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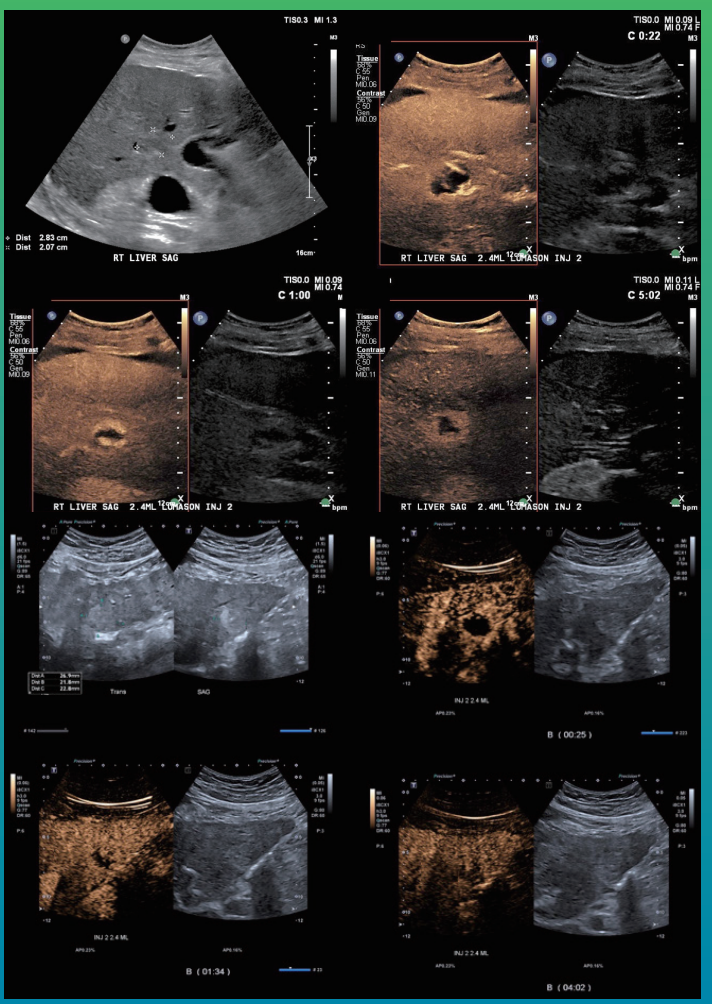

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Case Reports

REVIEW ARTICLE

Contrast-Enhanced Ultrasound LI-RADS: A Pictorial Review

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Abstract: The American College of Radiology has implemented the Liver Imaging Reporting and Data System (LI-RADS) to help detect, interpret, and guide the management of suspected lesions on surveillance imaging for hepatocellular carcinoma (HCC) in patients with cirrhosis. The classification of indeterminate nodules with a grading algorithm can be used for multiple imaging modalities (US, CT, and MRI) and incorporates multiple imaging features to appropriately classify observations with different likelihood of being HCC. Contrast-enhanced ultrasound (CEUS) LI-RADS has been fully implemented since 2017. The aim of this pictorial article is to provide a comprehensive review of CEUS LI-RADS utilization, discuss its advantages, and highlight areas for potential improvement.

Key words: Hepatocellular carcinoma; Liver imaging reporting and data system; LI-RADS; Contrast-enhanced ultrasound

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Hepatocellular carcinoma (HCC) was responsible for approximately 850,000 deaths worldwide in 2020 and is projected to cause an estimated 1.3 million deaths by 2040 [1]. Many people in East and Southeast Asia develop HCC due to Hepatitis B viral infection, while in the United States and Europe, hepatitis C and nonalcoholic steatohepatitis are the leading cause of HCC development [2,3]. HCC has a poor prognosis with a survival of 6-20 months if detected in its advanced stage [4]. However, with early detection and treatment, long-term survival can be accomplished [5]. Currently, the American College of Radiology [6] has implemented the Liver Imaging Reporting and Data System (LI-RADS) to help detect, interpret, and guide the management of suspected lesions on surveillance imaging for HCC in patients with cirrhosis. For the classification of indeterminate nodules, LI-RADS is a grading system that has multiple categories as follows: LI-RADS 1 (definitely benign), LI-RADS 2 (probably benign), LI-RADS 3 (intermediate probability of malignancy), LI-RADS 4 (probably HCC), and LI-RADS 5 (definitely HCC). Other categories in the LI-RADS algorithm are LI-RADS-TIV (tumor-in-vein), LI-RADS -M (definitely malignant, not specific for HCC), and LR-NC (non-categorizable). The algorithm can be used for multiple imaging modalities (US, CT, and MRI) and incorporates multiple imaging features to appropriately classify observations with different likelihood of being HCC. Contrast-enhanced ultrasound (CEUS) LI-RADS has been fully implemented as a part of LI-RADS since 2017 [7]. Specific risk stratification categories for HCC included. The aim of this pictorial essay is to provide a comprehensive review of CEUS LI-RADS utilization, discuss its advantages, and highlight areas for potential improvement.

Major Features in LI-RADS

Currently, there is a LI-RADS algorithm for ultrasound without contrast used to screen for suspicious nodules. This classification contains two scored components:

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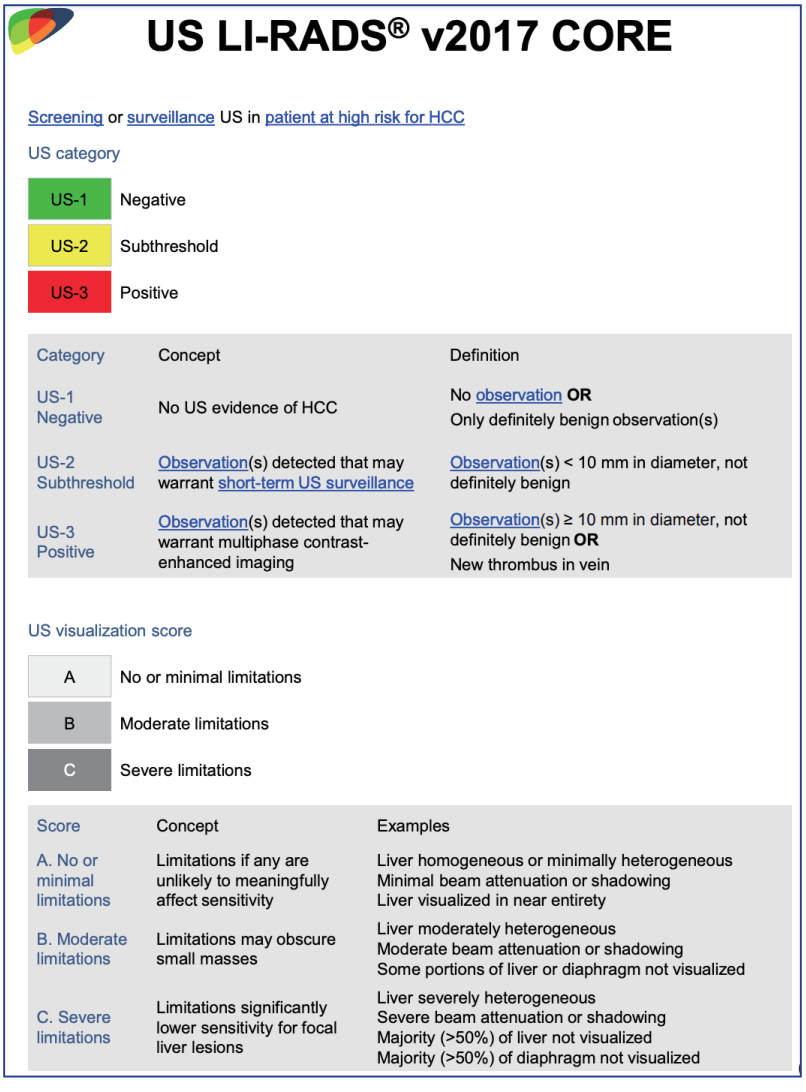
detection and visualization [8]. Detection scores contain US-1 Negative, US-2 Subthreshold, and US-3 Positive, which help guide management [9]. Anything US-3 warrants visualization with multiphase contrast-enhanced imaging. Visualization pertains to expected sensitivity and includes Visualization A: No or minimal, Visualization B: Moderate limitations, and Visualization C: Severe limitations [9]. This system is summarized in Table 1.

CEUS LI-RADS (Table 2), use the following imaging criteria to characterize observations including size, arterial phase enhancement, washout timing and degree. Ancillary features are additional findings that can improve confidence when assigning a LI-RADS category and can bring an observation up or down in the classification system. The LI-RADS classification can be used on multiple imaging modalities with and without contrast including US, CT, and MRI [10]. Each imaging modality has its benefits and indications of usage. This review paper will explore the usage of CEUS when evaluating observations with the LI-RADS classification.



US LI-RADS® v2017 CORE

Screening or surveillance US in patient at high risk for HCC

US category

US-1	Negative
US-2	Subthreshold
US-3	Positive

Category	Concept	Definition
US-1 Negative	No US evidence of HCC	No observation **OR** Only definitely benign observation(s)
US-2 Subthreshold	Observation(s) detected that may warrant short-term US surveillance	Observation(s) < 10 mm in diameter, not definitely benign
US-3 Positive	Observation(s) detected that may warrant multiphase contrast-enhanced imaging	Observation(s) ≥ 10 mm in diameter, not definitely benign **OR** New thrombus in vein

US visualization score

A	No or minimal limitations
B	Moderate limitations
C	Severe limitations

Score	Concept	Examples
A. No or minimal limitations	Limitations if any are unlikely to meaningfully affect sensitivity	Liver homogeneous or minimally heterogeneous Minimal beam attenuation or shadowing Liver visualized in near entirety
B. Moderate limitations	Limitations may obscure small masses	Liver moderately heterogeneous Moderate beam attenuation or shadowing Some portions of liver or diaphragm not visualized
C. Severe limitations	Limitations significantly lower sensitivity for focal liver lesions	Liver severely heterogeneous Severe beam attenuation or shadowing Majority (>50%) of liver not visualized Majority (>50%) of diaphragm not visualized

Table 1 Current US LI-RADS algorithm from the American College of Radiology [6].

Contrast-Enhanced Ultrasound Overview

Imaging acquisition

After ensuring that the plane for imaging and patient breathing are satisfactory, an injection of microbubbles contrast agent is made through the antecubital vein of either arm. Two commercial contrast agents are currently used for CEUS LI-RADS characterization in United States. These include, SonoVue (Bracoo Diagnostics, Italy) and Definity (Lantheus Medical Imaging, USA). SonoVue with an initial dosage of 1.5-2.4 mL; Definity with an initial dosage of 0.10 mL. Following

microbubble injection is a 5-10 L saline flush [11,12,13]. Typically, a single injection of contrast highlights a single nodule on the scan, but multiple injections can be used as additional evaluation, if needed. A timer begins once the flush has been injected, and continuous imaging begins until at least peak arterial phase enhancement is seen, but recording and imaging can be continued up to 60s after the flush to evaluate for early washout. Intermittent imaging occurs 30-60 sec after the first minute to evaluate unequivocal clearance of microbubbles from circulation [13,14]. This can potentially identify mild and late washout a major feature required for in LI-RADS 5 categorization.

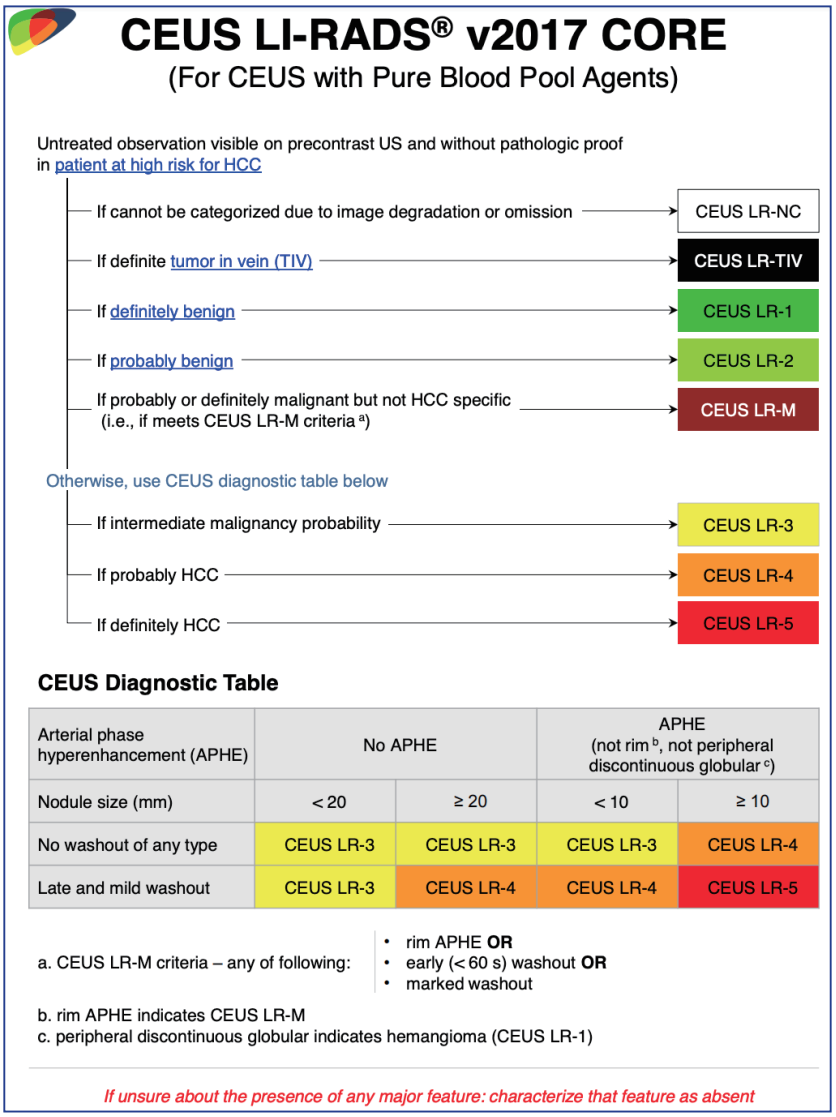


Table 2 Current CEUS LI-RADS algorithm used from the American College of Radiology [6].

CEUS LR-1 lesions

CEUS LR-1 (definitively benign) includes hemangiomas, cysts, and focal fat deposition. In a retrospective study, lesions identified as LR-1 were all found to be benign [15]. Hemangiomas are classically identified on CEUS by their discontinuous globular peripheral enhancement. Fast-filling hemangiomas can be optimally identified on CEUS due to their dynamic real-time imaging, and this pattern is not typically seen in either contrast-enhanced CT or MRI, as they appear as homogenous hyper-enhancing nodules in the arterial phase. Iso-enhanced, echogenic, and non-mass-like appearance on pre-contrast US with iso-vascularity on arterial and portal venous phases with no washout is characteristic of focal fat deposition, whereas focal fat sparing is described as a hypoechoic lesion on the arterial and venous enhancement with no washout. Simple cysts show up with no enhancement, and intrahepatic hematomas are included in LR-1. Management includes routine surveillance [6].

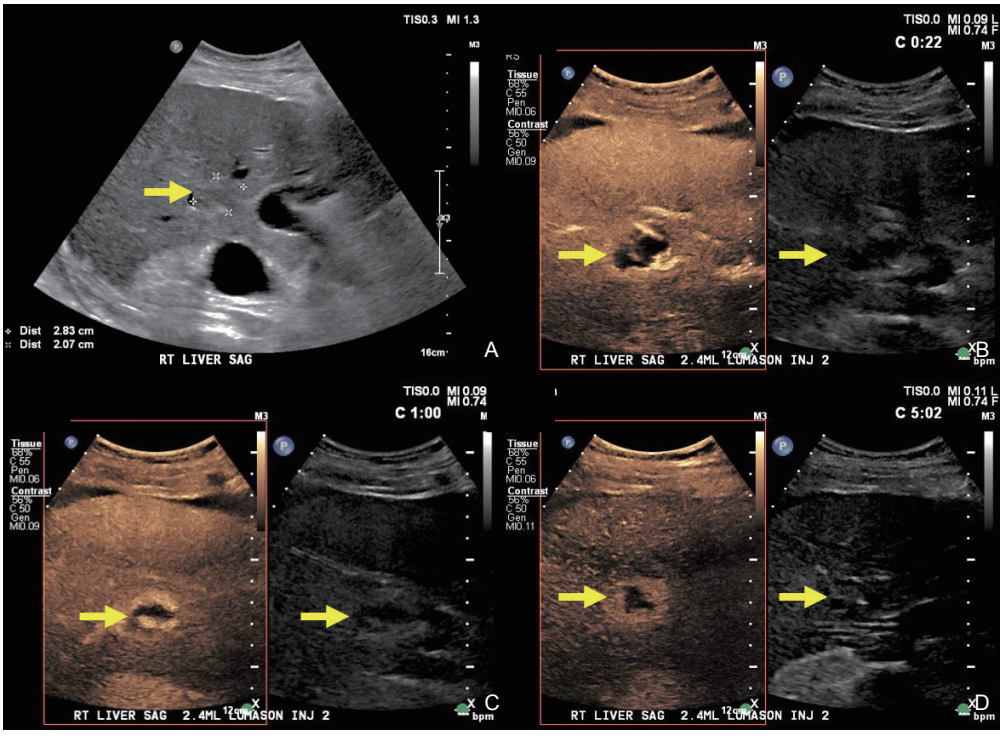


Figure 1 (A) Sagittal image of a hepatic segment 8 isoechoic solid observation measuring 28 mm; (B) At 22 seconds, the lesion demonstrates peripheral globular enhancement during the arterial phase; (C and D) At 1 minute and 5 minutes post injection show no washout with continued peripheral globular enhancement.

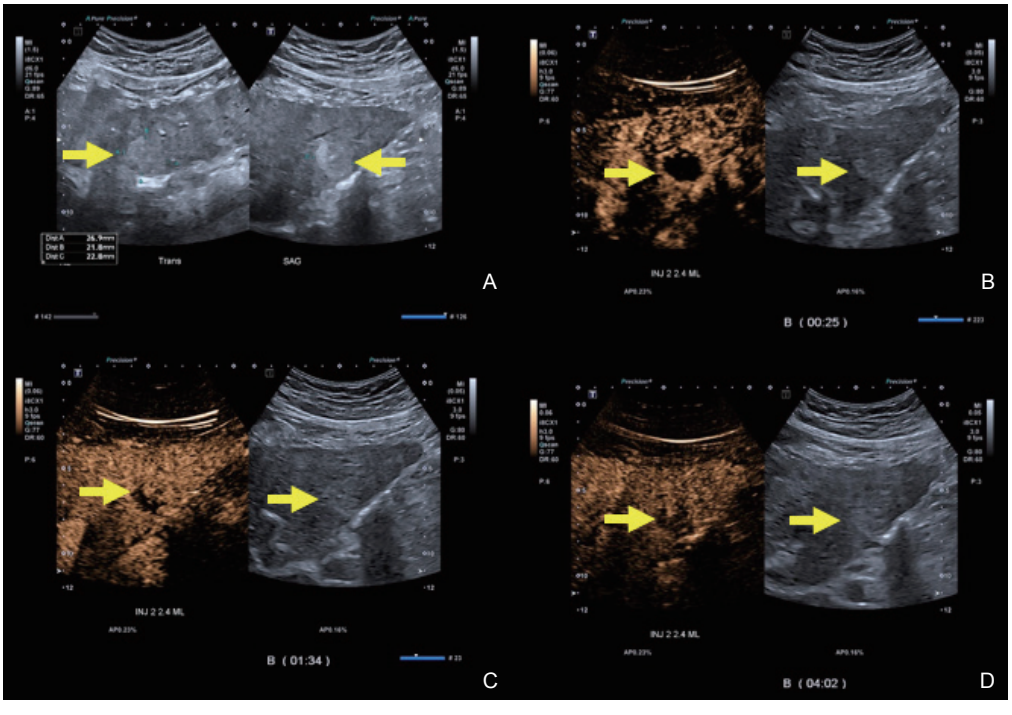


Figure 2 (A) Sagittal and transverse images of a hepatic segment 3 hyperechoic solid observation measuring 27 mm; (B) This image is at 25 seconds, demonstrating peripheral globular enhancement during the arterial phase with areas of non-enhancement; (C and D) Images obtained at 1- and 4-minutes post-injection showing iso-enhancement with no washout.

CEUS LR-2 lesions

CEUS LR-2 (probably benign) are nodules that are still not concerning for malignancy. In retrospective studies, lesions identified as LR-2 have been found to be malignant in up to 8% of cases [15]. Typical LIRADS 2 findings include hemangiomas without characteristic findings or LR-3 observations stable for over 2 years [13]. CEUS LR-2 requires the identification of an enhancing

nodule < 10 mm, atypical iso-enhancing nodule of any size, or atypical hepatic fat deposition/sparing. LR-3 nodules with interval size stability for at least 2 years are downgraded into this category [7]. This category often comprises typical regenerative nodules, and management includes regular surveillance.

CEUS LR-3 lesions

CEUS LR-3 (indeterminate probability of malignancy) includes a large group of observations of different sizes and is a more conservative classification for radiologists who do not want to rule out the possibility of malignancy. In retrospective studies, these have been found to be malignant in 49.5% of cases [16]. LR-3 includes nodules 10 mm with iso-enhancement in all phases, nodules < 20 mm with no arterial phase enhancement but showing late washout and mild degree of washout, and nodules < 10 mm that do show arterial phase enhancement but no washout. Management includes repeat imaging in 3-6 months or alternative imaging in 3-6 months. These nodules may require biopsy and a multidisciplinary discussion of the patient and their findings [17].

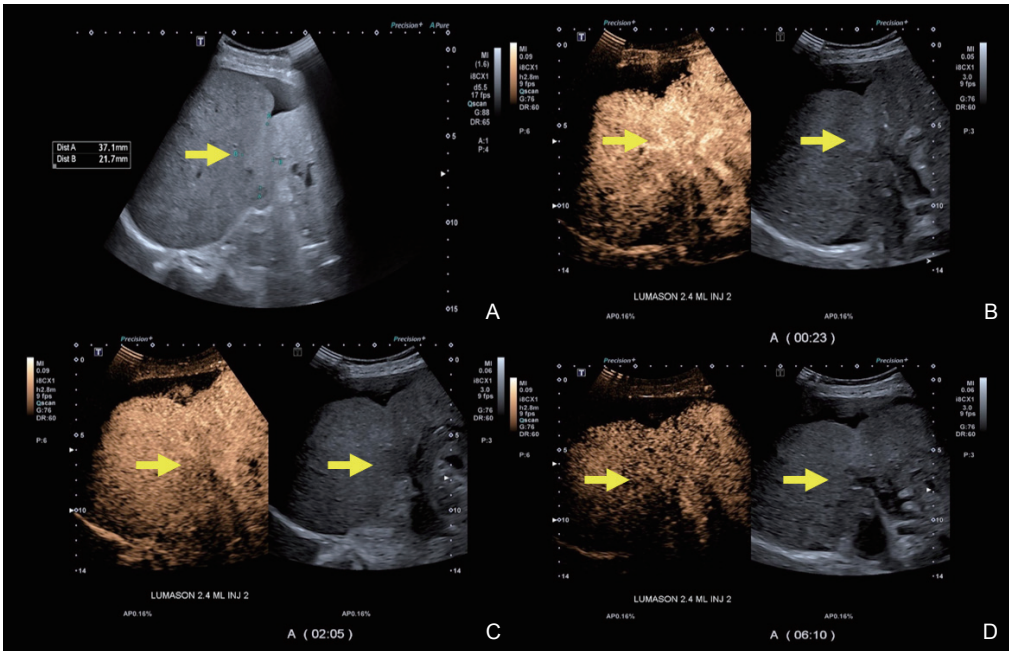


Figure 3 (A) Sagittal image of a hepatic segment 6 solid isoechoic observation measuring 37 mm; (B) This image is at 23 seconds, demonstrating global iso-enhancement during arterial phase; (C and D) Images obtained at 2- and 6-minutes post-injection show an iso-enhanced observation with no washout.

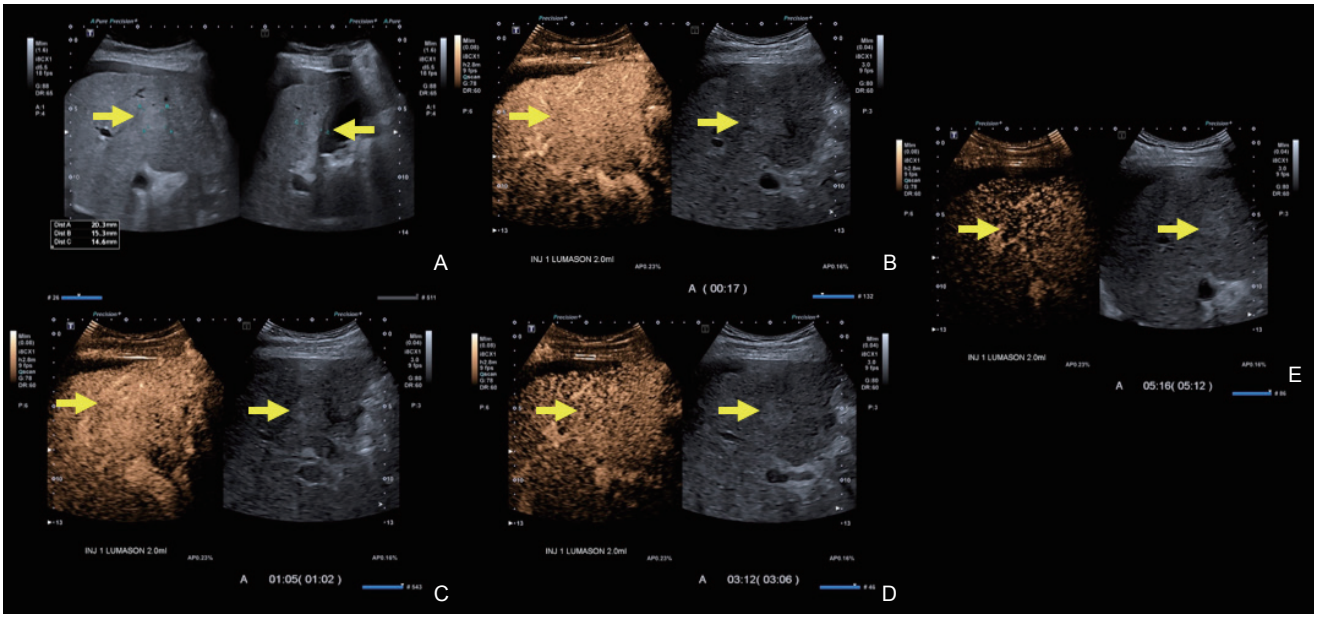


Figure 4 (A) Sagittal and transverse images of a hepatic segment 5 hyperechoic solid observation measuring 20 mm; (B) This image is at 17 seconds, demonstrating global iso-enhancement during the arterial phase; (C-E) Images obtained at 1-, 3-, and 5-minutes post-injection show iso-enhancement with no washout.

CEUS LR-4 lesions

CEUS LR-4 (probably HCC) are nodules that are highly suspicious for HCC but lack the specific requirements for diagnosing HCC. In retrospective studies, these have been found to be malignant in 88% of cases [16]. Requirements include nodules with arterial phase enhancement but no washout measuring 10 mm, nodules with arterial phase enhancement and late washout and mild degree washout measuring < 10 mm, and nodules measuring 20 mm with no arterial phase enhancement and late-onset washout with a mild degree of washout. The LR-4 category highlights the relevance of APHE on CEUS, which is associated with nodules of HCC, unlike on CT or MRI, where APHE can detect Arterioportal shunts (APS). CEUS does not show abnormalities in the presence of a known APS [17]. Management for these very likely HCC nodules includes biopsy, treatment, or short-interval follow-up.

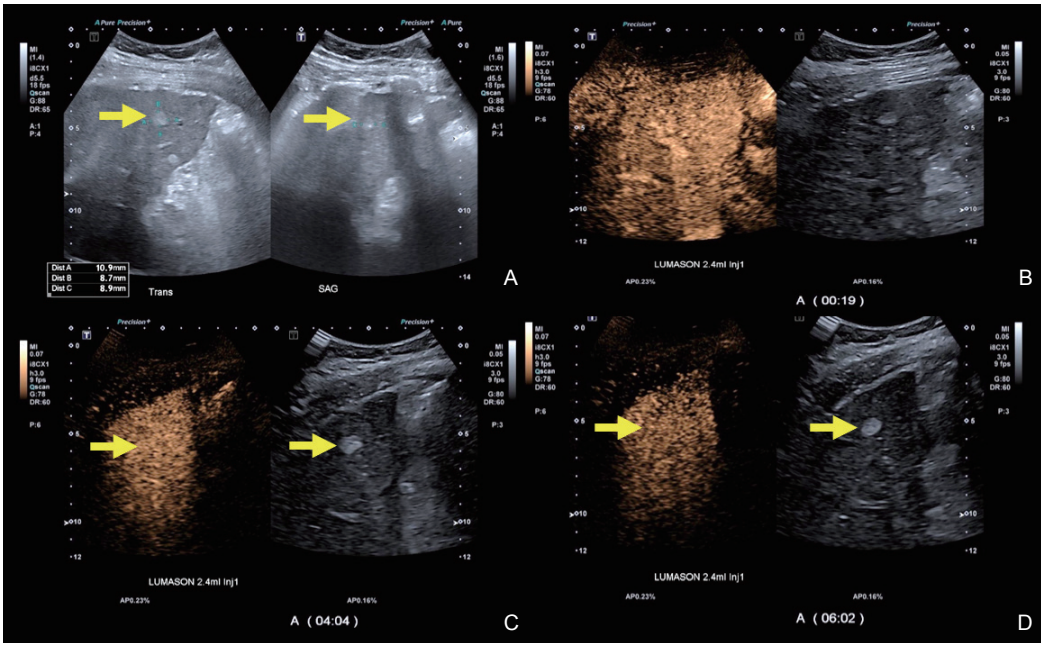


Figure 5 (A) Sagittal and transverse images of a hepatic segment 8 solid hyperechoic observation measuring 11 mm; (B) This image is taken at 19 seconds, demonstrating global hypo-enhancement during arterial phase; (C and D) Images obtained at 4- and 6-minutes post-injection show no washout.

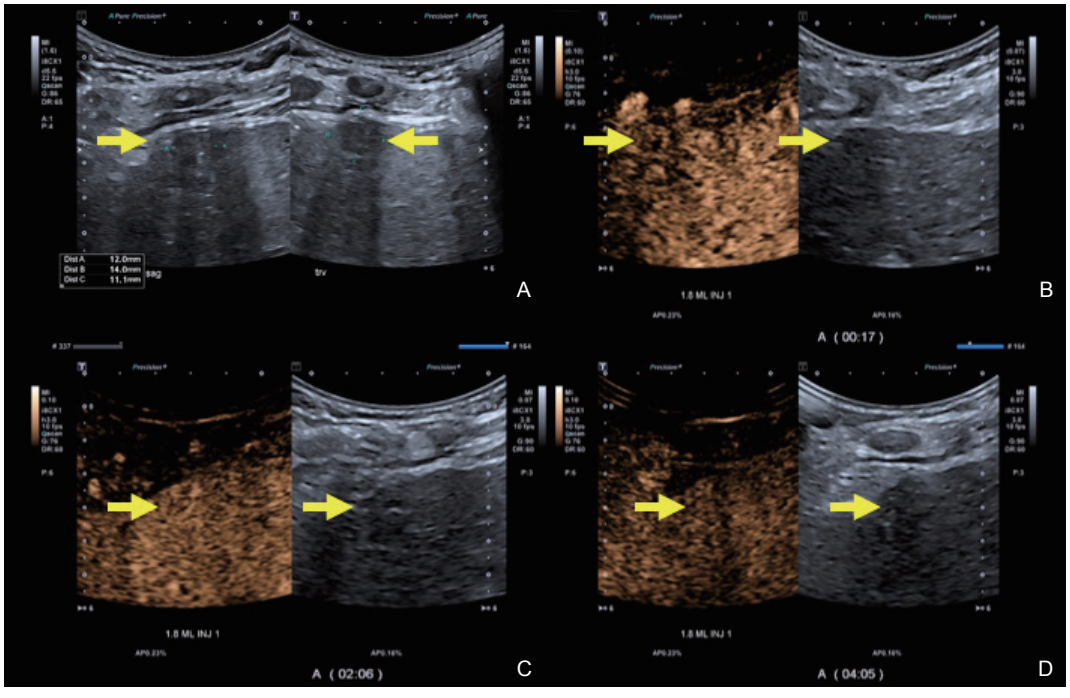


Figure 6 (A) Sagittal and transverse images of a hepatic segment 4 hypoechoic solid observation measuring 14 mm; (B) Image at 17 seconds, demonstrating global iso-enhancement during the arterial phase; (C and D) Images at 2- and 4-minutes post-injection show iso-enhancement with no washout.

CEUS LR-5 lesions

CEUS LR-5 (definitely HCC) are nodules that do not require biopsy, as they are nearly definite for HCC. This category is designed to have a high positive predictive value and specificity when diagnosing HCC to minimize the amount of false positive diagnoses of HCC. According to a multicenter retrospective study of 1006 lesions, 519 lesions were classified as LR-5, and 98.5% of those lesions were malignant [16]. At most institutions, LR-5 interpretation is sufficient evidence to proceed directly with resection of locoregional therapy. The criteria for LR-5 are a nodule measuring 10 mm and arterial phase enhancement with late-onset washout and mild degree washout. Management includes systemic therapy, locoregional therapy, surgical resection, or transplantation.

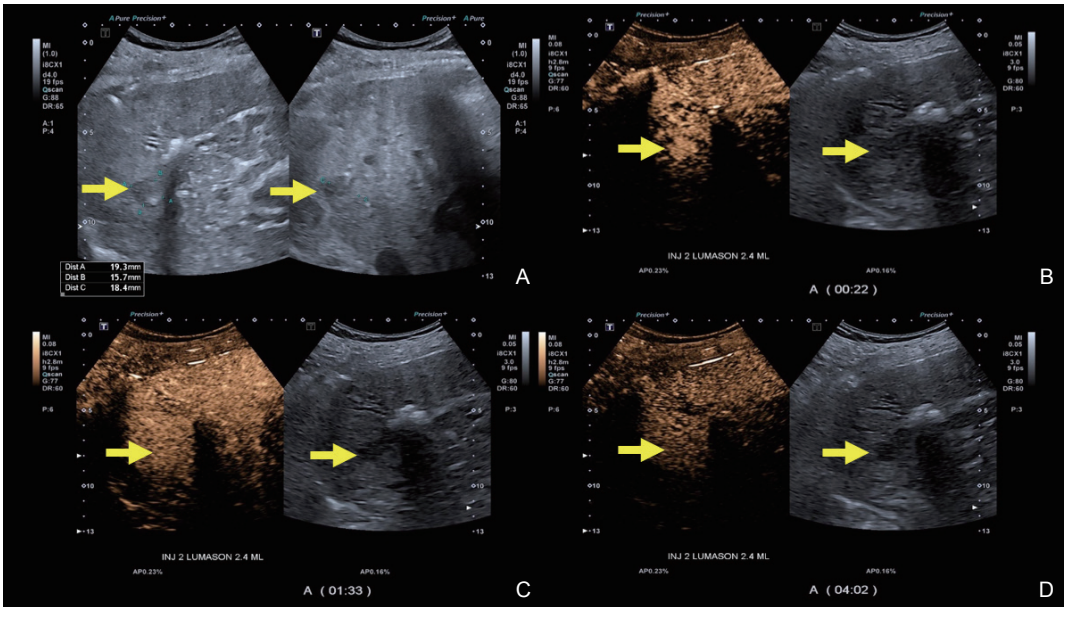


Figure 7 (A) Sagittal and transverse images of a hepatic segment 6 solid hyperechoic observation measuring 19 mm; (B) At 22 seconds the lesion demonstrates global hyper-enhancement during the arterial phase; (C and D) Images obtained at 1- and 4-minutes post-injection show an iso-enhanced observation with no washout.

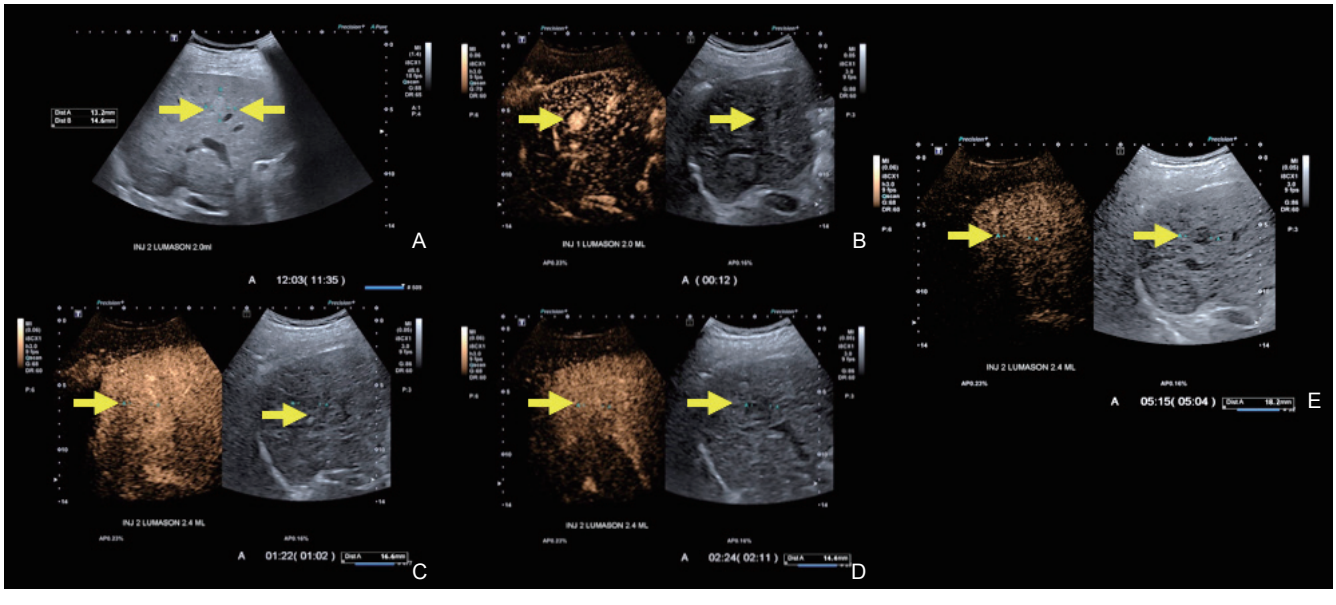


Figure 8 (A) Sagittal and transverse images of a hepatic segment 6 with mixed echogenicity solid observation measuring 18 mm; (B) At 12 seconds the lesion demonstrates global hyper-enhancement during the arterial phase; (C-E) Images obtained at 1-, 2-, and 5-minutes post-injection show iso-enhancement with no washout.

CEUS LR-TIV lesions

CEUS LR-TIV (tumor in vein) can be identified with real-time arterial enhancement in CEUS and can be differentiated from a thrombus. Retrospective studies have shown that with lesions categorized as LR-TIV, the malignancy rate was 92%, with 79% of them being HCC [18]. This classification is applied when there is an apparent soft tissue found within a vein. It is not necessary to identify an associated parenchymal mass to make the diagnosis of LR-TIV. If there is a tumor in the vein that is neighboring an LR-5 tumor, the tumor in the vein is definitely due to HCC. However, if there is no contiguous LR-5 lesion, the tumor in the vein can be interpreted as "probably due to HCC," "may be due to non-HCC malignancy," or "etiology uncertain" [19]. Patients with this category receive alternative imaging, biopsy, or treatment.

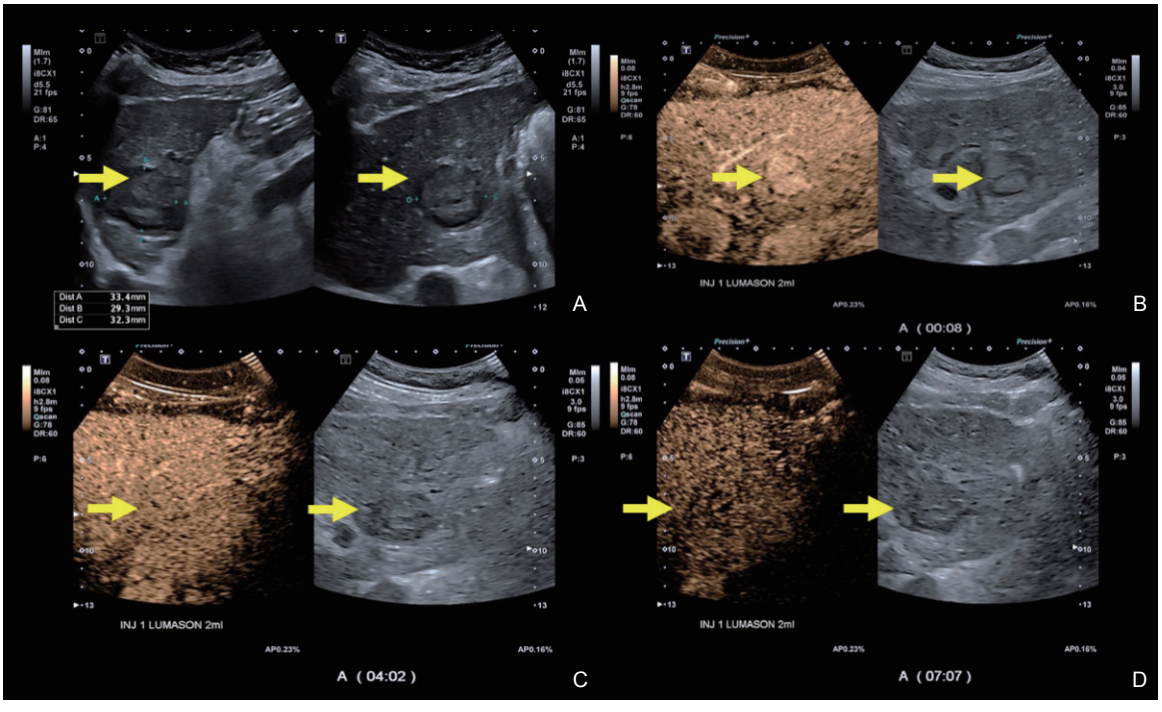


Figure 9 (A) Sagittal and transverse images of a hepatic segment 2 solid isoechoic with circumscribed margins measuring 33 mm; (B) At 8 seconds the lesion demonstrates global hyper-enhancement during the arterial phase; (C and D) Images obtained at 4- and 7-minutes post-injection show mild weak washout.

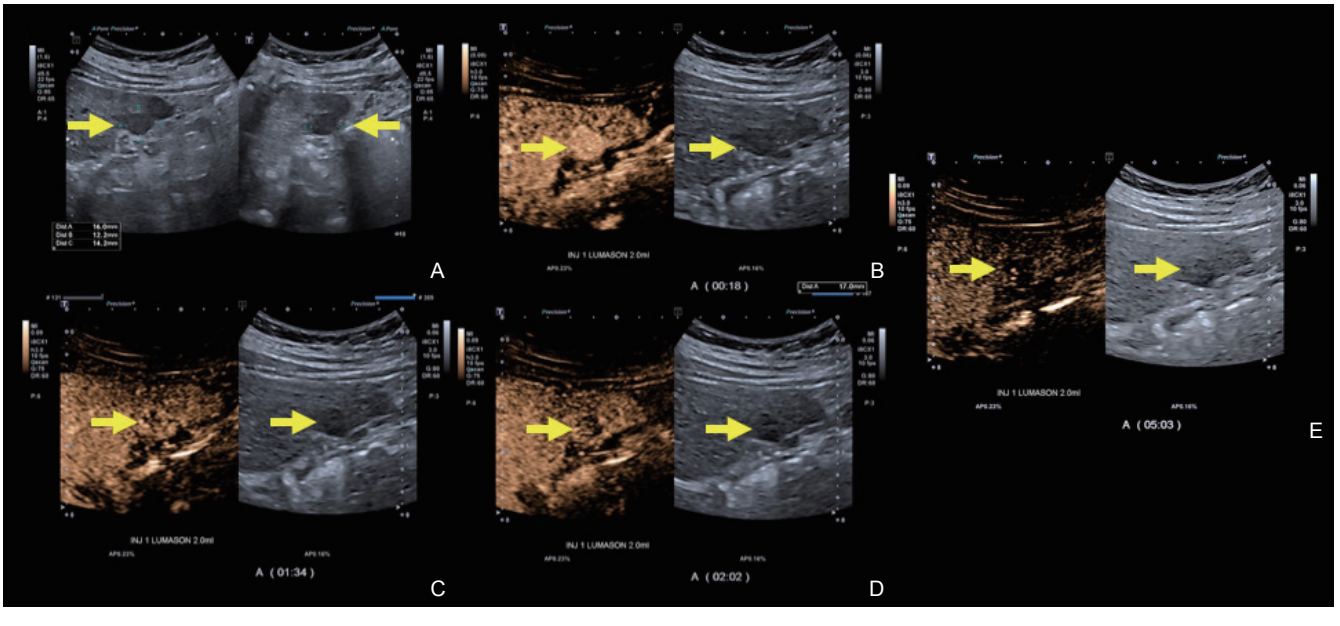


Figure 10 (A) Sagittal and transverse images of a hepatic segment 5 hypoechoic solid observation measuring 16 mm; (B) At 18 seconds the lesion demonstrates global hyper-enhancement during the arterial phase; (C-E) Images obtained at 1-, 2-, and 5-minutes post-injection show mild washout.

CEUS LR-M lesions

CEUS LR-M (malignant) is a nodule that is malignant but may not be HCC. In retrospective studies, lesions in LR-M were identified as 48% HCC, 38% intrahepatic cholangiocarcinoma (ICC), and 14% HCC-ICC or of other cellular origin [20]. There is no size threshold for LR-M. Criteria that place nodules in this category are early washout relative to the liver within 60 seconds of contrast injection, marked washout resulting in a "punched-out" appearance within 2 minutes after contrast injection, and arterial phase rim enhancement followed by washout (regardless of onset or degree). Management depends on the kind of cancer the nodule is and where it has metastasized from. Biopsy is typically used to identify the type of cancer, which will then guide treatment [7].

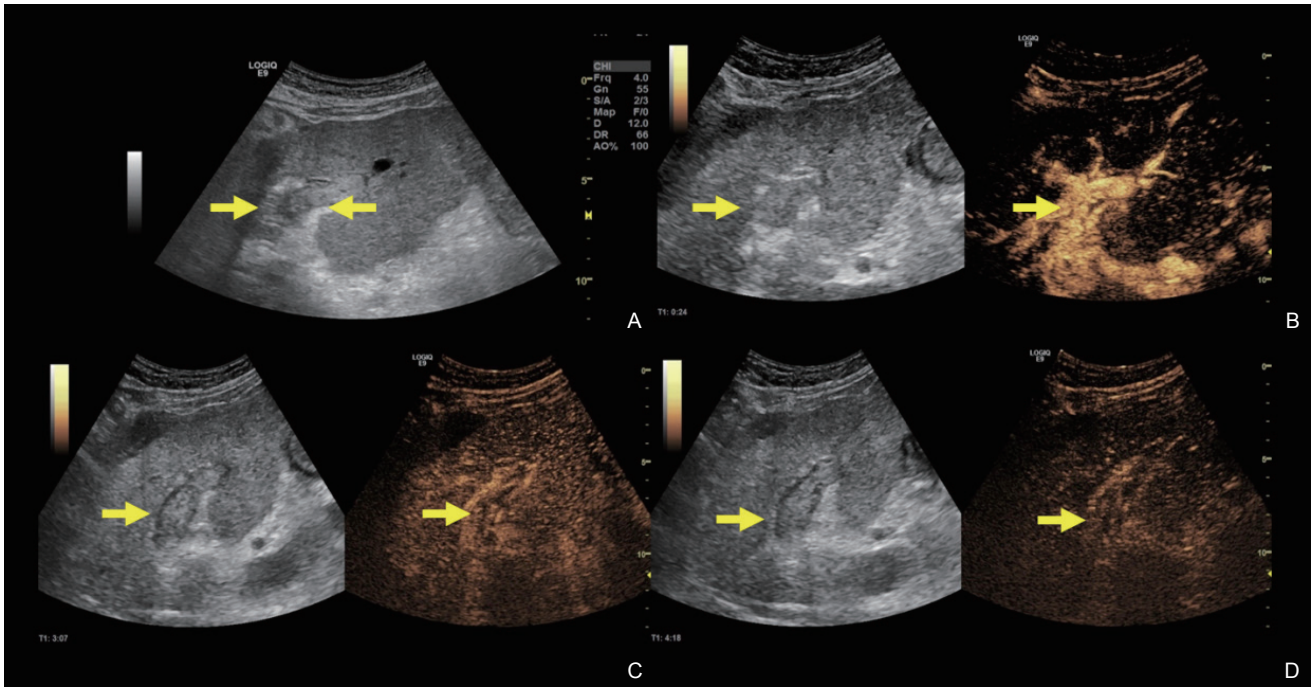


Figure 11 (A) Transverse image of a hepatic segment 4 solid isoechoic with irregular margins; (B) This image is at 24 seconds, demonstrating global hyper-enhancement during the arterial phase; (C and D) Images obtained at 3- and 4-minutes post-injection, showing mild washout.

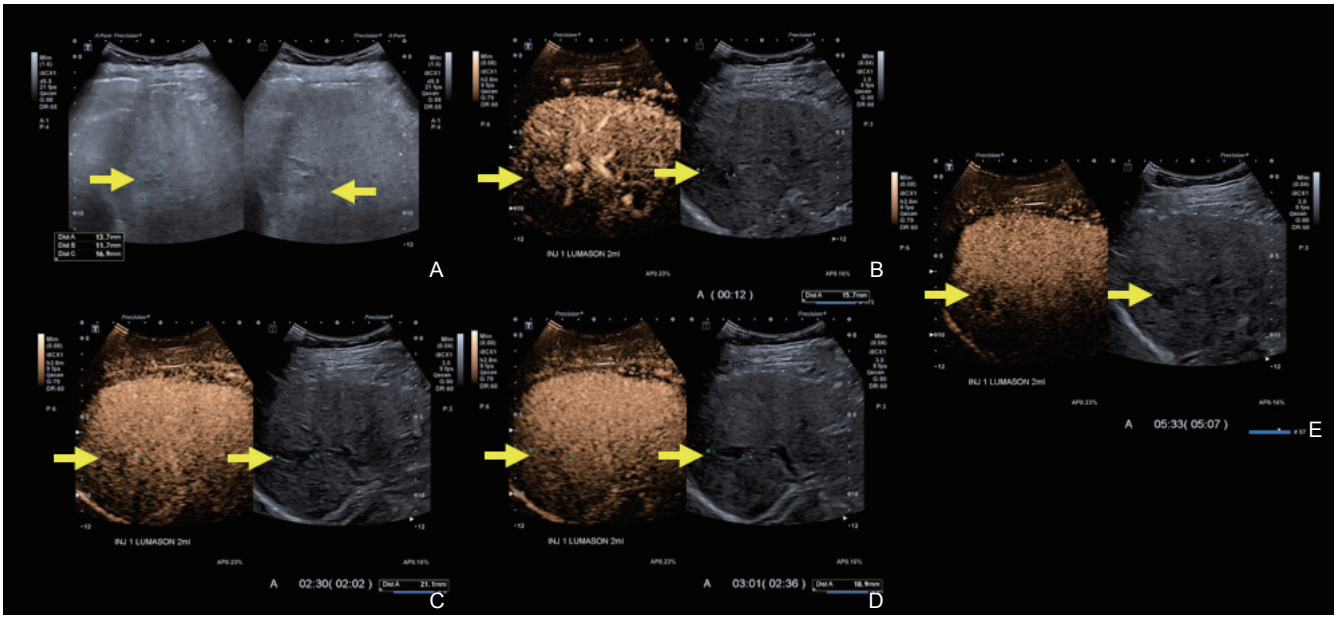


Figure 12 (A) Sagittal and transverse images of a hepatic segment 8 infiltrative hypoechoic solid observation measuring 17 mm; (B) This image is at 12 seconds, demonstrating global hyper-enhancement during the arterial phase; (C-E) Images obtained at 2-, 3-, and 5-minutes post-injection, demonstrating mild washout.

CEUS LR-NC lesions

CEUS LR-NC (non-categorizable) is a category given when images are insufficient for assessment. This can be due to imaging protocol not being followed, equipment failures, patient movement, or artifacts obscuring proper visualization. This can lead to a lack of detection of diagnostic features needed to assign an appropriate category. Management is repeat imaging with the same or alternate modality in 3 months or less [7].

CEUS Advantages

CEUS has benefits compared to its imaging counterparts. It uses dynamic real-time imaging, while CT and MRI are visualized after the contrast has been injected. Based on the LI-RADS algorithm, it is very important to visualize the contrast in the right timing (arterial vs. early washout vs. late washout) [20,21]. This advantage allows CEUS to depict early and late contrast arterial phase enhancement, whereas CT and MRI may

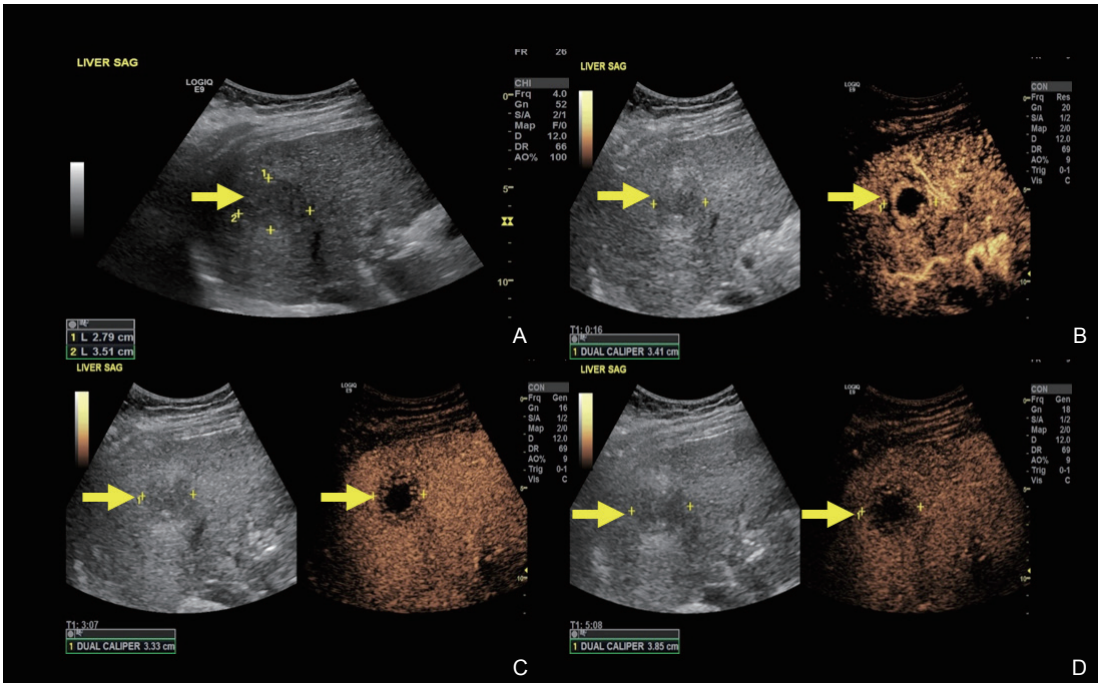


Figure 13 (A) Sagittal image of a hepatic segment 7 solid hypoechoic observation measuring 35 mm; (B) At 16 seconds the lesion demonstrates rim enhancement during the arterial phase; (C and D) Images obtained at 3- and 5-minutes post-injection, showing mild washout.

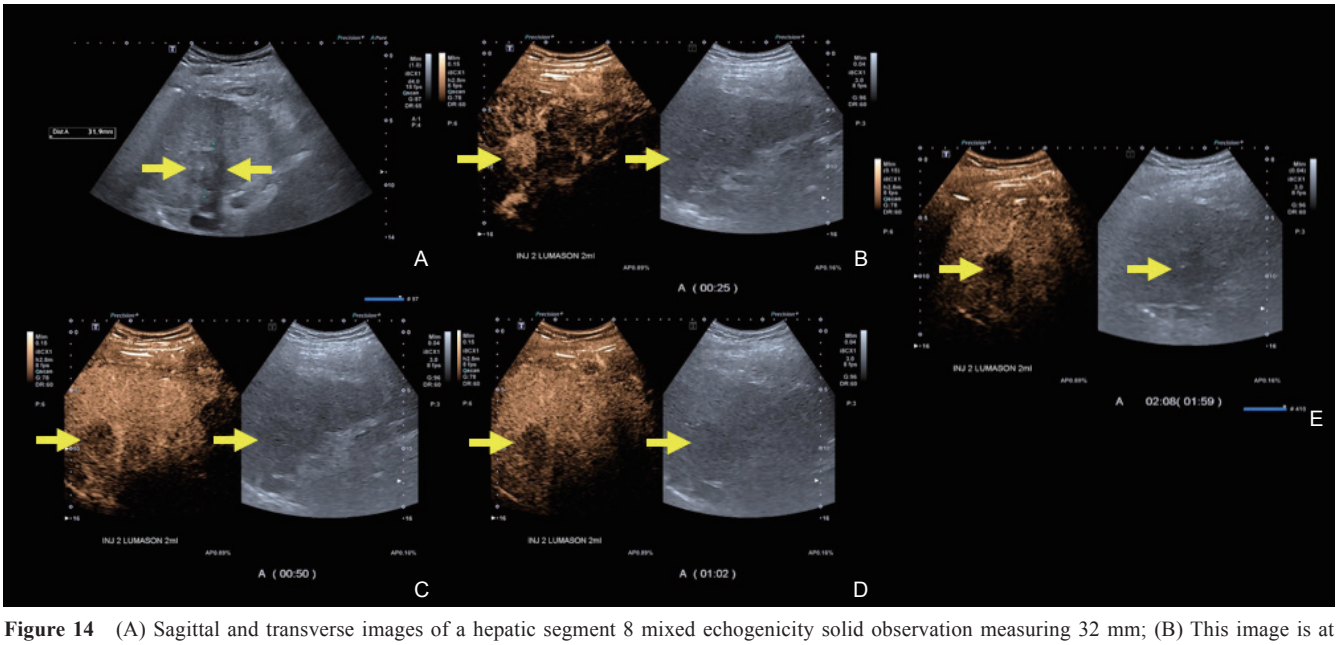


Figure 14 (A) Sagittal and transverse images of a hepatic segment 8 mixed echogenicity solid observation measuring 32 mm; (B) This image is at 25 seconds. The image demonstrates global hyper-enhancement during arterial phase; (C) This image is at 50 seconds post-injection, showing marked washout; (D and E) Images obtained at 1- and 2-minutes post-injection continuously demonstrating marked washout.

miss this important category for LI-RADS grading if the timing is not accurate.

The ability to see arterial phase enhancement changes in real time allows CEUS to identify typical features of benign cysts and hemangiomas, which rapidly fill and wash out [13]. Microbubbles serve as pooling agents when injected into blood, allowing rapid changes to be effectively visualized in CEUS. This is something that static imaging, such as CT and MRI, is not able to take advantage of and can lead to the misclassification of some benign observations [21]. CEUS has other practical uses in the interventional setting including improving the visibility of lesions to biopsy, differentiating tumors in the vein from a thrombus, and monitoring ablation therapy [22].

Limitations

CEUS has many potential benefits in identifying HCC. However, there are limitations to this tool. CEUS may not improve the ability to identify nodules, as this depends on the sonographer's and observer's ability to locate the nodule, making this tool more prone to false negatives if the nodule cannot be located [9]. Operator preparation that focuses on technical training and interpretation can overcome this limitation.

Ultrasound also has a limited ability to identify lesions in patients with a large body habitus and fatty tissue because of sound beam attenuation from the extra tissue. CEUS also has some difficulty identifying nodules less than 10 mm in size, nodules with coarse heterogeneous cirrhotic liver, and poorly cooperating patients [7].

The LI-RADS classification itself has a problem with many nodules being placed in LR-3 (indeterminate probability) [7,22]. This uncertain category in LI-RADS reduces the diagnostic probability of the system itself. Some have proposed doing away with LR-3 and reorganizing criteria in LR-4, 3, and 2 to improve diagnostic certainty within the system [23]. Variance in ultrasound equipment is another limitation to CEUS, as the ability to detect microbubbles, screen brightness, machine resolution, signal persistence, and power can vary from machine to machine. Work to standardize CEUS imaging parameters are ongoing and may overcome this variability via off-line analysis [23].

Conclusion

CEUS is a useful tool in LI-RADS that uses real-time imaging to look at important characteristics such as arterial enhancement and washout timing to characterize indeterminate liver nodules in the presence of cirrhosis. This relatively new tool does have limitations that should be considered, such as observer/technician proficiency and experience, equipment used, and many LI-RADS-3 observations made among radiologists. Addressing these problems through standardization of training, ultrasound equipment, and reorganizing the LI-RADS system can make the identification of malignant nodules on images more accurate and efficient, leading to earlier management and, most importantly, improved patient outcomes.

Acknowledgments

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Conflict of Interest

Corinne E. Wessner has worked as a Bracco Diagnostics and SonSim consultant and was on the Speaking Bureau for Canon Medical Systems USA. John R. Eisenbrey has worked as a consultant for SonoSim. He is a Scientific Advisory Board member and received research grant support for Lantheus Medical Imaging as well as royalties from Elsevier and equipment and grant support from Siemens and GE Healthcare. Ji-Bin Liu received research and equipment support from GE Healthcare and Canon Medical. Andrej Lyshchik is an advisory board member and consultant for GE Healthcare and Bracco Diagnostics. He also receives research support from both entities as well as royalties from Elsevier. Both Osama Mahmoud and Ajay Makkena have no conflict of interest to declare.

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