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Review

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Contrast-enhanced ultrasound for hepatocellular carcinoma detection and diagnosis in the context of nonalcoholic fatty liver disease

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Abstract

The prevalence of nonalcoholic fatty liver disease (NAFLD) is increasing worldwide and is projected to become a major etiology of cirrhosis and hepatocellular carcinoma (HCC). HCC occurs more commonly in NAFLD patients who develop cirrhosis, though HCC is known to occur in the setting of noncirrhotic NAFLD as well. This is of particular importance given that the American College of Radiology (ACR) CT/MRI Liver Reporting and Data System (LI-RADS) algorithm may only be applied to a certain population of patients, and this population does not include those with noncirrhotic NAFLD. Conventional ultrasound (US) has long been in use for HCC surveillance, but contrast-enhanced US (CEUS) is a relatively newer modality, growing in use for assessment of liver lesions, and its use in HCC diagnosis has been formalized with CEUS LI-RADS. The use of US and CEUS in the assessment of liver lesions in NAFLD patients involves the consideration of certain particular nuances, and familiarity with these considerations will continue increasing in importance as the disease becomes more common.

Keywords: Hepatocellular carcinoma, contrast-enhanced ultrasound, nonalcoholic fatty liver disease

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) reflects a spectrum of diseases ranging from nonalcoholic fatty

liver (NAFL) to nonalcoholic steatohepatitis (NASH) and ultimately may progress to cirrhosis. NAFL is considered present when ≥ 5% of hepatocytes demonstrate an accumulation of lipid vacuoles in patients without other etiology of steatosis, such as excessive alcohol intake or viral infection. NASH reflects NAFL with the additional presence of hepatic inflammation and hepatocyte injury with ballooning, and at histology, NASH can appear identical to alcoholic steatohepatitis. Considered a hepatic manifestation of metabolic syndrome, NAFLD is associated with obesity, insulin resistance, dyslipidemia, cardiovascular disease, and chronic kidney disease; in fact, a recent consensus of international experts recommended renaming the disease to metabolic-associated fatty liver disease (MAFLD)[1,2]. NAFLD is the most common cause of diffuse liver disease in industrialized countries, and in the United States, a prevalence of 19%-46% has been reported[3,4].

The incidence of hepatocellular carcinoma (HCC) is increasing, and in several Western countries, NAFLD is the most rapidly increasing underlying etiology of hepatocellular carcinoma (HCC), displacing chronic hepatitis C infection[5]. Compared with HCC diagnosed in patients with chronic hepatitis B or C, NAFLD-related HCC is diagnosed at a later stage, occurs in slightly older patients, and is typically associated with worse survival outcomes[5]. A recent study reported that NAFLD-associated HCC showed slower tumor growth rates compared to viral and other etiologies[6]. Though the risk of HCC occurrence is lower in a patient with NAFLD than in a patient with chronic viral hepatitis, on a population basis, this is outweighed by the significantly greater prevalence of NAFLD than chronic viral hepatitis worldwide[5]. NAFLD-related HCC may occur with or without concomitant cirrhosis, and in fact, obesity and diabetes are known to be risk factors for the development of NAFLD-related HCC, independent of cirrhosis[7]. However, in patients with noncirrhotic NASH, HCC has been shown to occur more commonly at an advanced fibrosis stage[8,9].

ULTRASOUND FOR HCC SURVEILLANCE IN NAFLD

Surveillance with semiannual ultrasound (US) is widely employed for HCC screening in patients with cirrhosis of any cause and is recommended in the practice guidelines of major liver societies in Asia, Europe, and North America[10-12]. In addition, the recognition that HCC can occur in noncirrhotic NAFLD has prompted the American Gastroenterological Association to recommend HCC surveillance in noncirrhotic NAFLD patients with advanced fibrosis (stage F3)[5,13].

Multiphasic contrast-enhanced CT and MRI are more sensitive and specific for HCC detection and diagnosis than conventional US, but US remains the preferred method for HCC surveillance owing to its low cost and widespread availability. Diagnostic categories used in reporting US exams performed for HCC screening and surveillance are outlined by the American College of Radiology (ACR) in its US Liver Reporting and Data System (US LI-RADS) [Table 1]. However, there are well-known inherent limitations of US, including operator dependence, bowel gas shadowing, and patient-specific anatomical factors. Performing US in patients with NAFLD often entails additional limitations, including increased scanning depth due to obesity, and significant attenuation of the beam which occurs in marked steatosis, particularly in the right lobe [Figure 1]. Cirrhosis can present additional challenges for US when the liver is shrunken and high in the right upper quadrant, leading to greater lung and rib shadowing.

The inherent limitations of US necessitate an assessment of the adequacy of each exam performed for screening and surveillance. This has been formalized in US LI-RADS [Table 1], with US visualization scores of A, B, and C corresponding to no/minimal, moderate, and severe limitations in liver visualization, respectively[14]. LI-RADS is not applicable to all patients; currently, patients with NASH cirrhosis are included in the LI-RADS population, but patients with noncirrhotic NAFLD are not. Regardless, a screening ultrasound hampered by moderate or severe limitations for any patient warrants consideration for

Table 1. Diagnostic categories of US LI-RADS and CEUS LI-RADS

US LI-RADS and CEUS LI-RADS categories			
US LI-RADS		**CEUS LI-RADS**	
US Category		CEUS LR-NC	Observation cannot be categorized due to image degradation or omission
US-1 - Negative	No US evidence of HCC	CEUS LR-TIV	Definite tumor in vein
US-2 - Subthreshold	Observation(s) that may warrant short-term US surveillance	CEUS LR-M	Probably or definitely malignant, but not specific for HCC
US-3 - Positive	Observation(s) that may warrant multiphase contrast-enhanced imaging	CEUS LR-1	Definitely benign
US Visualization Score		CEUS LR-2	Probably benign
A	No or minimal limitations	CEUS LR-3	Intermediate probability of malignancy
B	Moderate limitations	CEUS LR-4	Probably HCC
C	Severe limitations	CEUS LR-5	Definitely HCC

CEUS: Contrast-enhanced ultrasound; HCC: hepatocellular carcinoma; LI-RADS: Liver Imaging Reporting And Data System; NC: non-categorizable; TIV: tumor in vein; US: ultrasound.

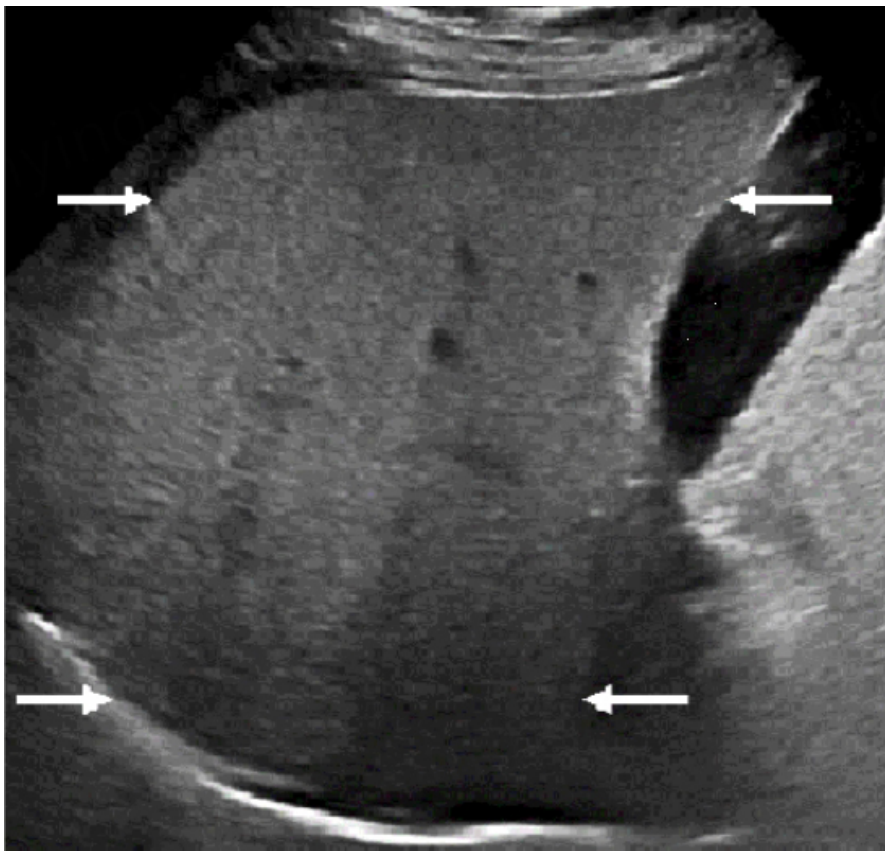

Figure 1. Beam attenuation in NAFLD. Diffuse fatty deposition in steatosis makes the liver echogenic (upper arrows) and, when marked, can also cause attenuation of the beam, leading to poor visualization of detail in the deeper portions of the liver (bottom arrows).

screening with multiphasic CT or MRI instead, at least intermittently, and this consideration will arise more commonly in the obese NAFLD population. Specific recommendations for alternative imaging after an exam with a suboptimal US visualization score have not yet been formalized in US LI-RADS.

On conventional greyscale US, HCC most commonly presents as a hypoechoic mass, though its appearance can vary, and it may be isoechoic (especially if small), hyperechoic (for example, if containing intracellular fat), or heterogeneous[15]. Additionally, the diffuse alteration of background liver parenchyma echogenicity in NAFLD can change the perceived appearance of focal lesions, including HCC. HCC is typically solid but may have internal cystic change due to necrosis or hemorrhage. HCC commonly presents as a well-defined mass, but more aggressive variants can be infiltrative in appearance, sometimes blending in with the background heterogeneous echotexture, leading to difficulty in detection. HCC can present with concomitant tumor-in-vein (with portal veins affected more often than hepatic veins), and this is especially common with infiltrative tumors. Conventional US does not have adequate specificity for HCC diagnosis, and hepatic masses detected by screening US are typically further evaluated with multiphasic contrast-enhanced CT or MRI. However, the use and acceptance of contrast-enhanced ultrasound (CEUS) in the workup of liver lesions is steadily increasing.

CEUS

CEUS is performed with the intravenous administration of an ultrasound contrast agent (UCA) composed of gas microbubbles enclosed in shells of lipid or protein, and imaging is performed using a low mechanical index, to minimize microbubble destruction and improve the production of nonlinear echoes from microbubble oscillation[16]. UCAs, in general, have a very good safety profile, with a low incidence of adverse reactions[17-19]. In the United States, the contrast consisting of sulfur hexafluoride lipid-type A microspheres (Lumason or SonoVue, Bracco Diagnostics Inc., Monroe Township, NJ) is approved by the Food and Drug Administration (FDA) for evaluation of liver lesions. The microbubbles in this contrast agent have a mean diameter of 1.5-2.5 μm and, typical of UCAs, remain completely intravascular because of their large size, with no extravascular interstitial phase. The typical dose of sulfur hexafluoride microspheres given is 1.5-2.5 mL, followed by a flush of 5-10 mL normal saline. An UCA can be administered intravenously several times during an examination, as needed for assessment of multiple lesions.

In contrast to whole-abdomen imaging obtained at multiple time points with CT and MRI, CEUS images are typically obtained while focusing on one lesion at a time, and the entire dynamic wash-in and wash-out of contrast through the lesion is captured continuously, commonly at a frame rate of 10/s[20]. The period over which the contrast administration is continuously observed is divided into several vascular phases[21]. The arterial phase begins at 10-20 s after contrast injection and lasts until 30-45 s; the portal venous phase begins at 30-45 s and lasts until 2 min; and finally, the late phase lasts from 2 min until clearance of microbubbles at 4-6 min. Continuous image recording is generally performed for the first 60 s after contrast administration, after which intermittent imaging (every 30 s) can be performed to the end of the late phase to minimize bubble destruction[21].

CEUS LI-RADS has been developed by the ACR as a standardized system for evaluation of liver lesions using CEUS in a certain patient population at risk for HCC[21]. CEUS LI-RADS categories can be applied only in adult patients (age ≥ 18) with cirrhosis (with a few exceptions), chronic hepatitis B, or a history of current or prior HCC [Table 1]. LI-RADS cannot be applied in patients with cirrhosis secondary to congenital hepatic fibrosis, or cirrhosis secondary to a vascular disorder such as cardiac congestion, diffuse nodular regenerative hyperplasia, Budd-Chiari syndrome, or hereditary hemorrhagic telangiectasia[21]. Thus, CEUS LI-RADS can be applied in those with NASH cirrhosis, but not in those with noncirrhotic NAFLD. Visualization of a suspicious lesion in a patient with noncirrhotic NAFLD will likely entail a multidisciplinary team discussion, correlation with serum alpha-fetoprotein, and consideration for biopsy.

As in CT/MRI LI-RADS, lesion size, arterial phase hyperenhancement (APHE), and washout are of critical importance in determining the CEUS LI-RADS category [Figure 2]. Just as with CT/MRI LI-RADS, for a lesion to be diagnosed as CEUS LR-5 definite HCC, it must show APHE in whole or in part. The APHE must be non-rim, as rim APHE is a feature of LR-M lesions, and also, the APHE must not be peripheral discontinuous globular, which is a feature of LR-1 hemangiomas. LR-M lesions are suspicious for malignancy but not specific for HCC, and the most common etiologies of LR-M lesions are cholangiocarcinoma, atypical HCC, combined hepatocellular cholangiocarcinoma, and metastasis.

Washout is evaluated differently with CEUS LI-RADS than with CT/MRI LI-RADS. In both algorithms, the presence or absence of washout is important. However, in CEUS LI-RADS, the degree and timing of washout are also critical in categorization. For a lesion to be diagnosed as CEUS LR-5 definite HCC, it must show washout that is both late and mild. Late onset of washout is defined in CEUS LI-RADS as being detected ≥ 60 s after contrast injection. Marked washout is seen in nodules with a "punched-out" appearance, nearly devoid of enhancement, while mild washout is seen in nodules that are hypoenhancing but not devoid of enhancement. Early washout (detected < 60 s after contrast injection) and marked washout are both considered features of LR-M lesions.

The most optimal usage of timing and onset of washout as CEUS LI-RADS features is an area of active research. For example, in a study of 264 liver nodules, Ding et al found that modifying the timing cutoff to 45 s instead of 60 improved the sensitivity and area under the curve for LR-5 in diagnosing HCC, and improved the specificity of LR-M in diagnosing non-HCC malignancies[22]. In a study of 2020 liver nodules, Zheng et al introduced a modification to categorize nodules as LR-5 when APHE and mild washout were observed, regardless of whether the washout was early or late; marked, punched-out washout remained a feature of LR-M. In this study, the proposed modification increased the positive predictive value (PPV) and specificity of LR-M in diagnosing non-HCC malignancies, while the PPV and specificity for LR-5 in diagnosing HCC remained high[23]. As with all ACR RADS, CEUS LI-RADS undergoes periodic revision with the goal of continually improving diagnostic accuracy, and with further revisions, the application of the washout feature may evolve.

CEUS in patients with NAFLD may be complementary to other imaging modalities. Thompson et al found that on MRI, increasing steatosis can lead to decreased visualization of washout and capsule appearance, both major features in CT/MRI LI-RADS, in NAFLD-associated HCC[24]. They postulated that increased background liver signal loss on fat-suppressed postcontrast T1-weighted images could be a potential cause for the decreased visualization of washout in these patients. For most lesions, CEUS is not typically hampered by such confounding signal loss, and could add supplemental value in the evaluation of NAFLD-associated liver masses with equivocal or absent washout on MRI. However, there may also be signal loss on CEUS in deeper lesions. Similar to the MRI study by Thompson mentioned above, decreased visualization of washout has also been observed in NAFLD-associated HCC with CT as well[25]. Aside from these slightly distinct findings in NAFLD-associated HCC, HCC detected in the noncirrhotic liver is similar in imaging appearance to HCC detected in the cirrhotic liver, though noncirrhotic HCC tends to present at a later stage, with a larger size, and with a greater likelihood of extrahepatic extension[26].

Another, more well-known advantage of CEUS is inherent in its dynamic image acquisition, because of which the arterial phase never fails to be observed. This can complement the occasional CT or MRI study in which the static time points obtained fail to capture the proper arterial phase, for example, in patients with poor cardiac output [Figure 3].

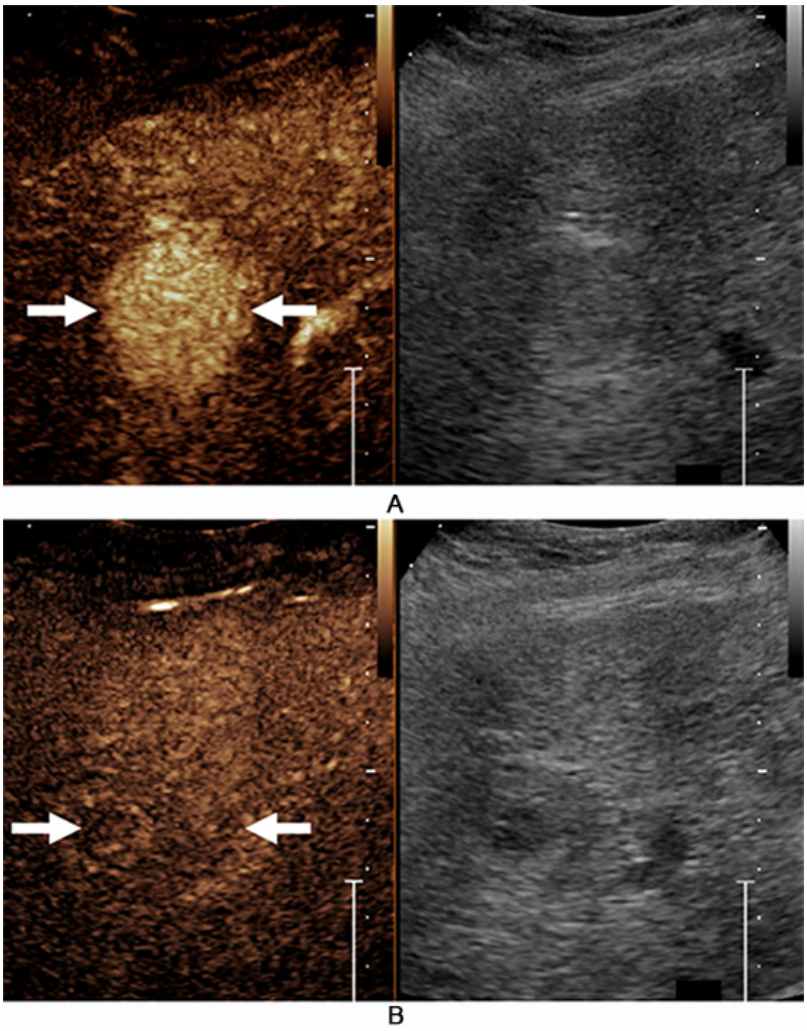

Figure 2. CEUS LI-RADS-5 HCC in a 78-year-old man with NASH cirrhosis. Arterial phase CEUS and grayscale images show APHE (arrows in A), and delayed images show washout (arrows in B), which is mild and late, occurring later than 60 s after contrast administration.

DIAGNOSTIC PERFORMANCE

The intended probability of an HCC diagnosis within each CEUS LI-RADS category is 0% (LR-1), < 20% (LR2), 20%-70% (LR-3), 70%-95% (LR4), and 100% (LR-5)[20,21,27]. These are overall similar to the probabilities of HCC within the same LR categories of CT/MRI LI-RADS, with the exception of LR-3, which may have a higher probability of HCC in CEUS LI-RADS than in CT/MRI LI-RADS. This is presumably due to the fact that LR-3 vascular pseudolesions (such as arterioportal shunts) are commonly detected with CT and MRI, but only rarely visualized with CEUS[28].

Accuracy in HCC diagnosis has been found to be fairly similar between CEUS and CT/MRI. A recent meta-analysis by Zhou *et al.* included 43 studies published between 2014 and 2021, and found the sensitivity, specificity, and accuracy of LR-5 categorization for the diagnosis of HCC to be 73%, 92%, and 78% for CEUS LI-RADS, and 69%, 92%, and 76% for CT/MRI LI-RADS, respectively[29]. Another recent meta-analysis by Li *et al.* produced similar results, using 39 studies from 2014-2020, and found the sensitivity and specificity of LR-5 categorization for the diagnosis of HCC to be 69% and 93% for CEUS LI-RADS, and 67% and 93%

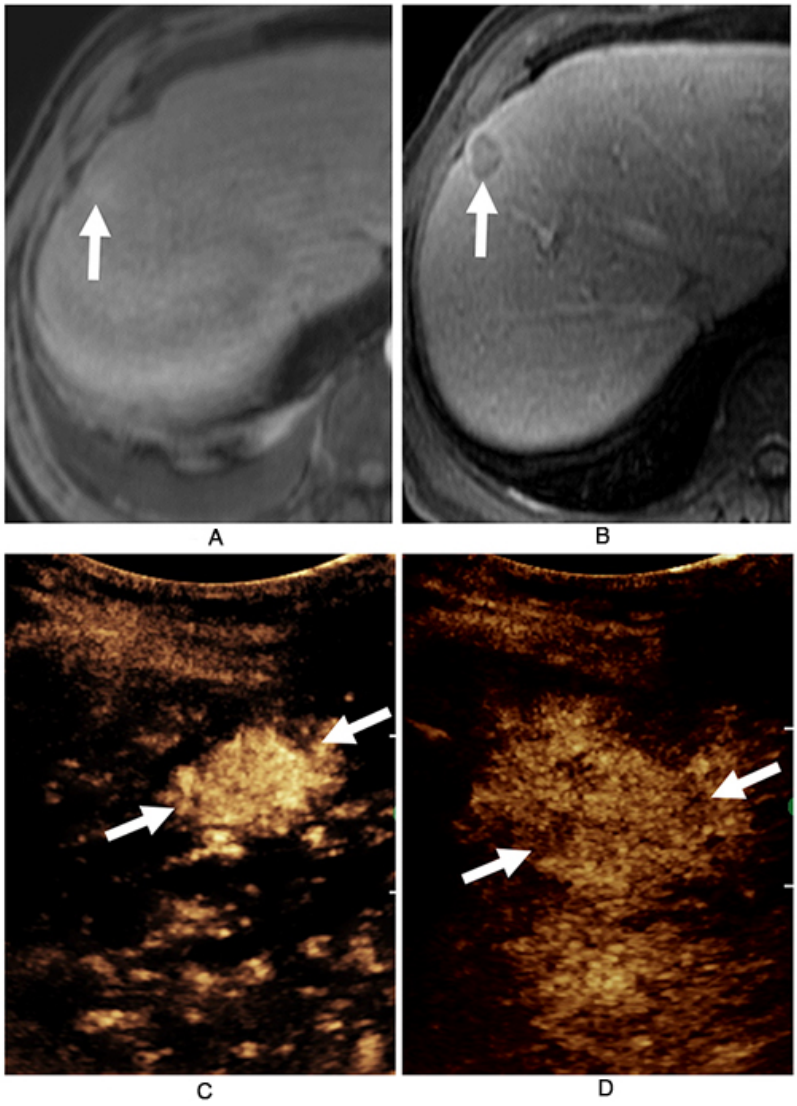

Figure 3. Superior demonstration of APHE with CEUS. MRI of a 2.3-cm liver lesion in a 71-year-old man with NASH cirrhosis shows minimal to absent APHE (arrow in A) but with clear washout and enhancing capsule at portal venous phase (arrow in B), meeting criteria for LR-4 with CT/MRI LI-RADS. At CEUS, the lesion shows clear APHE (arrows in C) and washout that is mild and late (arrows in D), meeting criteria for LR-5 with CEUS LI-RADS, diagnostic of HCC. The lack of clear APHE on the MRI was probably due to slightly early acquisition; the dynamic continuous acquisition of CEUS is not susceptible to this shortcoming.

for CT/MRI LI-RADS, respectively[30].

The impact of lesion size on the accuracy of HCC diagnosis with CEUS has been evaluated by several papers. Aubé *et al.* evaluated 342 liver nodules measuring 10-20 mm, and 202 liver nodules measuring 20-30 mm, and compared MRI, CT, and CEUS for the diagnosis of HCC in these lesions[31]. For the 10-20 mm nodule group, sensitivity with CEUS (39.6%) was inferior to MRI (70.6%) and CT (67.9%), but specificity with CEUS (92.9%) was superior to MRI (83.2%) and CT (76.8%). For the 20-30 mm group, sensitivity with CEUS (52.9%) remained inferior to MRI (72.3%) and CT (71.6%), but specificities for the 3 modalities were similar (91.5%, 89.4%, and 93.6%, for CEUS, MRI, and CT, respectively).

In a retrospective CEUS study by Pan *et al.*, 545 liver nodules were separated into two groups measuring < 20 mm and ≥ 20 mm[32]. Sensitivity, specificity, accuracy, and positive predictive value (PPV) were found to be very similar between the two groups: 55.6%, 85.7%, 60.5%, and 95.2% for the smaller group, respectively, and 57.6%, 88.6%, 59.8%, and 98.5%, for the larger group, respectively.

In another study, Huang *et al.* completed a retrospective CEUS study of 175 liver nodules, all ≤ 20 mm in size, and also found a high specificity of 97.1% for LR-5 in the diagnosis of HCC, but notably found a somewhat higher sensitivity of 73.3%, compared to the other studies mentioned above[33]. Finally, another study of CEUS in small HCCs measuring ≤ 20 mm detected an interesting difference in enhancement pattern, with liver nodules measuring ≤ 10 mm showing a longer duration of enhancement and later washout than liver nodules measuring 10-20 mm[34].

The inter-reader reliability of CEUS LI-RADS has been evaluated, and a recent meta-analysis reviewed data from 12 such studies published between 2018 and 2021[35]. This meta-analysis found mostly substantial inter-reader agreement in the determination of LI-RADS major features and LI-RADS categorization, with κ values of 0.73, 0.69, 0.54, 0.62, and 0.75, in readers' assessment of nonrim APHE, mild and late washout, rim APHE, early washout, and LI-RADS categorization, respectively.

One of the main aims of LI-RADS is to achieve high specificity for the LR-5 classification in the diagnosis of HCC and thus to ensure accurate diagnosis prior to treatment without requiring biopsy for these lesions[36]. As a result, however, there is less diagnostic specificity regarding lesions that fall into the LR-M category, and the reporting radiologist will need to provide a differential diagnosis. One study found that of 15 liver lesions classified as LR-M by CEUS, 47% were intrahepatic cholangiocarcinoma, 13% were combined hepatocellular cholangiocarcinoma, and 40% were HCC[27]. Thus, it must always be borne in mind that the classification of LR-M does not exclude HCC [Figure 4].

PATIENT MANAGEMENT

In the United States, the definitive diagnosis of HCC by CEUS alone remains problematic. This is due to the fact that liver transplantation is performed for HCC more commonly in the United States than in many other countries where resection is preferred, and in the United States, transplantation is considered the definitive curative treatment for HCC. Allocation of livers for transplant is managed by the United Network for Organ Sharing (UNOS), and currently, the addition of model for end-stage liver disease (MELD) exception points for HCC to patients awaiting transplant is dictated by the Organ Procurement and Transplantation Network (OPTN) criteria. The OPTN criteria are very similar to CT/MRI LI-RADS in classifying lesions as definitive HCCs (though not identical); however, currently, in the OPTN criteria, CEUS is not accepted for definitive diagnosis of HCC and thus cannot be used to award exception points. Consequently, any patient in the United States with a liver mass suspicious of HCC on CEUS for whom liver transplant is being considered will also require that the lesion meet OPTN criteria on a multiphasic contrast-enhanced CT or MRI exam. If it does not, biopsy may then be necessary.

In patients who are not being considered for liver transplant, this requirement is not an issue, and LR-5 lesions on CEUS may be considered definitive for HCC and treated as such. This is of particular importance in the NAFLD population, as in some of these patients, liver transplant may not be considered feasible because of multiple co-morbidities, affecting surgical candidacy. On the other end of the NAFLD spectrum, this is also of importance for patients with noncirrhotic NAFLD who have HCC, as hepatic resection is often preferred over transplant for these patients if they are otherwise appropriate surgical candidates. Acceptance of CEUS for HCC diagnosis by clinicians outside of radiology is increasing and has been helped

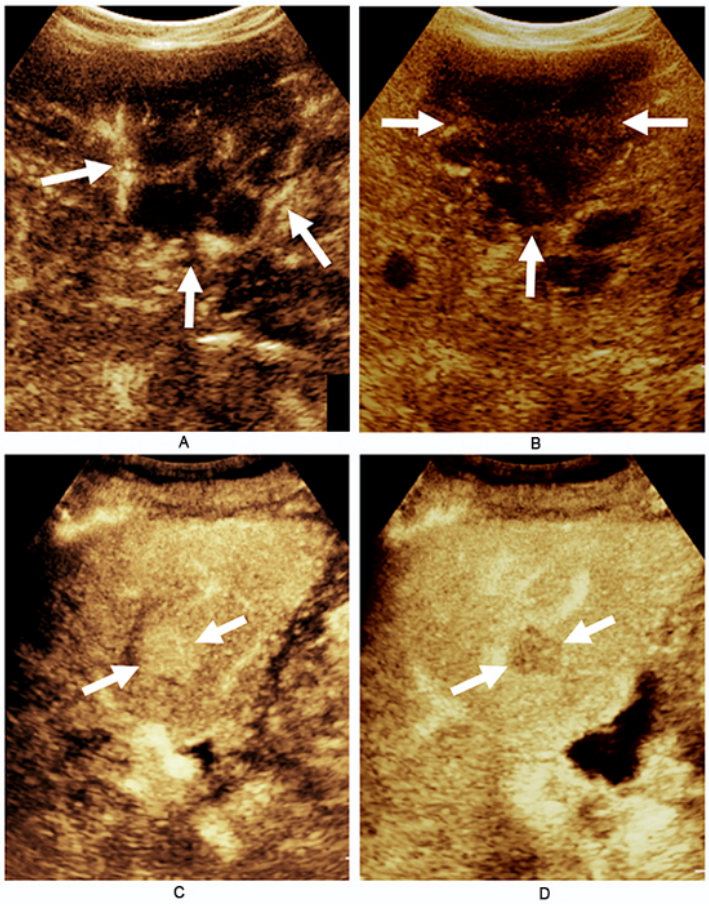

Figure 4. Examples of LR-M. A heterogeneous 4.6 cm liver mass shows rim APHE (arrows in A) that is incomplete, and washout that is early and marked (arrows in B), meeting the criteria for LR-M. Biopsy of this lesion showed HCC. Another LR-M liver lesion measuring 1.7 cm shows APHE (arrows in C), but early washout (arrows in D). Biopsy of this lesion showed metastatic neuroendocrine tumor.

by the formalization provided by CEUS LI-RADS.

CEUS can also be used to assess for residual or recurrent malignancy after locoregional therapy or surgical resection for HCC [Figure 5]. A recent meta-analysis of 43 publications showed a sensitivity of 85% and a specificity of 94% for CEUS in the detection of residual viable disease after locoregional treatment of HCC[37]. Furthermore, the meta-analysis showed no significant difference in diagnostic performance for detection of residual disease depending on the type of locoregional therapy [ablation *vs.* transarterial chemoembolization (TACE)]. It is worth noting that, unlike treatment-naïve HCC, in post-treatment assessment, residual or recurrent tumors may show APHE or isoenhancement[37,38]. Additionally, post-treatment residual or recurrent tumors may lack washout[39]. An enhancing nodular component of a treated lesion should be considered suspicious, while thin, smooth rim enhancement is commonly seen after locoregional therapy and is not considered suspicious. Though CEUS LI-RADS currently does not include a system for treatment response assessment (as with the LR-TR categories of CT/MRI LI-RADS), this is expected to be added in the next CEUS LI-RADS version.

During US-guided biopsies and thermal ablation procedures, CEUS has been shown to be valuable for increasing precision of intraprocedural guidance. A recent European multicenter study showed improved visibility and effectiveness of ablations guided with CEUS[40]. Additionally, immediate post-ablation CEUS

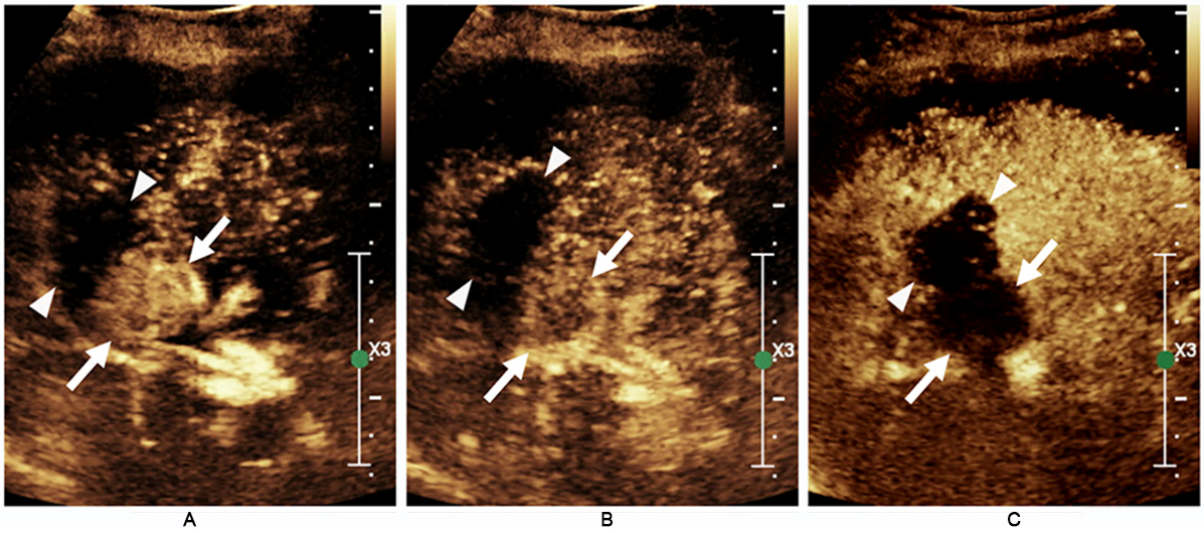

Figure 5. CEUS of post-ablation local recurrence of HCC in an 80-year-old man with NASH cirrhosis. CEUS shows a non-enhancing hepatic ablation zone (arrowheads in A, B, and C), with adjacent recurrent nodular tumor showing APHE (arrows in A) and washout which is late and mild (arrows in B). The patient underwent ablation of the local recurrence, and follow-up CEUS shows nonenhancement of the adjacent ablated area of recurrence (arrows in C).

during the procedure can confirm complete coverage of the intended lesion [Figure 6].

In patients who are to undergo liver resection for HCC, CT or MRI are typically preferred for evaluation, as these modalities are superior for surgical planning and assessment of vascular anatomy. Finally, CEUS is not suitable for staging in HCC patients, for which CT or MRI remain required.

FUTURE DIRECTIONS

Two future expansions of CEUS LI-RADS are expected in the next revision. Firstly, an algorithm of treatment response categories is expected to be incorporated into CEUS LI-RADS, as it already exists within CT/MRI LI-RADS. Secondly, the next revision is also expected to include the usage of the combined blood pool and Kupffer-cell agent perfluorobutane (Sonazoid, GE Healthcare, Oslo, Norway). This agent shows similar first-pass behavior to pure blood-pool agents, but beginning about 1 minute after administration, this agent begins being taken up by the reticuloendothelial cells of the liver, and thus produces a Kupffer phase, images of which are frequently obtained at 10 minutes following contrast administration[41,42]. Detection of Kupffer phase defects adds another tool in the evaluation of focal liver lesions, and studies with this agent have shown improvements in sensitivity and diagnostic performance of CEUS for HCC without loss of specificity[41,43,44]. Use of this agent has also been suggested for use in HCC surveillance, with one study showing no improvement in HCC detection rate, but a decrease in false referral rate (i.e., a decrease in surveilled patients being unnecessarily referred for further workup of a lesion with CT/MRI)[45]. Perfluorobutane is currently in use in many countries, but as of yet, is not approved for use in the United States by the FDA. CEUS with Perfluorobutane is included in the consensus clinical practice guidelines for management of HCC by the Japanese Society of Hepatology[46].

As stated above, in the United States, CEUS is not currently included in the OPTN criteria and so cannot be used to award MELD exception points for patients awaiting transplantation. Perhaps in the future, CEUS will be included, allowing for greater access to MELD exceptions for some patients. The importance of this is underscored, in fact, by the increasing prevalence of NASH cirrhosis and NAFLD-associated HCC in

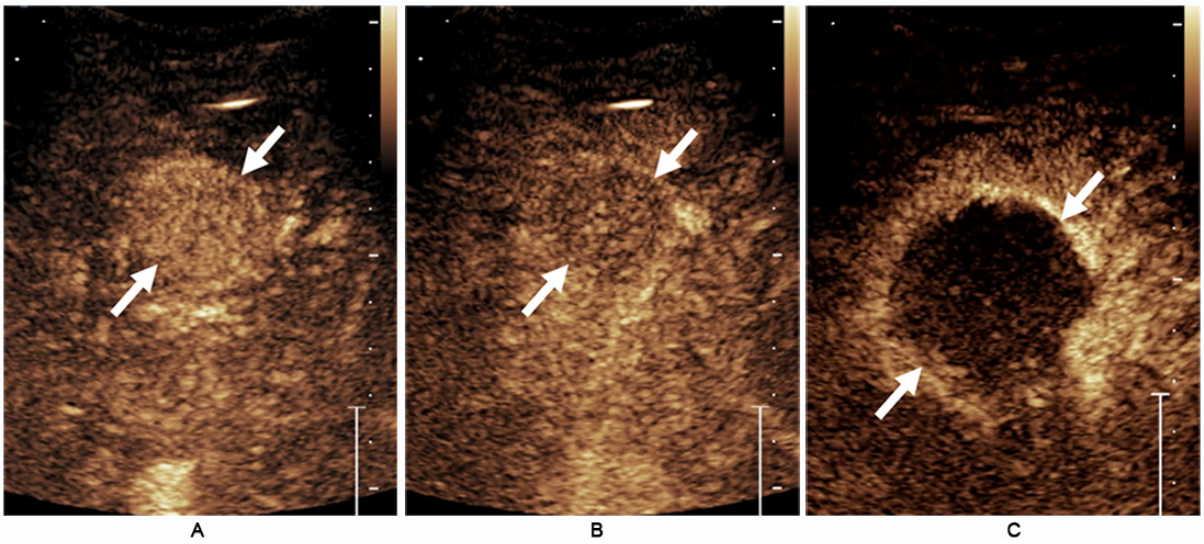

Figure 6. Intraprocedural CEUS to confirm adequacy of the ablation zone in a 64-year-old man with cirrhosis. Images acquired prior to ablation show a 3.5 cm LR-5 HCC in the right hepatic lobe with APHE (arrows in A) and washout which is late and mild (arrows in B). CEUS was performed intraprocedurally immediately post ablation, showing the nonenhancing ablation zone (arrows in C) and confirming complete coverage of the mass by the ablation.

general, as liver transplant waitlist times are projected to continue to increase[47].

SUMMARY

The disease spectrum NAFLD encompasses both NAFL and NASH, and may progress to cirrhosis. NAFLD is increasing in prevalence worldwide and is set to become a major cause of cirrhosis and HCC in the coming years. CEUS is a relatively newer technique compared to contrast-enhanced CT and MRI and is gaining acceptance and use in clinical practice. CEUS can be used for the definitive diagnosis of HCC using ACR CEUS LI-RADS, and evaluation for HCC in NAFLD patients entails certain special considerations. Among these nuances, perhaps the most important is that NAFLD-related HCC may occur without cirrhosis, a fact that requires greater awareness given that patients with noncirrhotic NAFLD are not included in the LIRADS population.

DECLARATIONS

Authors' contributions

Conceived the idea for the paper, wrote the paper, and created the figures: King KG
Edited the manuscript and provided additional thematic ideas: Depetris J
Edited the manuscript and provided additional thematic ideas: Patel MK
Edited the manuscript, provided additional thematic ideas, and provided figure ideas: Raman SS
Aided overall paper conception, edited the manuscript, and provided additional thematic ideas: Lu DS

Availability of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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