the type of contrast agent (CA) (first vs second generation and SONOVUE vs SONAZOID). The second-generation CAs (especially Sonazoid) may greatly improve diagnostic performance (POOLED SENS: 0.92; SPEC: 0.87, AUC: 0.96).

Barr [56] reviewed literature regarding sulfur hexafluoride microbubbles (Lumason in the USA and Sonovue in the rest of the world), and in particular outlined its main advantages: CEUS has similar specificity to CECT and CEMRI and CEUS may have increased sensitivity to CECT and gadolinium CEMRI; CEUS is less expensive than CECT or CEMRI; there is no significant difference of specificity (88% vs. 83%, $p = 0.11$) between CEUS and CT/MRI and sensitivity is significantly better with CEUS than CT/MRI (95% vs. 89%, $p = 0.033$); iCC can be differentiated from HCC based on rapidity and marked washout. Author concludes that international literature suggests a wide spread use of CEUS and that, in the USA, standard of care needs to change to include CEUS for characterization of FLL.

All the previous literature data has been obtained with DAS technology; in our experience, on the other hand, the new technology, called "plane wave" was used: Plane-Wave Imaging (PWI) [43] with Pixel compounding [44] is a new technology, able to enhance ultrasound visibility. The evolution of this new technology, called High Frame Rate, is able to better detect microvascularization of CEUS.

Comparison between the diagnostic accuracy data of DAS technology CEUS and that with "plane wave" technology demonstrates an advantage of the latter over that available in the literature (DAS system diagnostic accuracy: 84% vs "plane wave" system diagnostic accuracy: 88.6%); The present experience compares the plane wave CEUS technology (Conventional CEUS) with the "high frame rate" plane wave one (Hi-FR CEUS) to understand if this tool may be useful in the characterization of small hepatic nodules during follow up of cirrhotic patients. C-CEUS has a good performance (Sens: 88.6%; Spec: 88.6%; diagnostic accuracy:88%) but not optimal; instead HiFR-CEUS has an optimal performance (Sens: 94.7; spec: 93.2% overall diagnostic accuracy more than 93% (Table 2)). Differences in AUC (Fig. 1) are small but remarkable in comparison to diagnostic accuracy. An "optimal accuracy" is obtained when AUC is more than 90% [47].

Lastly, another recent Chinese experience with the same technology (57) confirmed that HIFR-CEUS provides more vascular information, which could help differentiate malignant from benign FLLs, especially for lesions 1–3 cm in size; HIFR-CEUS showed sensitivity, specificity, accuracy, and positive and negative predictive values comparable to our experience and higher than those for C-CEUS.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by FG. The first draft of the manuscript was written by FG and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Conflict of interest No authors have Any conflict of interest (any financial or personal relationship with a third party whose interest could be positively or negatively influenced by the article's content).

Ethical approval This is an observational study. The Codogno Hospital Research Ethics Committee has confirmed that no ethical approval is required.

Informed consent Informed consent was obtained from all individual participants included in the study.

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