



Expert consensus regarding the clinical application of liver contrast-enhanced US with Sonazoid (Sonazoid CEUS)

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Abstract

Sonazoid, a combined blood pool and Kupffer-cell agent, can be specifically phagocytosed by Kupffer cells in the liver, allowing lesion detection and characterization of focal liver lesions (FLLs) at the post-vascular phase, apart from the vascular phase, which is similar to that of other second-generation ultrasound (US) contrast agents. Sonazoid contrast-enhanced US (CEUS) is currently approved for use in some Asian countries. With the increasing use of Sonazoid CEUS for FLLs in clinical practice, developing consensus or guidelines to help standardize its use is required. The expert consensus aimed to review recent evidence and make evidence-based recommendations for radiologists and clinicians involved in the management of liver diseases regarding the use of Sonazoid CEUS in the surveillance or detection, characterization of FLLs, CEUS for interventional and intraoperative use, and tumor treatment response evaluation in patients with FLLs. This consensus was conducted without using artificial intelligence tools in accordance with the TITAN Guidelines 2025.

Keywords: consensus statement, contrast-enhanced US, liver, Sonazoid

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Introduction

With the introduction of second-generation US contrast agents (UCAs) and the advancement of contrast imaging techniques, the value of contrast-enhanced US (CEUS) was significantly improved in the management of focal liver lesions (FLLs). Two main types of UCAs are currently available for liver CEUS, including pure blood-pool agents [e.g., SonoVue (sulfur hexafluoride microbubbles, Bracco)] and combined blood-pool and Kupffer-cell agents [e.g., Sonazoid (perfluorobutane microbubbles, GE Healthcare)]. Unlike SonoVue, which cannot cross the vascular endothelium and is therefore assumed to generate pure vascular images, Sonazoid can be specifically phagocytosed by Kupffer cells in the liver, providing an additional post-vascular phase or Kupffer phase^[1–3]. Sonazoid with a long-term stable post-vascular phase is expected to play a role in the surveillance or detection, characterization of FLLs, CEUS for interventional and intraoperative use (IOUS), and tumor treatment response evaluation. With the increasing use of Sonazoid CEUS for FLLs, the number of published studies on related topics has been increasing recently, leading to an urgent need to develop consensus or guidelines to help standardize its use in clinical practice. Some of the following issues may exist in the currently available CEUS guidelines^[4–7]: (1) no or little recent evidence on Sonazoid CEUS is incorporated, (2) it can be used for patients at risk of HCC only, and (3) it does not include the diagnostic criteria or performance evaluations for Sonazoid CEUS. This work was conceived to address the gap; it aimed to review as much recent evidence as possible and make evidence-based recommendations for radiologists and clinicians involved in the management of liver diseases from medical institutions at all levels regarding the use of Sonazoid CEUS in patients with FLLs.

Consensus development methodology

Consensus development methodology, including literature search, question development and recommendation formation, was detailed in Supplemental Digital Content Materials, available at: <http://links.lww.com/JS9/F98>. This consensus was conducted without using artificial intelligence tools in accordance with the TITAN Guidelines 2025^[8].

Technical aspects

Sonazoid, a combined blood pool and Kupffer-cell agent, can be specifically phagocytosed by Kupffer cells in the liver, with a phagocytic rate of 99%^[1]. Sonazoid CEUS allows additional characterization of FLLs during a long and stable post-vascular phase, apart from the vascular phase, similar to other second-generation UCAs^[4–6]. It is currently approved for use in Japan, Korea, Singapore, and China. Technical aspects, including contrast agent, setting conditions, definitions of imaging phases and

HIGHLIGHTS

- Sonazoid CEUS is recommended in patients at risk of hepatocellular carcinoma (HCC) for diagnosing HCC, characterizing dysplastic nodules and early HCC, differentiating HCC from non-HCC malignancies, and characterizing indeterminate nodules detected in CT/MRI.
- Sonazoid CEUS can be used to differentiate malignant lesions from benign lesions in patients without risk of HCC.
- Sonazoid CEUS is recommended for interventional (percutaneous biopsy or local ablation therapy) and intraoperative use.
- Sonazoid CEUS can be used to evaluate the treatment response in patients underwent locoregional therapies (ablation/transcatheter arterial chemoembolization/radiotherapy) or systematic treatment.

imaging features, were detailed in Supplemental Digital Content Materials, available at: <http://links.lww.com/JS9/F98>. Some special tips about contrast-enhanced intraoperative US (CEIOUS) were also provided.

Section 1 Surveillance and detection

Clinical Question 1: Is Sonazoid CEUS recommended for HCC surveillance in patients at risk of HCC?

Consensus Statements #1 Sonazoid CEUS with post-vascular phase imaging and defect reperfusion imaging may serve as an HCC surveillance tool in patients at risk of HCC.

*(Recommendation level: 2, Evidence level: B)
(Agree 49, Disagree 0, Abstain 0)*

According to the Chinese guideline for the diagnosis and treatment of primary liver cancer, risk factors of HCC mainly include liver cirrhosis of all causes, hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infection, excessive alcohol consumption, nonalcoholic fatty hepatitis, long-term consumption of aflatoxin-contaminated food, and a family history of HCC, especially males >40 years of age^[9]. Semi-annual abdominal US with or without measurement of α -fetoprotein levels is recommended for HCC surveillance in high-risk patients^[10–12]. However, US makes it difficult to detect small HCC in patients with liver cirrhosis manifested by architectural distortion^[6,13,14]. A long and stable post-vascular phase of Sonazoid CEUS is expected to be particularly sensitive in detecting small HCC that presents as a post-vascular defect throughout the liver in those with coarsened hepatic echotexture^[6]. In addition, the formation of regenerative nodules in the cirrhotic liver results in a high rate of false-positive or indeterminate surveillance results using US, which is related to increased physical harm and clinical and financial burden^[15–17]. Patients may benefit from the post-vascular phase of Sonazoid CEUS in reducing false referrals because these regenerative nodules do not present

as a post-vascular defect^[18]. Suppose a defect at the post-vascular phase is identified, it can be further characterized as HCC if it shows a positive defect reperfusion sign following the reinjection of Sonazoid^[19]. Several studies^[20–23] have recognized the potential of Sonazoid CEUS to improve the efficiency of HCC surveillance. According to two studies by Kudo *et al*, a defect with a positive reperfusion sign was very sensitive for the detection of small HCC in cirrhotic patients under surveillance^[21,22]. A prospective multicenter intraindividual comparison study (SCAN trial) showed a slightly increased detection rate for early HCC (1.1% vs 0.8%, $P = 0.160$) and a significantly reduced false referral rate (4.4% vs 1.1%, $P < 0.001$) after adding Sonazoid CEUS to US during HCC surveillance^[20]. Another multicenter prospective study reported that the lesion size at first detection during HCC surveillance using Sonazoid CEUS was significantly smaller than that using US (13.0 mm vs. 16.7 mm, $P = 0.011$) in patients with HCV-related liver disease^[23]. More evidence is needed to validate these findings in the population with HBV-related liver disease.

Cost-effectiveness is another important factor in determining whether Sonazoid CEUS is suitable for HCC surveillance. A Japanese study including patients with HCV-related liver disease showed that Sonazoid CEUS was cost-effective when compared to the no surveillance group and the US surveillance group^[24]. However, the generalizability of the above finding to wider populations may be limited.

In summary, Sonazoid CEUS with post-vascular phase imaging and defect reperfusion imaging may serve as an HCC surveillance tool in patients at risk of HCC.

Clinical Question 2: Can Sonazoid CEUS be used for the detection of liver metastasis in patients with extrahepatic malignancy?

Consensus Statements #2 Sonazoid CEUS with post-vascular phase can improve the detection of liver metastasis; workup testing for liver metastasis in patients with extrahepatic malignancy may be an indication for Sonazoid CEUS.

(Recommendation level: 2, Evidence level: B)
(Agree 49, Disagree 0, Abstain 0)

The typical imaging findings of metastasis at the vascular phase on Sonazoid CEUS are very clear: rim arterial phase hyperenhancement (APHE) followed by washout earlier and clearer than HCC. At the post-vascular phase, it usually shows a marked defect because such lesions do not contain Kupffer cells^[4,5]. However, the short duration of vascular phase makes complete imaging of all liver segments impracticable, leading to limited utility in lesion detection^[5]. In contrast, the post-vascular phase lasts long enough for a detailed scan, which has been proven to be very sensitive for the detection of liver metastasis^[25–29]. A second contrast administration can be used to further confirm the metastatic nature by demonstrating the enhancement within the areas of defect. Some studies have shown that CEUS is of particular usefulness with small liver metastases less than 10 mm when compared to US (58% vs 16%, $P < 0.001$)^[25] or SonoVue CEUS (72.1% vs 64.0%, $P < 0.001$)^[29]. It was reported that the performance of Sonazoid

CEUS for the detection of liver metastasis from gastrointestinal cancer was quite similar to that of F-18 fluorodeoxyglucose (FDG) PET/CT (Sensitivity, 100% for both; Specificity, 97.5% vs 98.7%)^[26]. In summary, Sonazoid CEUS with post-vascular phase can improve the detection of liver metastasis; workup testing for liver metastasis in patients with extrahepatic malignancy may be an indication for Sonazoid CEUS.

Section 2 Characterization of FLLs

The frequency of various tumor entities is different in patients with and without high risk of HCC^[30–32]. In patients without risk factors for HCC, malignant and benign lesions are equally common. The most common malignant lesions are metastasis (35–37.7%) and HCC (6.1–7.6%); a positive history of extrahepatic malignancy increases the probability of metastasis. The most common benign lesions in patients without risk factors for HCC are hemangioma (18–22.4%) and focal nodular hyperplasia (FNH) (9.8–16.1%)^[30,31]. In patients at risk of HCC, HCC dominates (75–76.6%), which is more common than metastasis (2.6–4.3%)^[32].

Patients at high risk of HCC

Clinical Question 3: Is Sonazoid CEUS recommended to diagnose HCC in patients at high risk of HCC?

Consensus Statements #3: Sonazoid CEUS is recommended to diagnose HCC when high-risk patients have incidental findings on screening US.

(Recommendation level: 1, Evidence level: B)
(Agree 49, Disagree 0, Abstain 0)

Unlike other malignancies, the diagnosis of HCC relies heavily on noninvasive imaging in patients at risk of HCC. Contrast-enhanced CT and MRI are globally recognized as the first-line imaging modalities for diagnosing HCC^[9,10,12,33,34]. As for CEUS with microbubbles, an early study claimed that 47.6% (10/21) of intrahepatic cholangiocarcinoma (ICC) showed a similar enhancement pattern on CEUS to HCC – that was, APHE followed by washout, contributing to a greater risk of misdiagnosis than CT and MRI^[35]. However, it has been increasingly realized that CEUS allows the real-time assessment of specific APHE patterns as well as the onset and degree of washout (not just its presence), thus being able to accurately characterize HCC^[36–38]. In addition, Sonazoid CEUS possesses a unique post-vascular phase, at which malignant lesions that lack functioning Kupffer cells show a defect at imaging; this property makes it comparable with the hepatobiliary phase at MRI with gadoxetic acid, in which lesions show hypointensity at imaging due to intra-lesion depletion of functioning hepatocytes^[39]. One study evaluating the diagnostic sensitivity of imaging modalities in patients with liver cirrhosis for diagnosing HCC (≤ 2 cm) showed that when applying the diagnostic criterion of APHE and post-vascular defect, Sonazoid CEUS outperformed dynamic CT and was similar to MRI (CT, 52.9%; Sonazoid CEUS, 67.6%; MRI, 76.5%)^[40]. Two recent retrospective studies concluded that when including post-

vascular findings as major imaging features, the diagnostic accuracy for diagnosing HCC of Sonazoid CEUS was comparable to that of CT/MRI in patients at high risk of HCC^[41,42]. However, Sonazoid CEUS cannot be applied to some application scenarios. First, Sonazoid CEUS cannot be applied if the accessibility of the target observation to CEUS is blocked by ribs, lungs, and bowel gas^[43]. Second, CEUS does not allow the simultaneous assessment of the local lesions, tumor N-staging, and M-staging.

In summary, Sonazoid CEUS can be as accurate as contrast-enhanced CT and MRI for the characterization of HCC in patients at high risk of HCC. Sonazoid CEUS should be used for the characterization of FLLs when high-risk patients have incidental findings on US.

Clinical Question 4: What are the diagnostic criteria for HCC using Sonazoid CEUS in high-risk patients?

Consensus Statements #4-1: CEUS Liver Imaging Reporting and Data System (LI-RADS) can be applied to Sonazoid CEUS in high-risk patients. The diagnosis of HCC can be made if a nodule ≥ 10 mm shows non-rim APHE and late (>60 s) and mild washout on Sonazoid CEUS.

(Recommendation level: 1, Evidence level: A) (Agree 43, Disagree 0, Abstain 6)

To facilitate clinical communication and scientific collaboration, well-defined, standardized, and uniform diagnostic criteria for HCC on Sonazoid CEUS should be established. CEUS Liver Imaging Reporting and Data System (LI-RADS, LR)^[7], the diagnostic algorithm published for standardizing image acquisition, interpretation, and reporting of hepatic observations in high-risk patients, has been actively adopted in clinical practice. CEUS LI-RADS stratifies the probability that an observation represents HCC on a spectrum from LR-1 (definitely benign) to LR-5 (definitely HCC) based on major features and also includes LR-M (probably malignant but not HCC specific), LR-TIV (tumor in vein), and LR-NC (not characterizable because of image omission or degradation). According to CEUS LI-RADS, nodules ≥ 10 mm with non-rim APHE and late (>60 s) and mild washout are classified as the LR-5 category. The overarching goal of the LR-5 category is to provide high specificity for HCC and exclusion of non-HCC malignancies^[44] so that lesions classified as LR-5 can be diagnosed as HCC without requiring biopsy confirmation. However, the latest CEUS LI-RADS version (v2017) applies only for CEUS exams performed with pure blood-pool agents, not addressing the use of Sonazoid.

Recently, several studies have explored whether CEUS LI-RADS v2017 can be applied to Sonazoid CEUS^[45–48]. A prospective intraindividual study with 59 participants by Kang *et al* showed that the diagnostic sensitivity and accuracy of Sonazoid CEUS is higher than SonoVue CEUS for the diagnosis of HCC in high-risk patients using the same CEUS LR-5 category (Sensitivity, 79% vs 54%, $P = 0.01$; Accuracy, 0.9 vs 0.8, $P = 0.01$), without losing specificity (100% for both)^[46]. The findings were not verified in a subsequent prospective intraindividual study also by Kang *et al*, which reported similar

diagnostic values using the same LR-5 diagnostic criteria for Sonazoid CEUS and SonoVue CEUS (Sensitivity, 59.0% vs 55.7%, $P = 0.578$; Specificity, 90.9% vs 93.2%, $P = \text{N/A}$; and Accuracy, 72.4% vs 71.4%, $P = 0.802$)^[47]. The relatively low sensitivity and high specificity of both Sonazoid CEUS and SonoVue CEUS are consistently reported in more recent prospective studies (Li *et al*: Sensitivity, 60% vs 58%, $P = 0.41$; Specificity, 96% vs 95%, $P > 0.99$; and Accuracy, 67% vs 65%, $P = 0.51$; Huang *et al*: Sensitivity, 74.6% vs 80%, $P = 0.25$; Specificity, 100% for both; and Accuracy, 77.4% vs 82.3%, $P = 0.25$)^[45,48]. In summary, CEUS LI-RADS can be applied to Sonazoid CEUS in at-risk patients. The diagnosis of HCC can be made if a nodule meets the LR-5 criteria (i.e., a nodule ≥ 10 mm with non-rim APHE and late and mild washout) on Sonazoid CEUS. The LR-5 criteria of Sonazoid CEUS can achieve similar diagnostic performance for HCC to that of SonoVue CEUS.

Consensus Statements #4-2 The diagnosis of HCC can be made if a lesion with a maximum diameter larger than 10 mm shows non-rim APHE and no vascular-phase washout but post-vascular defect.

(Recommendation level: 1, Evidence level: A) (Agree 42, Disagree 0, Abstain 7)

Although the high specificity for HCC can be achieved using CEUS LI-RADS v2017, high sensitivity for diagnosing HCC will be beneficial in identifying candidates for treatment and for improving survival, which is preferred in regions that rely primarily on local treatments rather than transplantation^[49]. In several CEUS studies that focused on the additional value of post-vascular defect for diagnosing HCC^[41,45,50–53], 73.1–88.3% of HCCs showed washout at the vascular phase, while 90.4–98.2% showed post-vascular defect at the post-vascular phase, which indicated that post-vascular defect has the potential to increase the sensitivity for HCC diagnosis. However, post-vascular defect was not specific to HCC, which could also be observed in 93.3–100% of non-HCC malignancies and 16.7–56.3% of benign lesions, usually hemangioma. The findings strongly suggest that the diagnosis should not be determined by relying solely on findings of the post-vascular phase but by comprehensive consideration of both vascular-phase and post-vascular-phase findings.

The benefits of post-vascular defect may be available only under certain conditions. Some studies found that in a preset lesion with a maximum diameter ≥ 10 mm, non-rim APHE, and no washout at the vascular phase on Sonazoid CEUS, if a post-vascular defect was further observed in the lesion, 97.1–100% of them were then confirmed as HCCs^[45,50–52]. Under such conditions, post-vascular defect may be accepted as an alternate imaging feature of late and mild washout. Therefore, several studies proposed that in addition to the CEUS LR-5 category, the diagnosis of HCC can also be made if a lesion with a maximum diameter larger than 10 mm shows non-rim APHE and no washout but post-vascular defect on Sonazoid CEUS^[41,45,50–54]. A prospective study conducted in Japan concluded that the above-modified criteria have higher sensitivity for HCC (67.3% vs 51.9%, $P = 0.0047$) without sacrificing the

specificity (92% for both) when compared to CEUS LI-RADS v2017^[51]. A retrospective multicenter study by Hwang *et al* reported that a sensitivity of 75.3% with a specificity of 91.3% was achieved using CEUS LI-RADS v2017, while the modified criteria incorporating post-vascular defect have a higher sensitivity of 81.3% ($P = 0.041$) without compromising the specificity (91.3%)^[52]. Another retrospective study with 203 participants by Hwang *et al* drew a similar conclusion (Sensitivity, 83.2% vs. 74.2%, $P = 0.008$ and Specificity, 63.6% vs. 69.7%, $P = 0.500$)^[53]. A retrospective study with 304 FLLs by Li *et al* found that the modified criteria (CEUS LI-RADS v2017 OR ≥ 10 mm, non-rim APHE, no washout, and post-vascular defect) resulted in significantly increased sensitivity for HCC (81% vs 69%, $P < 0.001$) without significant loss of specificity (83% vs 87%, $P > 0.99$)^[50]. The effectiveness of the modified criteria has been further validated in a prospective multicenter study with 424 observations, which aimed to compare the diagnostic performance of SonoVue CEUS and Sonazoid CEUS for HCC diagnosis^[45]. Another retrospective study that aimed to compare the modified criteria applied to Sonazoid CEUS and CT/MRI LI-RADS yielded similar results and strongly strengthened the findings^[41]. Currently, the role of post-vascular defect in diagnosing HCC has been fully acknowledged in several Asian-country-specific guidelines^[6,10,55].

In summary, in addition to the CEUS LR-5 category, the diagnosis of HCC can also be made if a lesion with a maximum diameter larger than 10 mm shows non-rim APHE and no vascular-phase washout but post-vascular defect on Sonazoid CEUS.

Clinical Question 5: Can Sonazoid CEUS be used to differentiate early HCC from dysplastic nodules (DNs)?

Consensus Statements #5 Sonazoid CEUS may be helpful for characterizing DN and early HCC, but still remains challenging overall.

(Recommendation level: 2, Evidence level: C) (Agree 36, Disagree 0, Abstain 13)

Characterization of early HCC in high-risk patients is an important issue in the clinical setting, facilitating early diagnosis and treatment strategies. Pathologically, HCC develops in a multi-step fashion from a regenerative nodule to a low-grade DN, high-grade DN, early HCC, nodule-in-nodule early HCC, well-differentiated HCC, and eventually to overt HCC^[56]. A progressive shift of intra-nodular blood supply from portal flow to arterial flow is one of the key changes during hepatocarcinogenesis, which can be visualized by associated vascular findings (i.e., APHE and washout pattern) on Sonazoid CEUS^[10]. However, most early HCCs are mainly fed by portal flow instead of arterial flow, similar to DN, leading to a lack of typical APHE and washout patterns of HCC. Kudo *et al*^[57] reported that 75% (12/16) of early HCCs had arterial hypo-vascularity without washout. Another key alteration during hepatocarcinogenesis is the decrease in the number and function of Kupffer cells, which can be visualized by associated post-vascular findings (i.e., post-vascular defect) on Sonazoid CEUS^[10]. Post-vascular defect may be an important finding to differentiate early HCC from DN with high specificity. On Sonazoid, a mild defect at the post-

vascular phase was observed in 0% (0/8) of DN, 25% (4/16) of early HCCs, and 100% (5/5) of nodule-in-nodule early HCC^[57]. Nevertheless, its sensitivity was low. Overall, differentiating between DN and early HCC remains challenging.

Clinical Question 6: Can Sonazoid CEUS be used to differentiate HCC from non-HCC malignancies?

Consensus Statements #6 Sonazoid CEUS can be used to differentiate HCC from non-HCC malignancies, including ICC and metastasis.

(Recommendation level: 2, Evidence level: B) (Agree 35, Disagree 8, Abstain 6)

The differential diagnosis of HCC and non-HCC malignancies, particularly ICC in patients at risk of HCC, is of importance since prognosis and treatment options of the two differ. Since a high specificity of characteristics imaging findings on Sonazoid CEUS for diagnosing HCC in high-risk patients can be achieved (see Clinical question 4), misdiagnosis of non-HCC malignancy as typical HCC is less likely. Different from HCC, non-HCC malignancies, including ICC and metastasis, usually present as rim APHE, early washout (<60 s), and marked washout (<2 min) at the vascular phase on Sonazoid CEUS, which are referred to as LR-M criteria according to CEUS LI-RADS v2017^[7]. Among the three imaging features, early washout had the highest sensitivity, ranging from 85% to 100% with a high specificity of 82–90.6% for identifying non-HCC malignancies (vs HCC), while rim APHE had the highest specificity of 98.0–100% with a low sensitivity of 19–50%^[45,51,54]. However, some subsets of HCC with atypical appearance show overlapping LR-M features. It was reported that the probability of HCC for the LR-M category was 33.3–76.4% using CEUS LI-RADS v2017^[45,46,50]. Difficulties persist in differentiating non-HCC malignancies from the subset of atypical HCC.

The diagnostic value of marked defect at the post-vascular phase on Sonazoid CEUS has been explored. It was reported that a marked post-vascular defect was commonly observed in non-HCC malignancies than in HCC because such lesions do not contain Kupffer cells, while some early HCCs showed a mild defect at the post-vascular phase because Kupffer cells can remain inside early HCC lesions^[4]. The results of a previous study reported that all ICCs (6/6) and metastases (9/9) had marked post-vascular defect, while only 25.0% (16/64) of HCCs showed marked post-vascular defect^[54]. In a multicenter prospective study, 75% (30/40) of non-HCC malignancies exhibited marked post-vascular defect, while only 26.1% (90/345) of HCCs showed marked post-vascular defect^[45]. Li *et al* found that 93–100% of observations ≥ 10 mm with non-rim APHE, early washout (<60 s), and a mild post-vascular defect represented HCC^[45,50]. They proposed that the subset of LR-M observations showing early washout can be reassigned as the LR-5 category, thus improving the sensitivity for diagnosing HCC without a significant loss of specificity^[41,45,50].

In summary, Sonazoid CEUS can be used to differentiate HCC from non-HCC malignancies. The role of marked defect at the post-vascular phase and the modified criteria by Li *et al* in differentiating HCC from non-HCC malignancies are needed to be validated in further studies.

Clinical Question 7: Is Sonazoid CEUS recommended to characterize indeterminate nodules detected in contrast-enhanced CT or MRI in high-risk patients?

Consensus Statements #7 Sonazoid CEUS is recommended to characterize indeterminate nodules detected in contrast-enhanced CT or MRI in high-risk patients due to its superior sensitivity to detect APHE and to show Kupffer-cell activity.

(Recommendation level: 1, Evidence level: B) (Agree 49, Disagree 0, Abstain 0)

Contrast-enhanced CT and MRI are most commonly used for noninvasive diagnosis of HCC in high-risk patients. Imaging hallmarks of HCC on contrast-enhanced CT or MRI include non-rim APHE, enhancing capsule, and nonperipheral washout^[58]. However, not all lesions present as typical findings, resulting in some HCC characterized as indeterminate nodules. Approximately 20% of high-risk patients undergoing HCC surveillance are found to have indeterminate nodules on diagnostic imaging, of which management remains challenging^[59,60]. In several practice guidelines^[10,12,33,34], CEUS can be used as a second-line modality in cases where CT and MRI are indeterminate. Unlike CT and MRI, CEUS permits real-time imaging, virtually eliminating the possibility of arterial phase mistiming and allowing the characterization of APHE missed on CT and MRI^[39]. According to previous studies^[53,61–64], some HCC without APHE on CT and MRI presented as APHE on Sonazoid CEUS (ranging from 13% to 80%). In addition, Sonazoid CEUS allows the evaluation of FLLs at the post-vascular phase. In a recent Korean retrospective study^[64], a total of 49% (31/63) of HCC lesions in the absence of washout on MRI presented as a post-vascular defect at the post-vascular phase. The presence of both APHE and post-vascular defect on second-line Sonazoid CEUS could identify additional HCCs, thus potentially improving the sensitivity for diagnosing HCC^[41,64,65]. In summary, Sonazoid CEUS is recommended as a problem-solving modality to further stratify HCC probability in those indeterminate nodules on contrast-enhanced CT and MRI.

Patients without risk of HCC

Clinical Question 8: Can Sonazoid CEUS be used to differentiate malignant lesions from benign lesions in patients without risk of HCC?

Consensus Statements #8-1 Sonazoid CEUS can be used to differentiate malignant lesions from benign lesions in patients without risk of HCC.

(Recommendation level: 1, Evidence level: B) (Agree 38, Disagree 0, Abstain 11)

The most common malignant lesions in patients without risk factors for HCC are metastasis and HCC, while the most common benign lesions are hemangioma and FNH^[30,31]. The clinical evidence^[66–72] confirmed that each of these common lesions has its own distinctive enhancement and washout patterns at the vascular phase, which were relevant for differentiating malignant from benign lesions. HCC exhibited similar imaging findings in patients with or without risk of HCC; the characteristic imaging findings of other common lesions are described later. Post-vascular defect is not considered an independent feature for characterizing malignant vs benign lesions or for a specific lesion type characterization. If an observation with a post-vascular defect is accidentally found, reinjection of Sonazoid is strongly suggested for characterizing vascular patterns of the target observation.

Several studies have proved the feasibility and effectiveness of Sonazoid CEUS in differentiating malignant lesions from benign lesions, with a sensitivity of 84.6–97% for HCC with a specificity of 92–95%, and a sensitivity of 85–90% for metastasis with a specificity of 88–100%^[66–72]. When compared to SonoVue CEUS, a similar diagnostic efficacy for Sonazoid and SonoVue in diagnosing FLLs as malignant or benign could be achieved according to several prospective studies^[69,70]. A meta-analysis that was performed to evaluate the diagnostic accuracy of CEUS in differentiating malignant from benign lesions concluded that Sonazoid CEUS demonstrated the highest diagnostic accuracy among three major UCAs (DOR, SonoVue: Levovist: Sonazoid = 118.82: 62.78: 227.39)^[71]. When compared to CT, Sonazoid CEUS has a higher accuracy for the diagnosis of hepatic malignancies^[66,72]. In summary, Sonazoid CEUS can help differentiate malignant lesions from benign lesions in patients without risk of HCC.

Consensus Statements #8-2 Sonazoid CEUS can accurately diagnose common benign lesions based on characteristic vascular-phase findings, such as typical hemangioma and FNH.

(Recommendation level: 1, Evidence level: B) (Agree 48, Disagree 0, Abstain 1)

On Sonazoid CEUS, peripheral discontinuous nodular APHE with partial or complete centripetal fill-in at the vascular phase is indicative of hemangioma. A phase III multicenter study showed that the diagnostic accuracy for the characterization of hemangioma during the vascular-phase imaging on Sonazoid CEUS was 100% (17/17)^[66]. The typical vascular patterns could achieve a high sensitivity of 84–90% with a specificity of 83–99% for hemangioma^[67,68,70,72]. On post-vascular phase imaging, hemangiomas may exhibit iso-enhancement or slight hypo-enhancement relative to surrounding liver parenchyma (post-vascular defect)^[73].

Characteristic vascular-phase findings of FNH on Sonazoid CEUS include central artery and stellate vascularity, spoke-wheel sign, and centrifugal enhancement. At the vascular phase on Sonazoid CEUS, the spoke-wheel sign could be observed in 71.0% (44/62) of FNH^[74]. In a retrospective study for the evaluation of FNH, 77.4% (24/31) of FNH displayed a central scar, and 80.6% (25/31) of FNH showed centrifugal enhancement^[75,76]. Another retrospective study that included 31 FNH smaller than 3 cm concluded that Sonazoid CEUS was

better than SonoVue CEUS in terms of depicting the presence of a central scar [55.6% (5/9) vs 15.8% (3/19); $P = 0.03$]^[76]. Based on the typical vascular patterns, Sonazoid could achieve a high sensitivity of 80–100% with a specificity of 83–100% for FNH^[67,68,70,72]. On the post-vascular imaging, about 91.9–93.5% of FNH showed isoechoic or slightly hyperechoic appearance without defect at the post-vascular phase^[74,75] because the number of intra-nodular Kupffer cells did not decrease^[77].

In summary, Sonazoid CEUS can be used to diagnose common benign lesions based on characteristic vascular-phase findings, such as typical hemangioma and FNH.

Section 3 CEUS for interventional and IOUS

Biopsy

Clinical Question 9: Is Sonazoid CEUS helpful when performing percutaneous biopsy of FLLs?

Consensus Statement #9 Sonazoid CEUS is recommended for use to increase the lesion conspicuity and quality of biopsy specimens, thus improving the technical success rate of biopsy, especially when lesions are poorly visualized on US.

(Recommendation level: 1, Evidence level: B) (Agree 48, Disagree 0, Abstain 1)

Percutaneous biopsy of FLLs is a common interventional procedure performed for diagnosis and staging. As an image-guided tool, US offers several distinct advantages over CT and MRI, including real-time imaging, free of radiation, and high availability^[78]. Nevertheless, one main challenge of US-guided biopsy is poor lesion conspicuity in some cases, particularly in the setting of underlying cirrhosis with cluttered and coarse parenchymal echotexture^[79]. For lesions that are poorly visualized on US, the use of Sonazoid CEUS can help improve lesion conspicuity^[80,81]. A Korean study showed that lesion conspicuity was improved during the vascular phase (84.0%, $P = 0.409$) and post-vascular phase (92.0%, $P = 0.022$) compared to US (77.3%)^[80]. A retrospective study showed that 15 of 16 (93.8%) focal hepatic lesions invisible on fusion imaging (US + CT/MRI) could be detected on Sonazoid CEUS, and the CEUS-guided biopsy success rate for these “invisible” lesions was 87.6% (14/16)^[81]. In addition to that, Sonazoid CEUS allows accurate positioning of viable areas instead of necrotic areas, improving the quality of biopsy specimens. Eso *et al* estimated the viable area of the target lesions during the vascular phase and performed a biopsy by aiming at the estimated viable area during the post-vascular phase on Sonazoid CEUS, yielding a higher technical success rate than US-guided biopsy [92.3 (60/65) vs. 76.8% (43/56), $P = 0.0167$]^[82].

Overall, Sonazoid CEUS is recommended to increase the lesion conspicuity and quality of biopsy specimens, thus improving the technical success rate of biopsy, especially when lesions are poorly visualized on US.

Ablation

Local ablation therapy via percutaneous, laparotomy, or laparoscopy approaches serves as an important nonsurgical treatment for small primary and metastatic liver tumors, with radiofrequency ablation (RFA) being the most commonly used technique^[83]. Usually, ablation is performed under US guidance owing to its real-time imaging, convenience, high availability, free of radiation, and low cost. With advanced MRI techniques, especially hepatocyte-specific MRI contrast agents, potential candidates for ablation with very small tumors can be identified^[84]. However, localizing these small tumors on US for ablation remains challenging due to poor lesion conspicuity. According to two prospective studies that enrolled patients with small HCCs (≤ 3 cm), 21.5–25.3% of lesions were invisible on US^[85,86]. In some cases, these inconspicuous lesions could be blindly ablated by placing an electrode into the expected area using anatomic landmarks. However, mistargeting or incomplete ablation may be frequently induced. Therefore, an effective image guidance tool for ablation should be equipped to identify and localize target lesions.

Clinical Question 10: Is Sonazoid CEUS helpful when performing local ablation therapy of liver tumors?

Consensus Statement #10-1 Sonazoid CEUS is recommended for use to increase the lesion visibility of small lesions and facilitate accurate insertion of ablation electrodes into the target lesions, thus improving technical feasibility and local tumor control of local ablation therapy when lesions are poorly visualized on US. (Recommendation level: 1, Evidence level: A) (Agree 49, Disagree 0, Abstain 0)

Current evidence highlighted the advantages of percutaneous Sonazoid CEUS with a unique post-vascular phase in guiding tumor ablation over US^[87–92]. First, Sonazoid CEUS allows better tumor visibility of small liver lesions compared to US^[29,87–89]. In a study with 716 HCCs, the detectability of HCC using Sonazoid CEUS detected additional 69 HCCs for percutaneous RFA, yielding an increased tumor detectability than US (93.2% vs. 83.5%, $P = 0.04$)^[87]. Similar results were drawn in a study by Miyamoto *et al* [Sonazoid CEUS, 96% (50/52); US, 57% (30/52), $P < 0.01$]^[88]. A prospective study enrolled 43 small HCCs (< 3 cm) that were poorly identifiable from the surrounding cirrhosis-related pseudo lesions and found that 72% (31/43) of lesions were sufficiently conspicuous to be identified as the index tumor for percutaneous RFA during the post-vascular phase^[89]. For the detection of colorectal liver metastasis (CRLM), a prospective study with 230 CRLM lesions showed that the detection rate of Sonazoid CEUS was 81.3%, significantly higher than 66.7% of US ($P = 0.016$)^[29]. However, for tumors located at the diaphragmatic dome or deep portions of the liver, where percutaneous localization is challenging, laparoscopic Sonazoid CEUS-guided ablation can improve the complete ablation rate and overall survival rate^[93].

Second, Sonazoid CEUS offers a wide temporal window to facilitate accurate insertion of ablation electrodes into the target lesions that are seen as a defect during the post-vascular phase, thereby avoiding mistargeting and eventually ensuring treatment efficacy, especially when the target lesion has poor conspicuity on US^[87–90,93,94]. In a single-center prospective study by Mukund *et al*, ablation applicator placement was performed during the post-vascular phase due to its stable nature and good lesion visibility, achieving a high technique efficacy of 95%^[90]. Complete ablation at a single session using Sonazoid CEUS-guided ablation was achieved in 94–96% of liver tumors according to another two studies^[88,94]. A tendency of less number of sessions needed for RFA of HCCs under the guidance of Sonazoid CEUS than US was also reported by Masuzaki *et al* (1.33 ± 0.45 vs 1.49 ± 0.76 ; $P = 0.0019$)^[87], Dohmen *et al* (1.19 vs 1.33 ; $P > 0.05$)^[91], and Minami *et al* (1.1 ± 0.2 vs 1.4 ± 0.6 ; $P = 0.037$)^[94]. In terms of local tumor control, Sonazoid CEUS-guided RFA could achieve much better local tumor control than US-guided RFA for HCC^[91] and CRLM^[92].

Taken together, Sonazoid CEUS is recommended to increase the lesion visibility of small lesions and facilitate accurate applicator placement in the target lesions, thus improving technical feasibility and local tumor control of local ablation therapy when lesions are poorly visualized on US.

Consensus Statement #10-2 Adding Sonazoid CEUS to fusion imaging with US and CT/MRI images can be used for guiding ablation of liver tumors that are poorly visualized on US or fusion imaging, with high efficacy and safety.

(Recommendation level: 2, Evidence level: B)
(Agree 49, Disagree 0, Abstain 0)

If fusion imaging equipment is available, fusing imaging with US and CT/MRI (FI) can be used to localize most small liver tumors with poor lesion conspicuity on US during the ablation procedure^[95]. For some small lesions that still fail to be identified on FI, Sonazoid CEUS can be combined with FI to further improve lesion conspicuity^[96–98]. A retrospective study by Min *et al* showed that after adding Sonazoid CEUS to FI, 83.3% (25/30) of small HCCs (mean size, 1.2 cm) that were inconspicuous on FI alone became conspicuous, thus facilitating accurate targeting for RFA^[96]. In a prospective study, Lee *et al* reported that 16.7% (21/126) of small HCCs (1–2 cm) were inconspicuous on FI, of which 90.5% (19/21) became conspicuous after adding Sonazoid CEUS^[97]. Another prospective study with 248 liver tumors (mean size, 1.6 cm), inconspicuous on US, showed that FI improved conspicuity in only 26.2% (65/248) of these lesions, while lesion conspicuity was observed in 87.7% (121/138) of patients after adding SonoVue CEUS to FI and 90% (99/110) with Sonazoid CEUS.

As for the efficacy of CEUS/FI-guided ablation for these invisible lesions on US or FI, the technical success rate was reported to be 89.2–99.6%^[96–99]; the 3-year local tumor progression rate was 5.9–10.5%^[97,99]. In terms of safety, the incidence of major complications for CEUS/FI-guided ablation was very low (0–4.3%)^[96–99]; the incidence of minor complications was 5.4% (2/37) in the CEUS/FI-guided group, lower than that in the

Sonazoid CEUS-guided group [15.1%, (29/192)] and FI-guided group [10.6%, (13/123)], although the differences are statistically significant ($P = 0.31$)^[99].

In general, adding Sonazoid CEUS to FI can be used for ablation of liver tumors that are poorly visualized on US or FI, with high efficacy and safety. However, it is not strongly recommended considering its low accessibility, poor convenience, and high costs.

Surgery

Clinical Question 11: Can contrast-enhanced IOUS using Sonazoid (Sonazoid CEIOUS) be helpful during the surgical procedure for primary and metastatic liver tumors?

Consensus Statements #11-1 Sonazoid CEIOUS can be recommended for IOUS to detect and locate additional lesions not seen on preoperative imaging and IOUS and to correctly diagnose lesions misdiagnosed on pre-operative imaging and IOUS, allowing for the adjustment of surgical treatment plan accordingly.

(Recommendation level: 1, Evidence level: B)
(Agree 49, Disagree 0, Abstain 0)

Hepatic resection is generally recognized and recommended for radical treatment in patients with resectable HCC and CRLM. IOUS is widely used as an intraoperative diagnostic tool for improved tumor detection and staging compared to preoperative imaging, thus affecting the surgical treatment^[100,101]. However, the differential diagnosis of newly detected nodules may be difficult on IOUS^[102]. On the other hand, some isoechoic or small occult lesions with poor conspicuity are likely to be missed by IOUS^[103,104].

Sonazoid CEIOUS with a long-time post-vascular phase allows investigating the whole liver intraoperatively for detecting additional lesions not seen on preoperative imaging and IOUS and stably locating each of them, as liver tumors were detected as a defect in most cases. If necessary, defect reperfusion imaging is allowed to evaluate the tumor perfusion, thus being able to correctly diagnose lesions misdiagnosed on preoperative imaging and IOUS, leading to more accurate tumor staging^[105–113]. A study with 192 consecutive patients showed that the sensitivity, specificity, and accuracy of Sonazoid CEIOUS for the diagnosis of lesions detected by IOUS were 65%, 94%, and 87%, respectively; Sonazoid CEIOUS identified 21 additional new lesions not detected by IOUS in 16 patients, of which 14 lesions (67%) in 11 patients were confirmed HCC^[108]. For the detection of CRLMs, Sonazoid CEIOUS is the most sensitive when compared with preoperative MRI and IOUS (preoperative MRI, 0.87; IOUS, 0.80; CEIOUS, 0.94) according to meta-analyses^[111,112]. Arita *et al* reported that IOUS missed 10 CRLMs detected by preoperative imaging and detected newly 21 CRLMs not seen on preoperative imaging, while Sonazoid CEIOUS correctly diagnosed all CRLMs detected either by preoperative imaging or IOUS and

an additional 17 CRLMs with a median diameter of 0.5 cm not detected by preoperative imaging or IOUS. This study concluded that Sonazoid CEIOUS is useful in hepatic resection for CRLM, even if preoperative EOB-MRI and IOUS are performed^[113].

The above characteristics facilitate adjusting surgical treatment plans accordingly^[107,109,111,113,114]. A total of eight small lesions in seven patients were additionally detected and correctly diagnosed as HCC on Sonazoid CEIOUS, of which three (42.9%) patients received an additional partial hepatectomy^[109]. Results of three prospective studies showed that the planned surgical procedure changed in about 14–26% of operations for CRLM based on Sonazoid CEIOUS findings, indicating the effect of Sonazoid CEIOUS on surgical strategy^[107,113,115]. A meta-analysis showed that new CRLMs on Sonazoid CEIOUS were identified in 247 patients, thus affecting the surgical plan in 128 patients. Among them, 71% (91/128) of patients undergo a more extensive hepatectomy, and 11.7% (15/128) are considered inoperable^[111].

In summary, Sonazoid CEIOUS can be recommended for IOUS to detect and locate additional lesions not seen on preoperative imaging and IOUS, and to correctly diagnose lesions misdiagnosed on preoperative imaging and IOUS, allowing for the adjustment of surgical treatment plan accordingly.

Consensus Statements #11-2 Sonazoid CEIOUS can be helpful in identifying clinically relevant disappearing liver metastases (DLMs) in patients undergoing hepatic resection following neoadjuvant chemotherapy, facilitating radical resection.

(Recommendation level: 2, Evidence level: B)
(Agree 35, Disagree 0, Abstain 14)

A survival benefit of neoadjuvant chemotherapy followed by hepatic resection in patients with resectable liver metastasis has been proven^[116,117]. With advances in chemotherapy drugs, about 15–24% of patients undergoing chemotherapy achieve a radiographic complete response, resulting in DLMs on preoperative cross-sectional imaging, generally, contrast-enhanced CT^[118–120]. However, DLMs do not necessarily mean a pathologic complete response, of which macroscopic and microscopic viable tumors can be observed in some cases (i.e., clinically relevant DLMs)^[121,122]. The difficulty of recognition and localization of these clinically relevant DLMs may pose challenges for radical resection.

IOUS can be used to address the issue. However, merely 21% (4/19) of clinically relevant DLMs are identified using IOUS^[118]. Several studies advocated for the introduction of Sonazoid CEIOUS in identifying clinically relevant DLMs after chemotherapy^[118,123,124]. Arita *et al* reported that Sonazoid CEIOUS identified 16 DLMs on preoperative CT and EOB-MRI, of which 15 (94%) were confirmed viable tumors, occupying 79% of the total 19 clinically relevant DLMs^[118]. A retrospective study showed that 26% (71/275) of DLMs on CT could be visible on EOB-MRI, and an additional 34% (94/275) were further identified on subsequent Sonazoid CEIOUS, of which 77% (127/165) were clinically relevant DLMs; only 8.2% (9/110) of DLMs not identified on

sequential EOB-MRI and Sonazoid CEIOUS were clinically relevant^[123]. Another study by Arita *et al* preliminarily proved the effectiveness of adding Sonazoid CEIOUS to “real-time virtual sonography” (i.e., fusion imaging with US and CT/MRI images) for detecting metastatic lesions after chemotherapy^[124].

In summary, Sonazoid CEIOUS can be helpful to identify clinically relevant DLMs in patients undergoing hepatic resection following neoadjuvant chemotherapy, facilitating radical resection. Before that, adequate pre-chemotherapy and preoperative imaging assessments, especially EOB MRI, are essential.

Consensus Statements#11-3: Sonazoid CEIOUS, especially when combined with the ICG fluorescent navigation system, may help better depict the tumor margin and resection line for performing liver resection, thus ensuring radical resection.

(Recommendation level: 2, Evidence level: C)
(Agree 43, Disagree 0, Abstain 6)

Hepatic resection, including non-anatomical resection and anatomical resection, which maximizes the resection of liver cancer tissue pathologically as well as the preservation of normal functioning liver physiologically, is generally recognized and recommended for liver tumors^[125]. For non-anatomical resection, a precise depiction of the tumor margin is the key to ensuring radical resection. Compared to IOUS, Sonazoid CEIOUS enabled better visualization of the tumor margin in all patients, even after preoperative chemotherapy^[107]. Patients following IOUS-guided hepatectomy for HCC with IOUS guidance are more inclined to have a positive surgical margin than those with Sonazoid CEIOUS (15% vs 0%, $P = 0.073$)^[106].

Anatomical resection, which leads to improved outcomes, is the preferred type of hepatic resection if indicated. One key to ensuring successful anatomical resection is to precisely depict the resection line. The resection line can be marked as an ischemic demarcation line through ligation of the corresponding pedicle for anatomical resection, which can be detected as a slightly dark line on IOUS^[100]. Compared to IOUS, Sonazoid CEIOUS more clearly provides an ischemic demarcation line and allows it to be repeatedly confirmed during the resection procedure, as the segment with a loss of blood flow shows hypoenhancing during the long-term post-vascular phase. According to the results of a prospective study, the planned resection line was altered in 7 (5.4%) of 129 operations based on Sonazoid CEIOUS findings^[107]. After further combining with the ICG fluorescent navigation system, the resection line could be more frequently detected than that of Sonazoid CEIOUS only in patients with HCC following anatomical resection [100% (22/22) vs 77% (17/22), $P < 0.018$], which might indicate that the improved efficacy of combining Sonazoid CEIOUS and ICG fluorescent navigation^[126].

In summary, Sonazoid CEIOUS, especially when combined with the ICG fluorescent navigation system, may help better depict the tumor margin and resection line for performing liver resection, thus ensuring radical resection.

Section 4 Tumor treatment response evaluation

Clinical question 12: Can Sonazoid CEUS help evaluate the tumor treatment response in patients who underwent locoregional therapies?

Patients with liver tumors who are ineligible for or unwilling to undergo surgical resection may benefit from locoregional therapies [such as ablation and transcatheter arterial chemoembolization (TACE), and radiotherapy]. These locoregional therapies tend to induce tumor necrosis rather than tumor shrinkage in size; size-based criteria, such as Response Evaluation Criteria in Solid Tumours (RECIST), may underestimate the treatment response. Instead, viable tumor appearance-based criteria such as modified Response Evaluation Criteria in Solid Tumours (mRECIST), European Association for the Study of the Liver (EASL) criteria, and LI-RADS treatment response algorithm are applied to provide a more reliable response evaluation in patients who underwent locoregional therapies^[127]. Sonazoid CEUS can offer important information about viable tumors through real-time perfusion imaging at the vascular phase and defect reperfusion imaging at the post-vascular phase^[4], and its use in assessing the treatment response following locoregional therapies has already been explored recently.

Consensus Statements #12-1: Sonazoid CEUS can be used for early detection of residual tumors and inadequate ablation margin shortly after ablation, as well as local recurrence during follow-up.

(Recommendation level: 1, Evidence level: B)
(Agree 48, Disagree 0, Abstain 1)

Incomplete ablation and local recurrence remain the common problems following ablation. Hence, immediate response and follow-up assessments are necessary. Sonazoid CEUS with a post-vascular phase allows for visualization of the post-ablation regions and a clear ablation margin. By comparing the ablation margin shown at the post-vascular phase to the tumor margin on US, Sonazoid can evaluate whether a safe ablation margin larger than 5 mm is achieved^[128]. In addition, Sonazoid CEUS with post-vascular phase and defect reperfusion imaging allows for the evaluation of whether viable tumors exist in the post-ablation regions. The enhancement at the vascular phase within the post-ablation regions and/or reperfusion adjacent to or in the ablated tumor in the defect reperfusion test indicates residual tumors or local recurrence^[129].

Sonazoid CEUS enables early detection of residual tumors and inadequate ablation margin shortly after ablation, facilitating a decision on whether additional ablation is needed to achieve a complete ablation and thus reducing the risk of local recurrence^[128,130]. In a retrospective study with 87 consecutive patients, Sonazoid CEUS was performed 3 h after percutaneous RFA to ensure an adequate ablation margin, thus yielding a low rate of 5-year cumulative local recurrence (2.3%)^[130]. A meta-analysis including 12 studies concluded that the complete ablation rate with the assistance of Sonazoid CEUS was higher (95%) than SonoVue

CEUS (87%)^[131]. As for the optimal time point for immediate posttreatment response evaluation, discrepant results have been reported in different studies (3 h after the procedure when the coagulated tumor outline was easiest to discern^[132], 15–22 h after RFA^[133], and 2 days after RFA^[134]). According to a meta-analysis^[135], the diagnostic performance for residual tumors was not significantly affected by the timing of post-treatment CEUS performed. As for the diagnostic performance, a study reported a high accuracy of 97% for residual tumors using 1-day 3D Sonazoid CEUS, which was in good concordance with the results obtained by 3D contrast-enhanced CT^[136]. A single-center prospective study showed that the fusion imaging combining Sonazoid CEUS and contrast-enhanced CT 1 day after RFA could be used to evaluate whether the ablation is complete with an accuracy of 96%^[137]. Another study with 86 HCCs from 70 patients demonstrated that Sonazoid CEUS 1–3 days after RFA is more sensitive than contrast-enhanced CT for the evaluation of a safety margin larger than 5 mm^[129].

Sonazoid CEUS can also play a role in detecting local recurrence after ablation^[5]. Compared to US (diagnostic accuracy, 0.773), Sonazoid CEUS performed better in the detection of local recurrence after RFA with an accuracy of 0.864^[138]. When compared to contrast-enhanced CT, the specificity of Sonazoid CEUS for detecting local recurrence was slightly higher than that of CT (96% vs 92%), although the sensitivity was lower [Sonazoid CEUS, 79% (Reader 1) and 83.9% (Reader 2); CT, 83.9% (Reader 1) and 90.3% (Reader 2)]^[139]. Frequently, more than one injection is required to evaluate multi-ablated lesions.

In summary, Sonazoid CEUS can be used for early detection of residual tumors and inadequate ablation margins shortly after ablation, as well as local recurrence during follow-up.

Consensus Statements #12-2: Sonazoid CEUS can be used to early evaluate the treatment response after TACE.

(Recommendation level: 1, Evidence level: B)
(Agree 48, Disagree 1, Abstain 0)

Retreatment is often needed in patients treated with TACE, making it crucial to early evaluate the post-treatment response for planning and adjusting treatment options in time. TACE is considered to be adequate if the treated lesion does not show tumor enhancement like before TACE, and the tumor volume does not increase. In contrast, viable tumors after TACE present as hyper-enhancement with various shapes inside or around the tumor at the arterial phase and hypo-enhancement/defect at the following phase on Sonazoid CEUS^[140].

The judgment of viable tumors by Sonazoid CEUS is not interfered with by the presence of parenchymal iodized oil deposition, enabling early response evaluation shortly after TACE. A study with 59 HCCs reached a similar conclusion, showing that the detection rate for viable tumor assessment by Sonazoid CEUS 1 day after TACE was significantly higher than that by contrast-enhanced CT 1 month after TACE [95.7% (45/47) vs 78.7% (37/47), $P < 0.05$]^[141]. This aligned with Xia *et al*'s findings that Sonazoid CEUS was more sensitive than dynamic CT 1 week after TACE in depicting viable tumor blood supply of HCC (58.1% vs 39.5%, $P < 0.01$)^[140]. Another retrospective study with 89 HCCs showed that the accuracy of Sonazoid CEUS 1–2 days after TACE

was non-inferior to contrast-enhanced CT 1 month after TACE in depicting the enhancement of viable tumor (83.1% for both)^[142]. Furthermore, a higher inter-reader agreement in interpreting Sonazoid CEUS images compared with CT or MRI images among experts could be achieved^[139,143]. In summary, Sonazoid CEUS can be used to early evaluate the treatment response after TACE.

Consensus Statements #12-3: The use of Sonazoid CEUS may be useful in evaluating the treatment response in patients who underwent radiotherapy.

(Recommendation level: 2, Evidence level: C)
(Agree 40, Disagree 1, Abstain 8)

A retrospective study with 59 patients with HCC has also explored the use of serial Sonazoid CEUS before and 1, 3, 7, 10, and 13 months following radiation therapy for monitoring local recurrence and showed that a reduction in tumor vascularity was observed in 100% of patients without local recurrence, while it was not observed in all patients with local recurrence^[144]. The above study concluded that Sonazoid CEUS may be useful in evaluating the treatment response of radiotherapy. However, current evidence is not sufficient to strongly support the use of Sonazoid CEUS in evaluating the response in patients who underwent radiation therapy.

Clinical question 13: Can Sonazoid CEUS be used to evaluate the treatment response in patients underwent systematic treatment?

Consensus Statements #13: Sonazoid-CEUS may be useful for evaluating the treatment response via assessing blood supply after systematic treatment.

(Strength of recommendation: 2, Quality of Evidence: C) (Agree 46, Disagree 1, Abstain 2)

Besides locoregional therapy, systematic therapy plays a crucial role in tumor treatment, especially for patients with advanced disease. Several studies have shown that Sonazoid CEUS can be used to assess the treatment response by evaluating vascular supply after 1–4 weeks of HCC treatment with systematic agents such as Sorafenib and Lenvatinib^[145–147]. A prospective study demonstrated that a reduction of vascular supply observed on Sonazoid CEUS 1 week following Sorafenib administration was significantly correlated with a decreased microvascular density on CD34-staining histological sections, which may be the basis for the application of Sonazoid CEUS to predict the response of systematic treatment^[148]. Quantitative perfusion parameters derived from Sonazoid CEUS have also been explored to evaluate the treatment response for HCC^[149]. Recent studies suggested that the use of time–intensity curve (TIC) analysis and quantitative parameters reflecting changes in blood supply, including peak intensity^[145], area under the tumor enhancement curve^[146], average arrival time^[150], and portal vein/hepatic artery arrival time^[151], were significantly correlated with treatment efficacy

and prognosis. It is conceivable that Sonazoid CEUS may also help predict the response for other intrahepatic malignant tumors, although it needs more evidence to support this possibility. In summary, Sonazoid CEUS may be a promising option for evaluating the tumor treatment response in patients who underwent systematic treatment.

In addition to the applications above, Sonazoid CEUS has also been explored for novel uses. For example, several recent studies aimed to investigate the potential value of Sonazoid CEUS in pre-operatively predicting the risk of microvascular invasion in HCC by establishing predictive models based on imaging features^[152–154], TIC-derived quantitative parameters^[155], and radiomics signature^[156], which will be one of the directions to be explored for Sonazoid CEUS in the liver in the future. More validation studies are encouraged.

Conclusions

The study reviewed recent evidence and made recommendations regarding several clinical questions related to Sonazoid CEUS in the management of FLLs. However, the current evidence for Sonazoid CEUS remains limited in many aspects, such as tumor depiction in the presence of different types of background liver parenchyma (steatosis, hepatitis, cirrhosis, chemotherapy-linked hepatopathy), as well as its use after chemoradiotherapy or after liver transplantation. As new data have been generated, the expert consensus will continue to be updated.

Ethical approval

The expert consensus on the clinical application of liver Sonazoid CEUS was registered in the Practice guideline REgistration for transPAREncy (PREPARE). (registration number PREPARE-2024CN484).

Consent

This article is based on expert consensus, thereby obviating the need for written informed consent.

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Author contributions

J.Z., P.L., L.L., K.Y., Y.Z., T.J., H.X., J.X., X.J., H.R.: conceptualization, data curation, writing – original draft, and writing – reviewing and editing. Y.L., W.C., X.-W.C., H.D., J.D., Y.D., W.D., H.H., G.H., W.H., Z.H., Y.H., B.L., J.L., K.-Y.L., Q.L., F.L., G.-J.L., L.L., B.L., W.L., Y.L., K.L., X.M., L.Q., J.R., H.W., L.W., X.W., W.W., X.-Y.X., B.X., D.X., H.Y., J.Y., M.Y., J.Y., M.-A.Y., X.Y., W.Z., Z.-B.Z.: methodology, data curation, and writing – original draft. J.Z., P.L., L.L.: conceptualization, project administration, supervision, writing – review and editing, and final approval of the version to be published.

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None.

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Data analyzed during the study are available from the corresponding author upon request.

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None.

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