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CEUS LI-RADS: algorithm, implementation, and key differences from CT/MRI

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Abstract

Contrast-enhanced ultrasound (CEUS) is a specialized form of ultrasound (US) performed with an intravenous injection of microbubble contrast agents. It has been successfully used for a variety of applications including characterization of liver tumors. In April 2014, the American College of Radiology (ACR) convened a working group of international experts to develop ACR CEUS Liver Imaging Reporting and Data System (CEUS LI-RADS). An initial version of CEUS LI-RADS was published in August 2016. Although the CEUS LI-RADS concept and principles for liver lesion characterization, using dynamic contrast enhancement features, are similar to those for CT or MRI, there are significant differences between CT/MRI and CEUS LI-RADS. Therefore, CEUS LI-RADS has different diagnostic features and a unique characterization algorithm. The size of a lesion, the type and degree of arterial phase enhancement, the presence of washout, and the timing and degree of washout are the major features used for categorization. This paper describes key differences between CT/MRI and CEUS, and provides a diagnostic algorithm of CEUS LI-RADS with detailed, step-by-step instructions and imaging examples of CEUS LI-RADS categories.

Key words: CEUS—HCC—Diagnosis—LI-RADS

Abbreviations

CEUS	Contrast-enhanced ultrasound
HCC	Hepatocellular carcinoma
LI-RADS	Liver Imaging Reporting and Data System
ICC	Intrahepatic cholangiocarcinoma
ACR	American College of Radiology
AASLD	American Association for the Study of Liver Disease
APHE	Arterial phase hyperenhancement
APS	Arterioportal shunts
TIV	Tumor in vein
MDD	Multi-Disciplinary Discussion

Contrast-enhanced ultrasound (CEUS) is a specialized form of ultrasound (US) performed with an intravenous injection of microbubble contrast agents. It is now a widely accepted imaging technique for many applications

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including characterization of liver tumors. With recent FDA approval of the microbubble contrast agent Lumason (SonoVue outside of USA, Bracco Diagnostics Inc. Monroe Township, NJ) for liver lesion characterization, CEUS Liver Imaging Reporting and Data System (LI-RADS) was added to the American College of Radiology (ACR) LI-RADS in 2016. Although the CEUS LI-RADS concept and principles for liver lesion characterization, using dynamic contrast enhancement features, are similar to those for CT or MRI, there are significant differences between CT or MRI and CEUS LI-RADS. Therefore, CEUS LI-RADS has different diagnostic features and a unique characterization algorithm.

Contrast agents for US are biodegradable microbubbles, measuring 3–5 μm in diameter. These microbubbles resonate under low-power US waves and generate harmonic signals. A contrast-specific US imaging mode is available on the majority of US scanners and utilizes this unique property of microbubbles, by highlighting signals from microbubbles while applying specific pulse sequences that suppress signals from tissues. Similar to CT and MRI, CEUS permits demonstration of a lesion and surrounding liver blood flow, including arterial phase hyperenhancement (APHE) and washout. Many studies, including several recent meta-analyses, have shown that CEUS has similar diagnostic performance to contrast-enhanced CT and MRI in focal liver lesion characterization [1–8].

The American Association for the Study of Liver Disease (AASLD) practice guidelines for HCC management initially included CEUS along with CT and MRI in an HCC diagnostic algorithm in 2005, but removed CEUS in a 2010 update due to the possibility of misdiagnosing intrahepatic cholangiocarcinoma (ICC) as HCC, an action based on one retrospective study [9]. Since then, there have been multiple studies investigating the accuracy of CEUS for focal liver lesion characterization. These studies have shown that ICCs often show arterial phase rim enhancement, unusual for HCC, and washout which tends to be much earlier than that of HCC, and of marked degree [10, 11].

In April 2014, the ACR convened a working group of international experts to develop ACR CEUS LI-RADS including radiologists and hepatologists from the United States, Canada, and Europe. Beta versions of the CEUS LI-RADS algorithm were presented at numerous national and international conferences in 2015 and 2016 [12–14]. Based on feedback from those presentations and through iterative refinement and consensus, the working group completed CEUS LI-RADS version 2016 on May 21, 2016. The algorithm was officially approved by the ACR LI-RADS Steering Committee on June 24, 2016. The system was published online in August 2016.

Key differences of CEUS from CT and MRI

The method of image acquisition

Acquisition of images for CEUS utilizes dynamic real-time imaging performed at the frame rates of about 10/s, thus providing the highest temporal resolution available today in abdominal imaging. This compares with more static imaging protocols for CT and MRI which are performed according to a predetermined timing regime or related to timing from an aortic contrast bolus. Therefore, CEUS may detect both early and late APHE that might be missed on CT or MRI due to mistiming of the arterial phase. Additionally, a strength of CEUS is its ability to show the rapidly changing arterial phase enhancement patterns which typify many benign tumors and especially flash-filling hemangiomas. Despite the rapidity of its occurrence, CEUS will typically show discontinuous peripheral puddles of enhancement and centripetal filling of the lesion. CT and MRI, by comparison, may often fail to reveal these rapidly changing features, showing only an enhanced mass in the arterial phase without the typical diagnostic enhancing pattern.

Contrast agent properties

Differences in contrast agent properties lead to different enhancement patterns on CEUS as compared with CT and MRI especially in non-hepatocellular malignancies, such as ICC, with permeable vascular endothelium and fibrous stroma. This results in persistent or increasing enhancement of ICCs in the portal venous and late phases on CT and MRI as the contrast agent passes the permeable endothelium into the tumor interstitial space with accumulation in the stroma. Purely intravascular microbubble contrast agents for CEUS show instead rapid onset and a marked degree of washout of ICCs, occurring very early and often within the time frame defined as the arterial phase. This discordance is an additional important indicator in ICC diagnosis. Increasing enhancement of ICC on CT or MRI may infrequently be associated with misdiagnosis as a benign tumor, while enhancement features on CEUS have a typical appearance for a malignant tumor; thus, combining the observations from these modalities may be beneficial [15].

Terminology: observation or nodule

On CT and MRI, there are many findings that may not represent true nodules, such as perfusion alterations; therefore, the terminology ‘‘observations’’ is used to describe focal signal abnormalities throughout their LI-RADS algorithm. On CEUS, most of the observations are true nodules, and the only exceptions are focal fatty

infiltration and sparing which would be categorized as CEUS LR-1 when findings are definite. Otherwise, the CEUS LI-RADS algorithm is used to categorize true liver nodules visible on pre-contrast ultrasound examination on patients at risk for HCC. It is recognized that nodules identified on the B-mode scan are a prerequisite for CEUS LI-RADS categorization at this time.

CEUS technique

Following careful determination of the optimal scanning plane, transducer location, and patient position and breathing, CEUS is performed with an intravenous injection of a microbubble contrast agent, ideally through an angiocath, preferably 20 gauge, placed in an antecubital vein of the left arm. There are two commercially available ultrasound contrast agents suitable for CEUS LI-RADS characterization of focal liver observations: Definity (Lantheus Medical Imaging, Billerica, MA) and recently FDA-approved Lumason (Bracco Diagnostics Inc., Monroe Township, NJ). The dose is 0.2 ml for Definity and 1.5–2.4 ml for Lumason, injected as a bolus followed by a 5–10 ml saline flush. These are guidelines and there are equipment-, transducer-, and patient-specific demands which may alter these choices.

A single injection generally focuses on a single nodule with maintenance of the transducer in a fixed location throughout at least the arterial phase and often the entire scan. Scanning the identified nodule in the plane of respiratory movement optimizes visualization by reducing out-of-plane motion from respiration. Frequently, multiple injections can be performed with Definity and up to 2 injections may be performed from a single vial of Lumason. Repeat injections may focus on the original nodule or other nodules as required. In the portal venous/late phase of enhancement, continuous sweeps to encompass the entire liver are invaluable to look for any regions of washout which may indicate additional pathology.

The timer is started at the beginning of the saline flush to coincide with the actual injection of the contrast agent.

As a minimum requirement, continuous imaging should be performed from the beginning of contrast flush through peak AP enhancement with image recording performed from the first bubble arrival through peak AP enhancement. Optionally, imaging and recording can be continued beyond the AP peak enhancement until 60 s after contrast flush, to fully evaluate APHE and document early washout, which occurs before 1 min.

After 1 min, intermittent imaging at 30–60 s intervals should be performed until there is unequivocal clearance of microbubbles from the circulation at about 4–6 min after contrast injection to detect mild and late washout, a major feature for LR-5 categorization. Intermittent imaging is important to minimize microbubble destruction and to have adequate late-phase enhancement. A still image should be acquired at 1 minute and at regular intervals following.

Major features of CEUS LI-RADS

Arterial phase hyperenhancement (APHE)

Arterial phase hyperenhancement (APHE) refers to arterial phase enhancement that is unequivocally greater than the background liver and does not show rim-like or peripheral discontinuous globular morphology. This feature can be considered present if it is demonstrated in either the entire nodule or in only a portion of the nodule (Fig. 1). Regardless of the extent of enhancement, the interpreter must be 100% confident arterial phase hyperenhancement is present prior to using this feature to categorize a nodule. This feature should be evaluated during the arterial phase of contrast enhancement usually occurring approximately 10–20 to 30–45 s after injection.

APHE on CT or MRI could be seen in a wide variety of both benign and malignant focal liver observations including a wide variety of liver masses and arterioportal shunts (APS). Accurate diagnosis of APS on CT and MRI commonly presents substantial diagnostic challenges. APS are commonly visualized on both contrast-enhanced CT and MRI in at-risk patients as ill-defined areas of APHE with no other associated findings on non-enhanced scans and show no washout on later phase images. Their appearance, therefore, is non-specific and either follow-up or other types of contrast-enhanced imaging may be required to confirm their benign nature.

By comparison, APS are not visualized on either precontrast or on CEUS. Therefore, when APS is suspected, a routine greyscale US will generally not show any abnormality or nodule to correspond with the APHE shown on CT/MRI. A negative US, therefore, supports the notion that the APHE on the CT or MRI is indeed related to shunting rather than a nodule. In other situations, where US/CEUS is performed following CT or MRI showing a positive observation with APHE, CEUS will only be performed if a true nodule is identified on US. As the vast majority of observations subjected to CEUS examination are true nodules, the observation of APHE on CEUS is of much greater significance than is APHE observation on a CT or MRI. As a result, a liver mass visible on precontrast demonstrating a typical APHE pattern (not rim or peripheral discontinuous globular) on CEUS should be characterized as a typical lesion of hepatocellular origin (CEUS LR-3, LR-4, or LR-5).

An additional unique benefit of CEUS for the assessment of nodules in an at-risk liver is the exquisite demonstration of the morphology of the arteries in the nodule at the time of washin of contrast in the early arterial phase. This is optimized with the selection of a

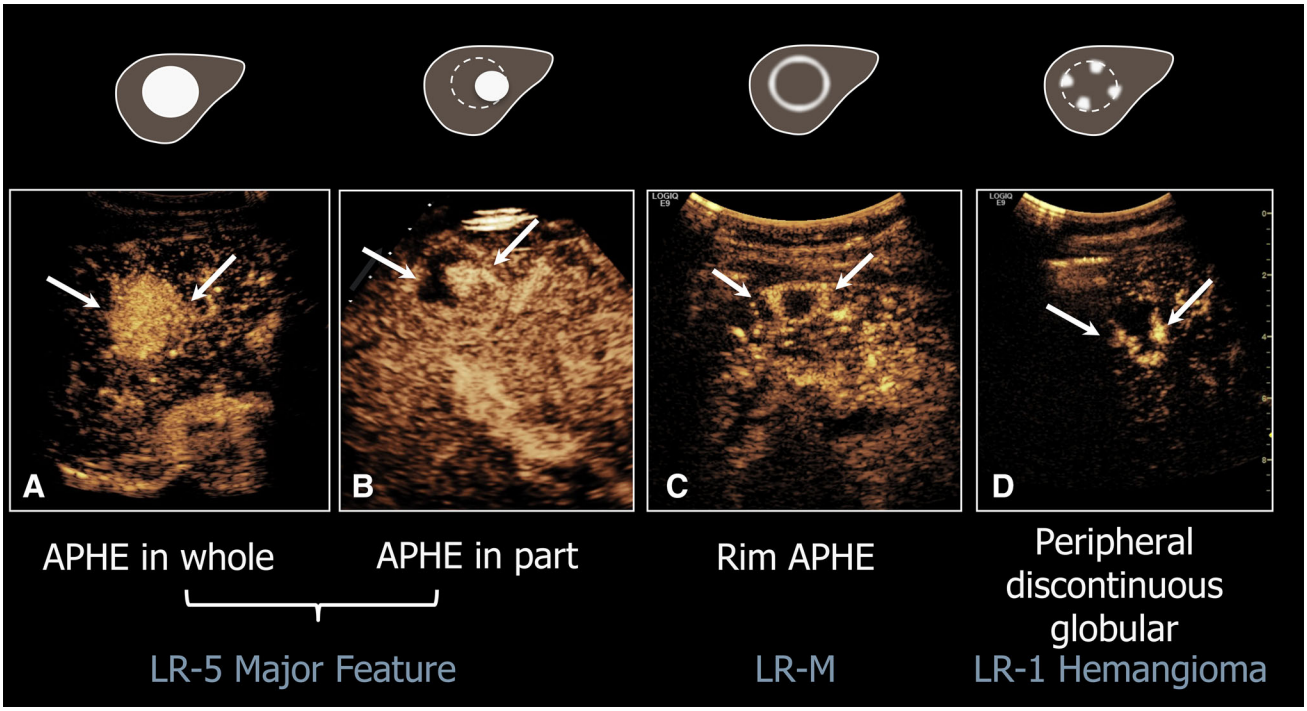


Fig. 1. Major feature of CEUS LI-RADS, APHE. **A** Schematics and associated CEUS images show diffuse APHE, characteristic of a small HCC (*arrows*), and **B** a nodule-in-nodule APHE, also a characteristic of HCC. These are classic features for LR-5. **C** Rim enhancement in the arterial phase is one of the requirements for the designation of LR-M. This pattern is common for ICC and also metastases, both included within LR-M. **D** Peripheral discontinuous globular enhancement is the classic pattern for a hemangioma which requires additionally also demonstration of sustained enhancement (Image reproduced with permission from the ACR).

bubble tracking option, available on many US systems. Dysmorphic vessel morphology (Fig. 2) and centripetal filling of a nodule are both associated with HCC.

Washout

Washout is the popular term for the visually assessed temporal reduction in enhancement of a nodule, in whole or in part, relative to the liver beginning in or after the arterial phase and resulting in portal venous or late phase hypoenhancement. Washout can be applied to any enhancing observation even in the absence of APHE.

On CT or MRI, the presence of washout is one of the major features for LR-5. On the other hand, on CEUS, all malignant lesions including HCC, ICC, and metastases have a strong tendency to show washout. Differentiation on CEUS between typical hepatocellular lesions (CEUS LR-3, LR-4, and LR-5) and malignant tumors with enhancement characteristics not specific for HCC (CEUS LR-M) relies on the onset and the degree of washout.

Washout onset: "Onset" refers to the time after contrast injection at which washout is first detected, recorded precisely in seconds, relative to liver. When initial washout onset is detected within 60 s of contrast injection, it is characterized as "early onset." When initial washout onset is detected at or after 60 s, it is characterized as "late onset" (Fig. 3).

Washout degree: The degree of nodule washout is assessed by comparing the degree of contrast enhancement of the nodule relative to the surrounding liver.

- Marked washout is diagnosed when the liver nodule becomes virtually devoid of contrast ("punched-out") within 2 min after contrast injection. Marked washout suggests a probable categorization as LR-M.
- Mild washout is diagnosed when the liver nodule becomes less enhanced than the surrounding liver, but still demonstrates some degree of persistent contrast enhancement.

Nodules initially demonstrating mild washout might eventually become virtually devoid of contrast ("punched-out").

- If this occurs within the first 2 min after contrast injection, it should be characterized as marked washout and LR-M should be considered.
- If this occurs after 2 min, the lesion is still categorized as showing mild washout.

Hepatocellular carcinoma typically shows washout with late onset (≥60 s) and of mild degree, while non-hepatocellular lesions, including ICC, show early onset

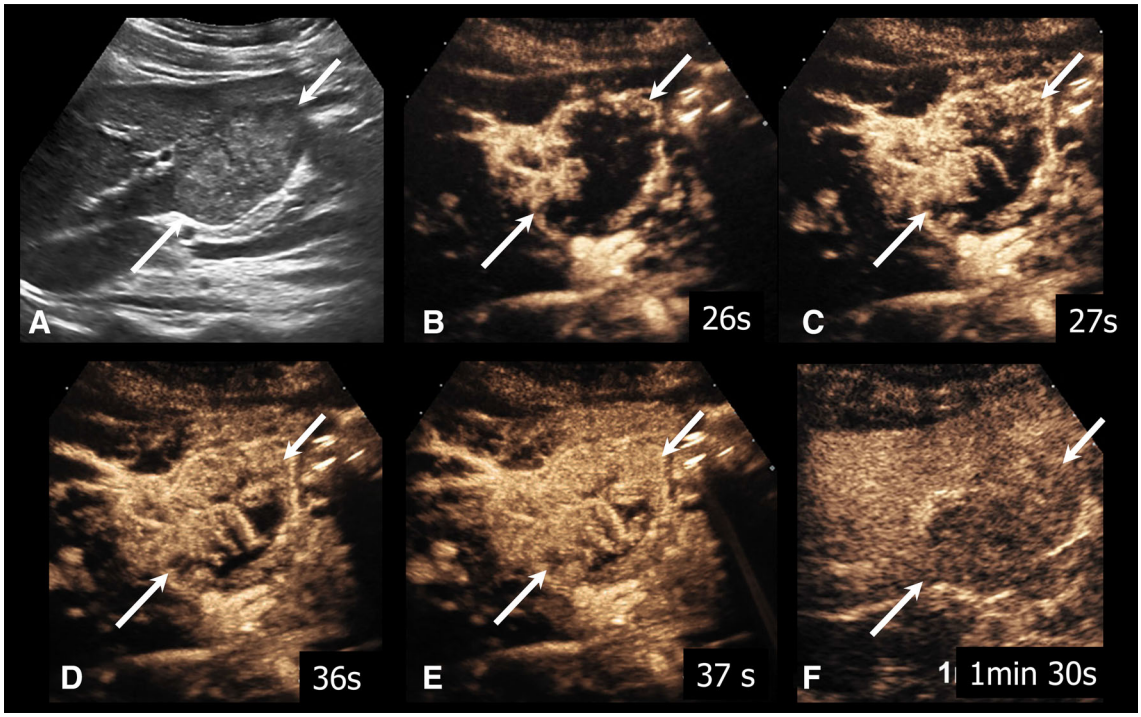


Fig. 2. Differences in CEUS from CT/MRI. Real-time imaging shows dysmorphic vessels in HCC in a 53-year-old male with HBV cirrhosis. **A** A greyscale image shows a mildly heterogeneous mass (*arrows*). **B**, **C**, **D**, and **E** Sequential frames in the arterial phase, taken with a bubble tracking technique, showing dysmorphic vessels and a centripetal filling pattern to complete fill-in (not shown). There is APHE. **F** Weak washout at 1 min 30 s (Image reproduced with permission from the ACR).

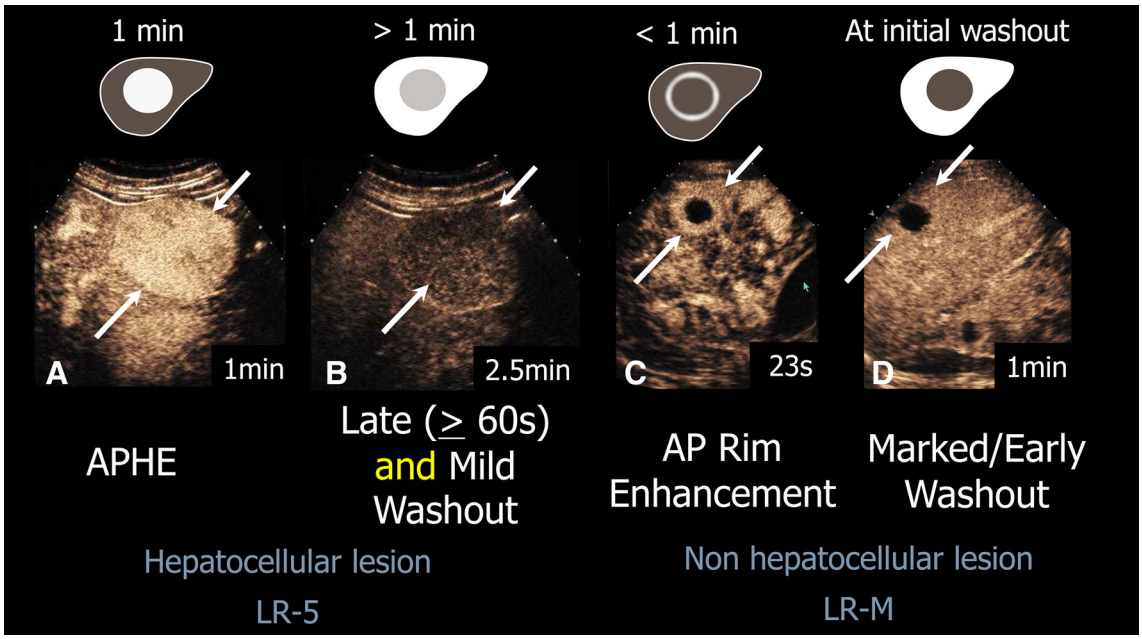
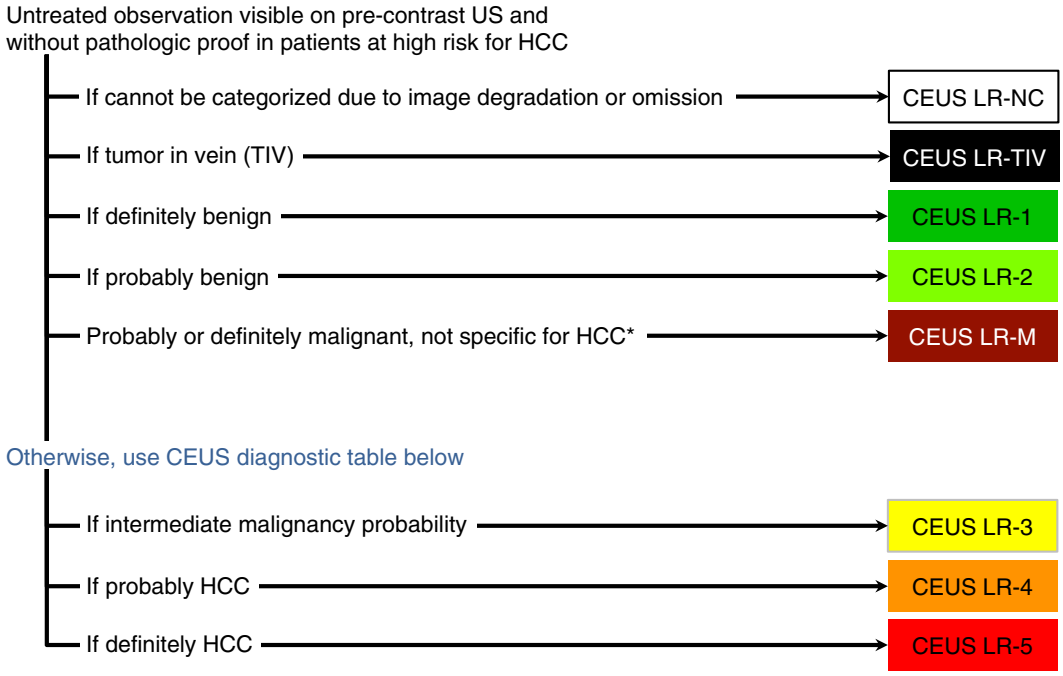


Fig. 3. Major feature of CEUS LI-RADS, washout. Schematics and images show the major features related to washout: TIMING and INTENSITY. **A**, **B**, Images showing a classic CEUS LR-5 (*arrows*) with APHE and late and weak washout, occurring after 1 min and appearing faded more than washed out. **C**, **D** Images showing a classic CEUS LR-M, a probably malignant tumor, with AP rim enhancement and marked punched-out washout occurring rapidly at 1 min (Image reproduced with permission from the ACR).



CEUS Diagnostic Table

Arterial phase hyperenhancement (APHE)	No APHE		APHE **	
Nodule size (mm)	< 20	≥ 20	< 10	≥ 10
No washout of any type	CEUS LR-3	CEUS LR-3	CEUS LR-3	CEUS LR-4
Late and mild washout	CEUS LR-3	CEUS LR-4	CEUS LR-4	CEUS LR-5

*** CEUS LR-M criteria:**
If rim APHE **OR**
early (<60s) washout **OR**
marked washout

**** APHE:**
- Not rim (indicates LR-M)
- Not peripheral discontinuous globular (indicates hemangioma)

If unsure about the presence of any major feature: characterize that feature as absent

Fig. 4. CEUS LI-RADS algorithm (Image reproduced with permission from the ACR).

(<60 s) and/or marked washout. Therefore, on CEUS, it is critical to carefully evaluate the timing of onset and the degree of washout. In order to reliably assess the timing of washout onset, we recommend initial real-time imaging and dynamic acquisition with low mechanical index (MI) up to 60 s after contrast injection, and intermittent imaging afterwards. Microbubble contrast agents are destroyed by even low-energy US. While real-time imaging is critical to assess arterial phase enhancement, continuous scanning of a large area of liver after 60 s will result in increased contrast agent destruction with no additional benefit. After an initial 60 s continuous recording, intermittent imaging for a few seconds every 30–60 s is recommended until near all contrast agent has disappeared from the circulation (usually 4–6 min after injection). This prolonged intermittent scanning is critical to detect late and mild washout, one of the major features of LR-5 nodules on CEUS.

Indications

CEUS is a valuable contributor to multimodality imaging for characterizing nodules in a cirrhotic liver [16]. CEUS may be used to.

- Assess nodules ≥10 mm detected at surveillance US;
- Assess LR-3, LR-4, and LR-M observations detected on prior CT or MRI;
- Characterize APHE for observations in which mistiming is suspected as the reason for its absence on prior CT or MRI;
- Assess biopsied observations with inconclusive histology;

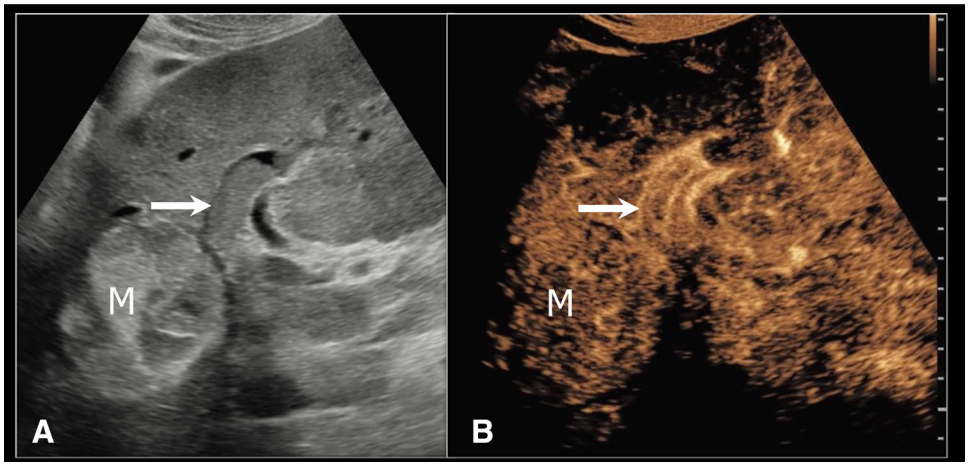


Fig. 5. CEUS LR-TIV. A 59-year-old male with HCV cirrhosis and new onset of ascites. **A** Sagittal greyscale US image shows a focal echogenic large liver mass (*M*). There is a soft tissue mass within the *ascending left* portal vein (*arrow*). **B** In the arterial phase, there is hyperenhancement of both the portal vein thrombus and the mass (Image reproduced with permission from the ACR).

- Guide biopsy or treatment of lesions that are difficult to visualize with pre-contrast US;
- Help select the most appropriate observation(s) or observation component(s) for biopsy;
- Monitor changes in enhancement pattern over time for selected LR-3 or LR-4 observations;
- Differentiate tumor in vein (''tumor thrombus'') from bland thrombus; and.
- Monitor therapy for treatment of HCC, both intraprocedural and following therapy (not addressed in the current version of CEUS LI-RADS).

CEUS is a focused exam and is not suitable for screening or surveillance. Rather, it is used to characterize lesion(s) identified on a screening and surveillance ultrasound or on CT/MRI. CEUS is also not suitable for staging the entire liver. Once a patient is diagnosed with any malignant lesion(s), a CECT or CEMRI is necessary for staging disease.

The CEUS LI-RADS algorithm

The CEUS LI-RADS algorithm is applied in a step-by-step manner to encompass the interpretation and reporting of all variety of imaging findings in patients at high risk for HCC. The algorithm (Fig. 4) is intended to be used from the first option through to the last option or the option which fits the observations in the case at hand, whichever occurs first. The algorithm includes, therefore, benign and malignant possibilities and provides different confidence levels for suggested diagnoses.

CEUS LR-NC

The first step of the CEUS LI-RADS Algorithm deals with the quality of the scan and the ability to make appropriate interpretations leading to an assignment to a specific category. Shortcomings of the technique or equipment and failures related to patient body habitus or observation size may all lead to an ultimate CEUS examination technical failure. Therefore, appropriate diagnostic features might not be documented or the observation may not be assigned an appropriate category and, therefore, should be classified instead as LI-RADS not categorizable or LR-NC. These determinations must be relayed to the referring physician with suggestions for their resolution, which most often involves recommendation for either contrast-enhanced CT or MRI.

CEUS LR-TIV

The next step in the algorithm is to evaluate for the presence of thrombus within the portal and/or hepatic veins. Identification of a soft tissue mass within the vein lumen associated with its APHE and then washout is diagnostic of tumor thrombus (Fig. 5). Avascularity of the thrombus, throughout all phases of enhancement, suggests bland thrombus, revascularization of which emphasizes the necessity of correctly timing the demonstration of enhancement and also the presence of washout. When TIV is present, indicate its likely etiology and describe vessel(s) involved. The majority of CEUS LR-TIV are HCC associated, but some may be related to ICC, H-ChC (hepatocholangiocarcinoma), or other non-HCC malignancies.

If TIV is contiguous with a CEUS LR-M lesion, describe it as ''may be due to non-HCC malignancy.'' If TIV is contiguous with a CEUS LR-5 lesion, then describe it as ''definitely due to HCC.'' If TIV is contiguous with a CEUS LR-4 lesion or associated with an infiltrative mass, then describe it as ''probably due to HCC.'' Otherwise, describe it as of ''unknown etiology.''

If unsure about the presence of TIV, do not categorize as TIV.

Management implications CEUS LR-TIV cases are usually referred to multi-disciplinary discussion (MDD) for consensus management. It may include alternative or repeat imaging, biopsy, or treatment.

CEUS LR-1

The next step in the algorithmic approach is to categorize all lesions which are definitely benign, CEUS LR-1.

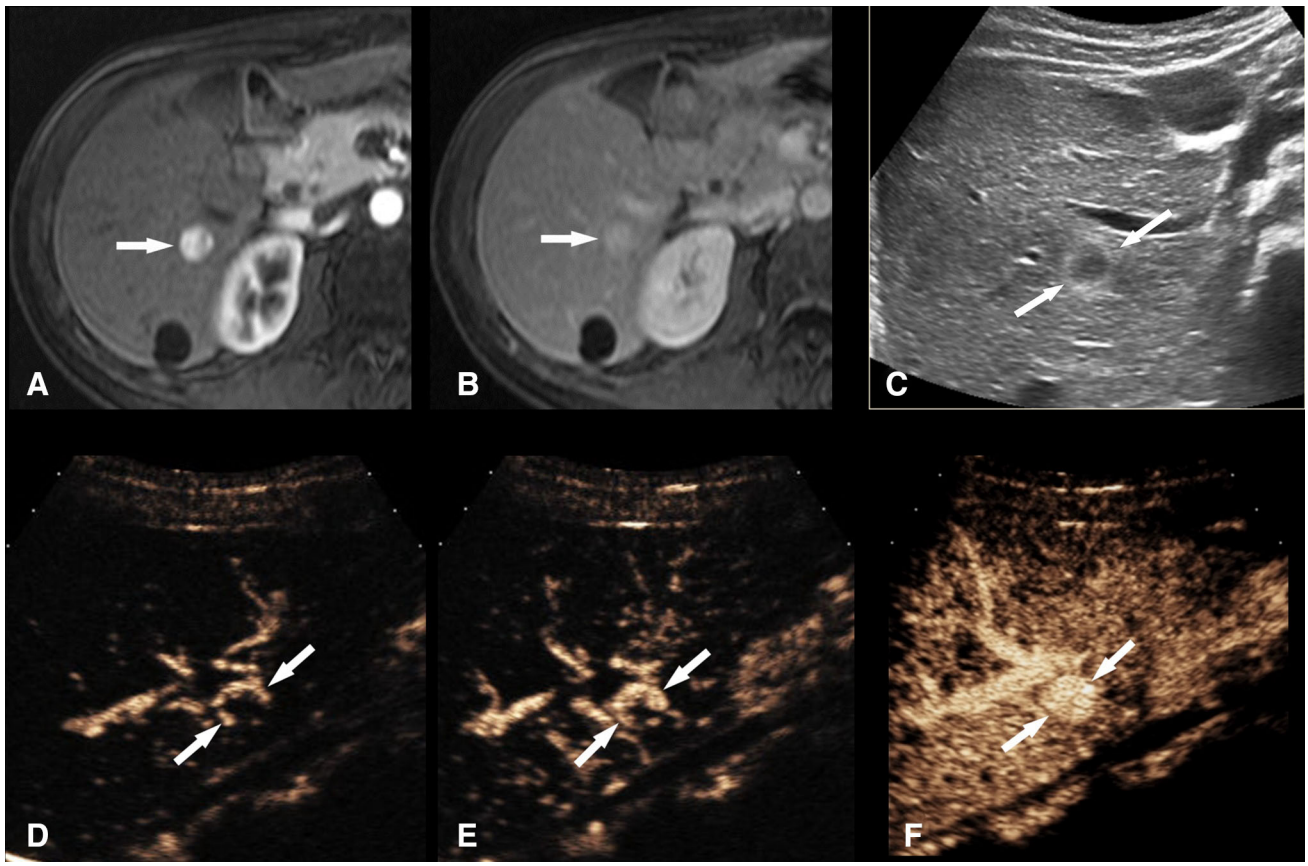


Fig. 6. CEUS LR-1, a flash-filling hemangioma. A 59-year-old female with chronic HBV and a nodule on outside surveillance US. **A** Contrast-enhanced T1-weighted MR scan in the arterial phase shows a slightly heterogeneous hyperenhancing nodule (*arrow*) in the liver. **B** The nodule (*arrow*) is homogenously hyperintense in the delayed phase. MR findings are indeterminate as the arterial phase enhancement pattern is non-specific and there is no washout. **C** A greyscale US image confirms the right lobe focal liver nodule with an echogenic rim. **D**, **E** and **F** Sequential frames in the arterial phase of CEUS showing progressive peripheral nodular enhancement with centripetal filling to complete fill-in. There is sustained enhancement to 5 min, not shown (Reproduced from: Kim TK, Jang HJ, Wilson SR. Ultrasound of Hepatocellular Carcinoma: The Important Contribution of Contrast Enhancement. Hepatocellular Carcinoma Diagnosis and Treatment (2016). Editors: Carr, Brian I. (Ed.) Humana Press, Springer Science.).

Hemangiomas are felt to be less common in the cirrhotic liver than the normal liver, but their presence in cirrhosis is indisputable. They have variable B-mode appearance and may appear echogenic, as they most often do in the non-cirrhotic liver, or they may also be hypoechoic or even mixed in echogenicity. Fortunately, on CEUS, their features are classic including discontinuous globular peripheral enhancement followed by variable fill-in, which is generally sustained (Fig. 6).

They occur most often in the patient with chronic hepatitis B infection and no cirrhosis but may also occur in the liver with cirrhosis and may additionally co-exist with HCC. Fast-filling hemangioma variant, with an increased incidence in small nodules, is most optimally studied with CEUS where the rapidly changing arterial phase enhancement is detected by the excellent temporal resolution of real-time CEUS.

Focal fat deposition and focal fat sparing may also occur within an at-risk liver. The former is characterized by an echogenic nonmasslike, nonspherical observation on precontrast US with isovascularity in both the arterial and portal venous phases on CEUS with no washout (Fig. 7). The latter is characterized alternately by a hypoechoic observation on baseline again with isoenhancement throughout all phases of CEUS imaging. As with hemangioma, if all features on greyscale and CEUS are in agreement, these fat-related lesions may also be confidently categorized as CEUS LR-1.

Simple cysts with classic benign morphology on greyscale US can be diagnosed as simple cysts without CEUS although more complex appearing lesions on the greyscale scan may require CEUS showing complete avascularity to be classified as CEUS LR-1.

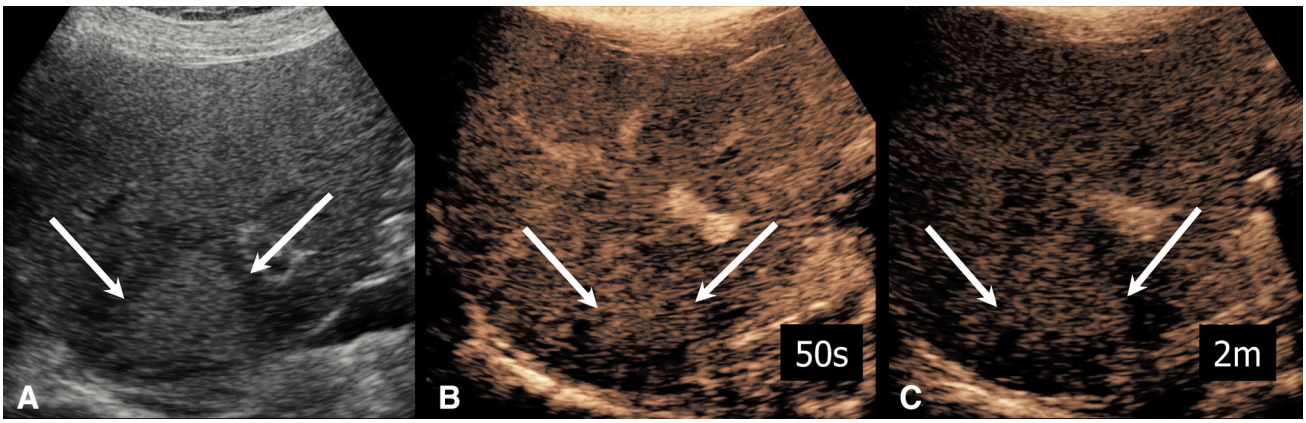


Fig. 7. CEUS LR-1, a focal fat deposition. A 56-year-old male with alcohol cirrhosis. **A** A sagittal greyscale US image shows a severely fatty liver with a deep focal echogenic mass (*arrow*) measuring about 3 cm in diameter. **B** In the arterial phase of CEUS and C the portal venous phase, there is isovascularity of the mass with the adjacent liver. There is no APHE and there is no washout. This is diagnostic of focal fat (Image reproduced with permission from the ACR).

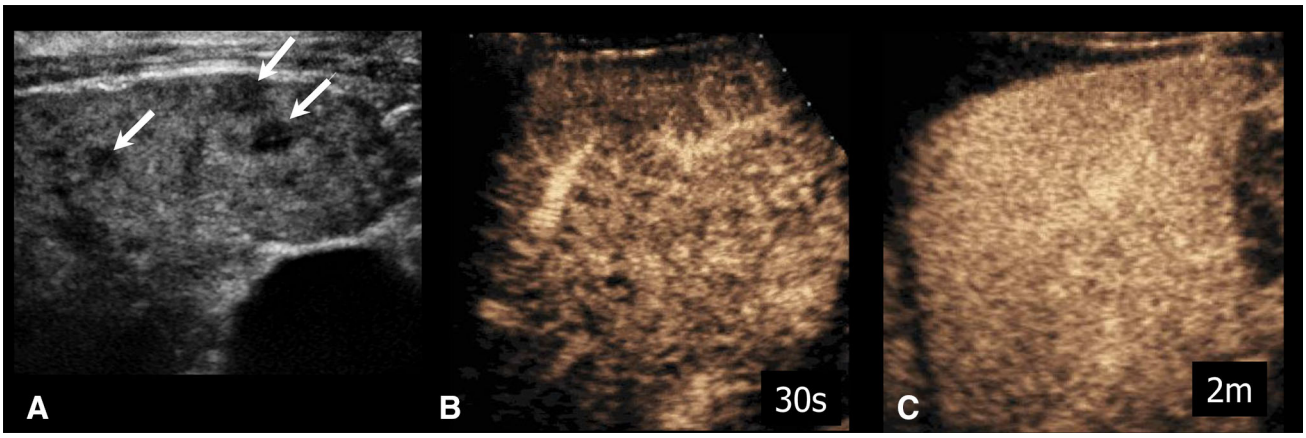


Fig. 8. CEUS LR-2, a probably benign nodule. A 50-year-old female with HCV cirrhosis. **A** A greyscale US image of the left lobe of the liver shows at least 3-subcentimeter hypoechoic nodules (*arrows*). **B** AP shows isovascularity with no evidence of APHE. **C** An image from a sweep of the left lobe in the portal venous phase shows a homogeneous liver with no washout or other alteration. Frequently, CEUS will remove concern about nodules shown on the greyscale scan by its demonstration of homogeneously enhancing parenchyma in all phases of enhancement (Image reproduced with permission from the ACR).

Management implications Patients with CEUS LR-1 may return to regular 6-month surveillance.

CEUS LR-2

After the elimination from consideration of definitely benign lesions, the next step is to identify lesions which are probably benign, CEUS LR-2. Criteria for categorization as CEUS LR-2 are currently very stringent and require identification of the following:

- Distinct isoenhancing solid nodule <10 mm
- Nonmasslike isoenhancing observation of any size, not typical hepatic fat deposition/sparing
- LR-3 nodules with interval size stability for ≥2 years

Since CEUS is generally recommended for characterization of definite nodules ≥10 mm, the vast majority of LR-2 nodules will be detected incidentally while performing CEUS for other observations. These small nodules are typical regenerative nodules and their probably benign categorization is useful and effective (Fig. 8). Nonmasslike isoenhancing observation of any size, not typical hepatic fat deposition/sparing would be categorized to LR-2.

Additionally, any observation previously categorized as CEUS LR-3 with an interval size stability for ≥2 years may be categorized as CEUS LR-2.

Observations that are not definitely benign (CEUS LR-1) and do not meet the above CEUS LR-2 criteria are categorized CEUS LR-3 or higher.

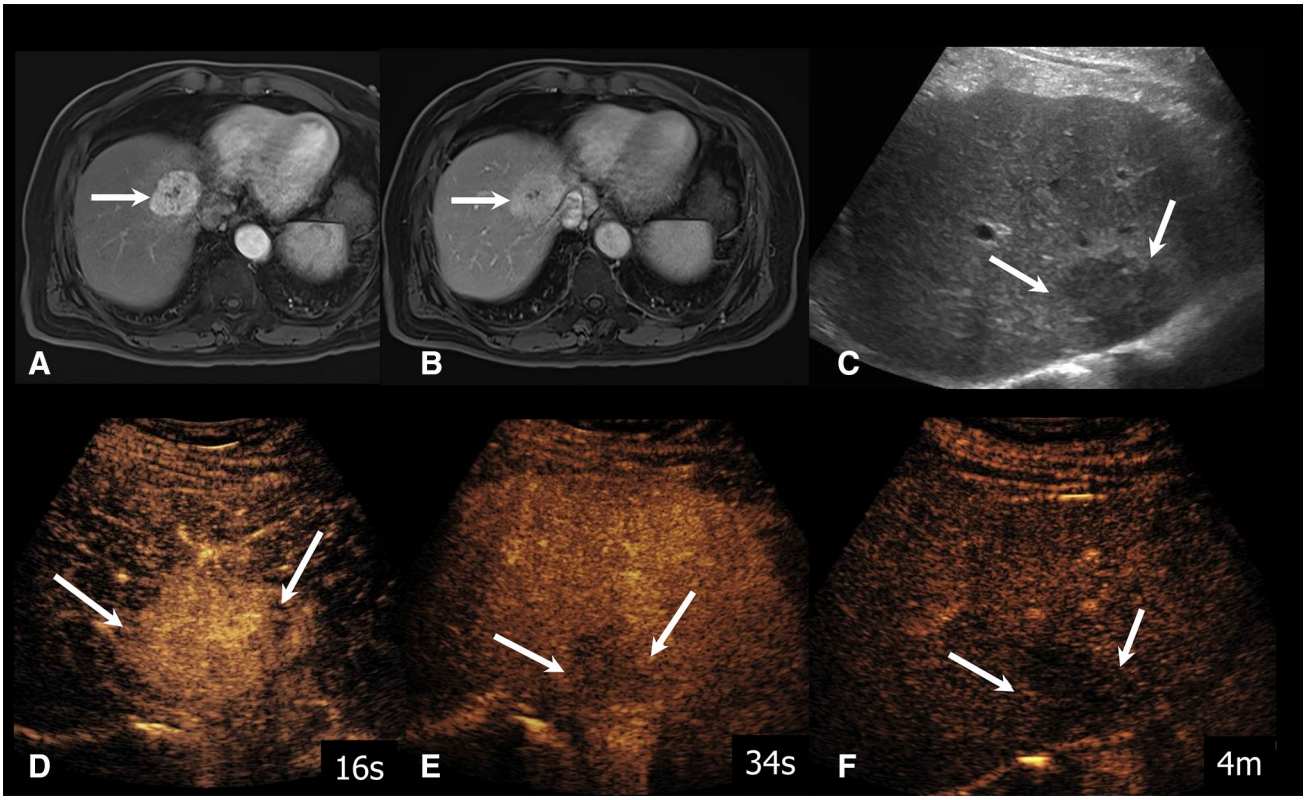


Fig. 9. CEUS LR-M, probably or definitely malignant nodule, not specific for HCC. A 78-year-old male with HBV and a growing nodule on MR, previously diagnosed 2 years earlier on MR as a hemangioma. Post-gadolinium MR images in **A** the arterial phase (*arrow*) and **B** the portal venous phase show obeservation with arterial phase enhancement with no washout in either the portal venous or the delayed phase. **C** The hypoechoic mass is confirmed on greyscale US. **D** In the arterial phase of CEUS, the mass shows APHE. **E** There is rapid washout prior to 1 min, shown at 34 s. **F** The washout is marked at 4 min, discordant with the sustained enhancement on MRI. Biopsy following CEUS shows cholangiocarcinoma (Image reproduced with permission from the ACR).

Management implications Patients with CEUS LR-2 may return to regular 6-month surveillance.

CEUS LR-M

The next step is to identify CEUS LR-M, a probably or definitely malignant nodule, not necessarily HCC (Figs. 9). These observations show a distinct solid nodule on precontrast US, with at least some enhancement in the arterial phase. There is no size threshold for LR-M. Although CEUS is usually performed to assess nodules ≥10 mm detected on surveillance US, smaller nodules with LR-M features may be identified during CEUS and should be categorized LR-M.

Any one of the following criteria mandates placement of the nodule in the CEUS LR-M category:

- Early washout relative to liver, within 60 s of contrast injection;
- Marked washout, resulting in a "punched-out" appearance within 2 min after contrast injection;
- Arterial phase rim enhancement, followed by washout (regardless of onset or degree).

Management implications Management of CEUS LR-M nodules is variable, depending on the type of malignancy suspected. However, biopsy is frequently needed for a CEUS LR-M observation, as there is a lack of specificity for an imaging diagnosis. ICC, hepatocholangiocarcinoma, and metastases account for the majority of tumors characterized as CEUS LR-M. Some poorly differentiated HCCs may also show the enhancement pattern of CEUS LR-M, especially rapid washout (Fig. 10). It is unknown how many LR-M lesions are actually HCC. One retrospective study showed that 40% (6/15) of LR-M lesions were HCCs, 13% (2/15) were hepatocholangiocarcinomas, and 47% (7/15) were cholangiocarcinomas [17]. In our unpublished data, 35% (11/31) of LR-M lesions were HCCs.

The CEUS LI-RADS diagnostic table

The remaining considerations within the algorithm address identified nodules, which develop by the process of hepatocarcinogenesis in the at risk liver. There are three considerations for all of these nodules, which categorize them as follows:

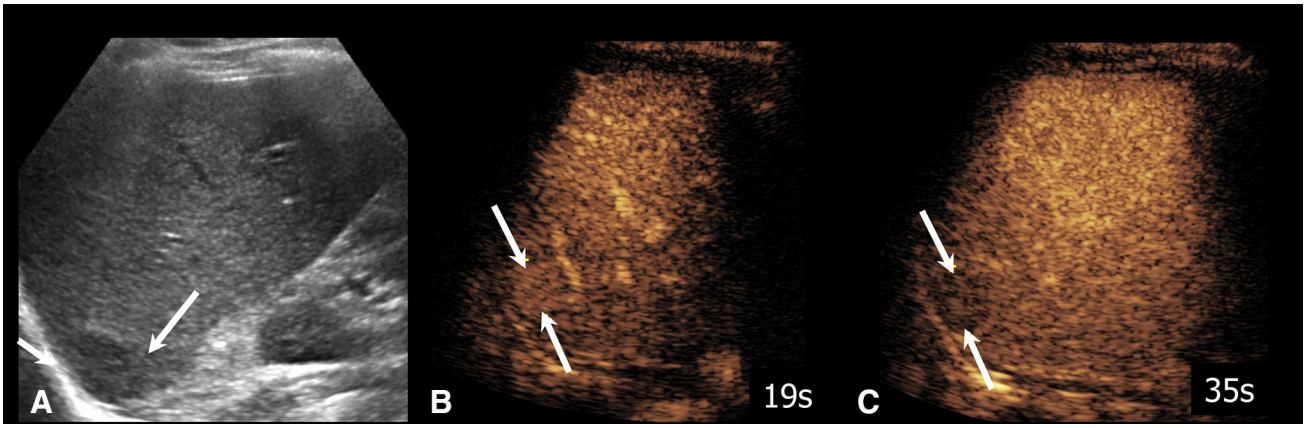


Fig. 10. CEUS LR-M, biopsy-proven HCC. A 62-year-old male with HCV cirrhosis. **A** Surveillance US shows a focal hypoechoic nodule in segment 7 (*arrows*). **B** There is typical APHE at 25 s. **C** There is rapid mild washout at 35 s (Image reproduced with permission from the ACR).

- CEUS LR-3—intermediate malignancy probability,
- CEUS LR-4—probably HCC, and.
- CEUS LR-5—definitely HCC.

This characterization is based on.

- Nodule size (<10, 10–20, and ≥20 mm),
- APHE (not rim or peripheral discontinuous globular), and.
- Washout, its presence, timing, and degree.

Accurate assignment of nodules to the CEUS LR-3, LR-4, and LR-5 categories requires a constant familiarity and referral to the CEUS LI-RADS Diagnostic Table (Fig. 3), included within the algorithm.

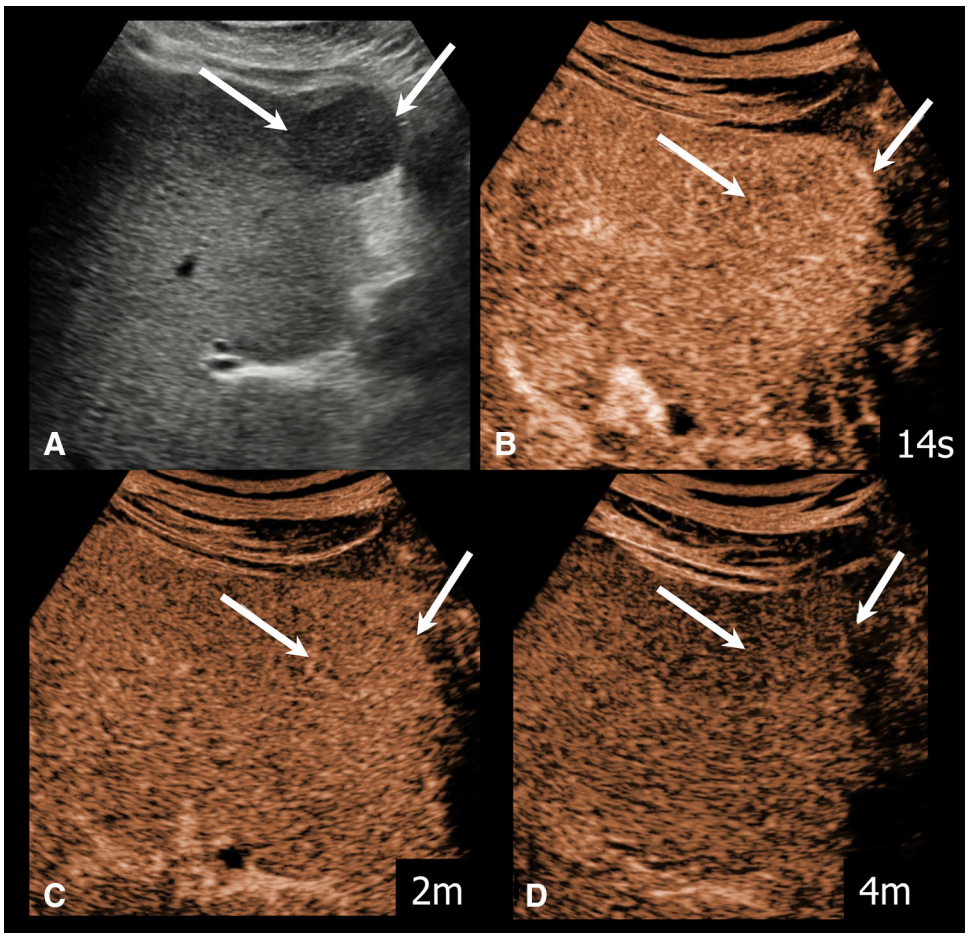


Fig. 11. CEUS LR-3, nodule ≥2 cm, no APHE, and no washout. A 64-year-old male with ethanol-related cirrhosis. **A** A surveillance US scan shows an exophytic hypoechoic nodule measuring just over 2 cm (*arrows*). **B** The nodule is isovascular at peak AP. **C** At 2 min and **D** at 4 min, the nodule remains isovascular with the adjacent parenchyma (Image reproduced with permission from the ACR).

CEUS LR-3

CEUS LR-3 nodules have an intermediate malignancy probability. They include nodules with a variety of sizes, with or without APHE, and with or without late and mild washout, making them a somewhat heterogeneous catch-all group intended to provide a conservative option which does not eliminate the possibility of malignancy.

CEUS LR-3 includes distinct solid nodules ≥10 mm with isoenhancement in all phases, nodules <20 mm which do not show APHE but do show late washout onset (≥60 s) and mild degree of washout. CEUS LR-3 also includes nodules <10 mm which do show APHE (not rim or peripheral discontinuous globular) but no washout (Fig. 11).

Management implications The suggested management of CT/MRI LR-3 observations is repeat imaging in 3–6 months or alternative imaging in 3–6 months. However, management implications for CEUS LR-3 nodules vary including alternative imaging, biopsy, or shorter interval surveillance. Additionally, they often require MDD.

Two recent studies [18, 19] show that most LR-3 observations detected at CT or MRI are benign or indolent lesions that can be followed safely without requiring MDD in all cases.

Less is known about the natural history of LR-3 observations detected at CEUS, but preliminary evidence suggests that such observations warrant closer scrutiny. By definition, all CEUS observations are distinctive nodules in a cirrhotic liver visible on pre-contrast B-mode images, which thus have high probability of being HCC, unless contrast enhancement features are diagnostic of a benign entity such as a hemangioma. A recent retrospective study [17] found that 60% (45/75) of CEUS LR-3 observations were HCC. Therefore, MDD should be considered for all CEUS LR-3 observations, because biopsy or alternative imaging in less than 3 months may be appropriate.

CEUS LR-4

CEUS LR-4 nodules are probably HCC. They are highly suspicious for HCC but lack the precise requirements for this diagnosis. They include nodules with APHE (not rim or peripheral discontinuous globular) but no washout measuring ≥10 mm and those with APHE (not rim or peripheral discontinuous globular), late washout onset (≥60 s), and mild degree of washout but measuring <10 mm. Nodules ≥20 mm with no APHE but with late washout onset (≥60 s) and mild degree of washout may also be characterized as CEUS LR-4 (Fig. 12).

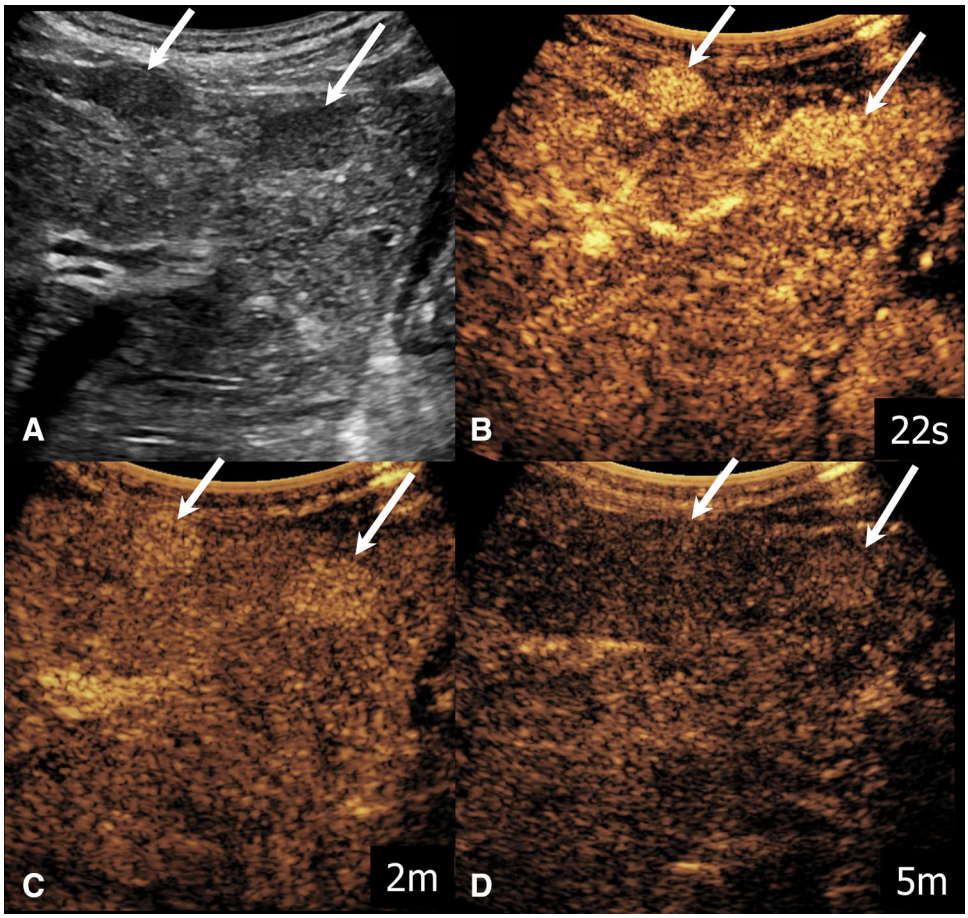


Fig. 12. CEUS LR-4, probably HCC. A 27-year-old male with cryptogenic cirrhosis. A surveillance US shows two nodules between 10 and 20 mm. **A** The greyscale US confirming two hypoechoic nodules (*arrows*). **B** There is typical APHE. **C** At 2.5 min, the nodules remain hyperenhanced. **D** At 5 min, the liver is now poorly enhanced. The nodules remain slightly more enhanced than the parenchyma. There is no washout. Subsequent biopsy is negative for HCC and short interval surveillance has continued to show interval stability for over 1 year (Image reproduced with permission from the ACR).

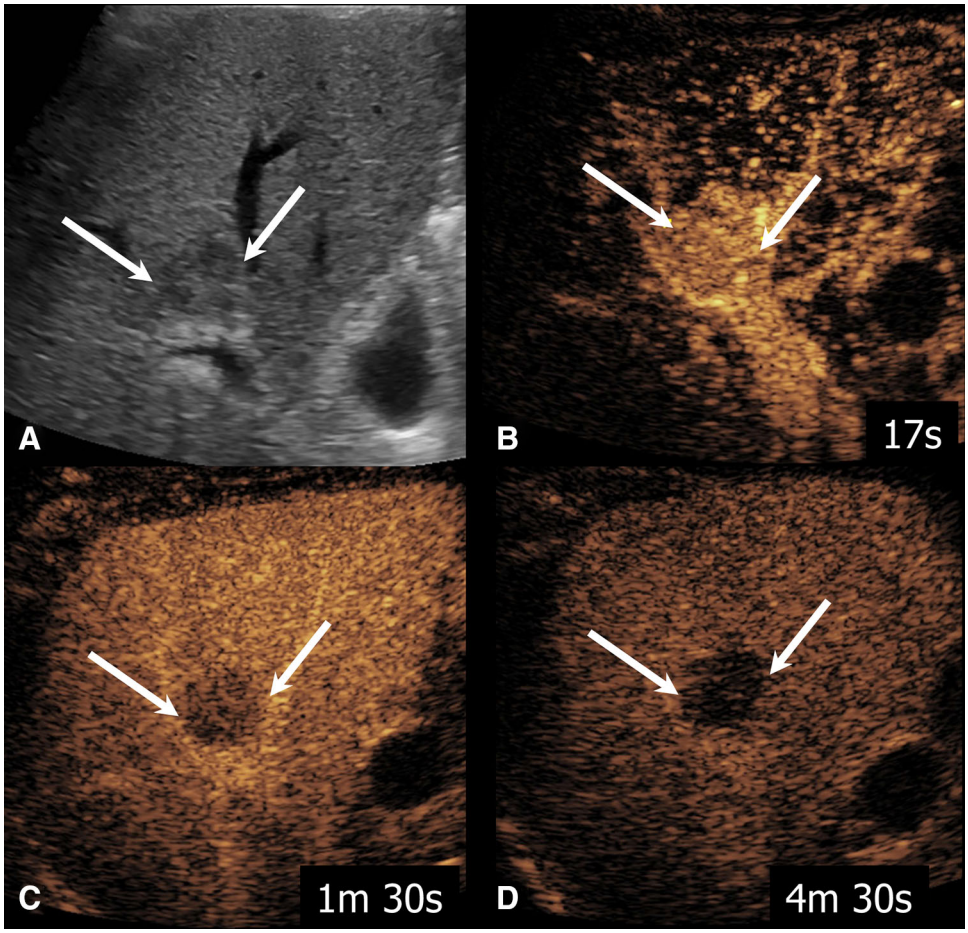


Fig. 13. CEUS LR-5, definitely HCC. A 64-year-old male with HCV cirrhosis. **A** Surveillance US shows a focal hypoechoic nodule measuring 1.7 cm (*arrows*). **B** There is typical APHE. **C** There is mild washout at 1.5 min. **D** At 4.5 min, there is a marked washout which does not influence the categorization. Biopsy following CEUS shows HCC (Image reproduced with permission from the ACR).

This category, CEUS LR-4, emphasizes the importance of typical APHE on CEUS, which is predominantly associated with nodules of hepatocellular origin, unlike CT or MRI where APHE is often detected in APS in the cirrhotic liver.

On CT and MRI, observations with APHE often represent APS [20], and therefore it is essential to have portal venous phase washout for diagnosis of HCC. CEUS, by comparison, does not show abnormality in the presence of known APS. Therefore, the significance of identification of a nodule with typical APHE alone on CEUS as a predictor of HCC is high [2].

Management implications CEUS LR-4 nodules are probable HCC, but not with 100% probability; therefore, these nodules require either biopsy, treatment, or short interval follow-up.

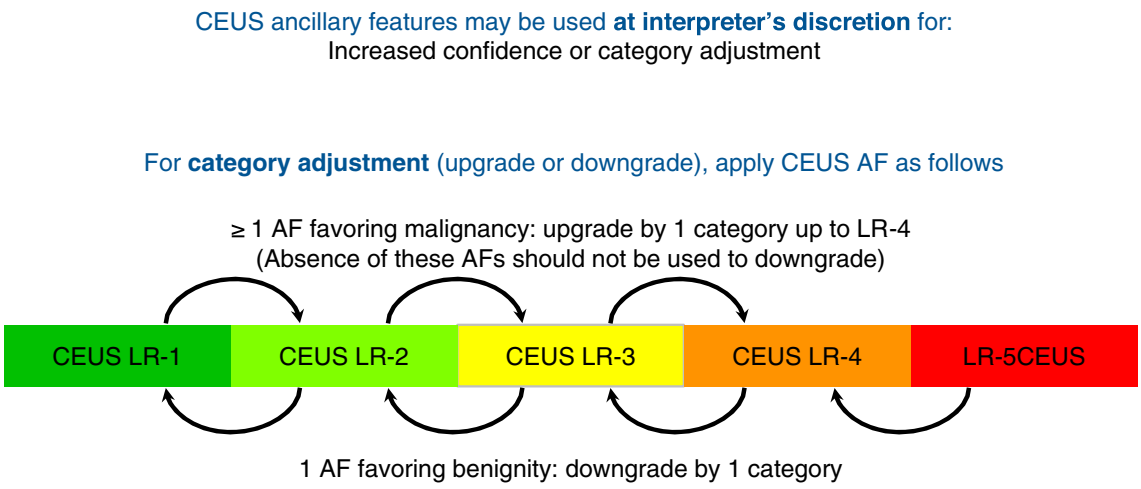
CEUS LR-5

CEUS LR-5 is definitely HCC with nearly 100% probability, and therefore confirmation with biopsy prior to treatment is deemed to be unnecessary. The diagnosis of HCC has rigorous criteria, all of which must be present for this categorization. There are three essential criteria including a size ≥10 mm, typical APHE (not rim or peripheral discontinuous globular), and late washout onset (≥60 s) with mild washout degree (Fig. 13).

Management implications CEUS LR-5 nodules may undergo locoregional therapy, surgical resection, or transplantation without requirement for tissue diagnosis.

Ancillary features and tie-breaking rules

Upon completion of the algorithm categorization, ancillary features (Fig. 14) may be used at the interpreter's discretion to increase diagnostic confidence, or to adjust a LR category. Use of ancillary features may be used to upgrade or downgrade a category, but may not be used to upgrade any nodule to LR-5. Although ancillary features are applied less often on CEUS than on CT and MRI, they are nonetheless very important. Ancillary features favoring malignancy, without specificity for HCC, include definite interval size increase, whereas definite interval size reduction or stability ≥2 years favor benignancy. Features favoring HCC, in particular, include a mosaic appearance of the nodule and a nodule-in-nodule appearance in the arterial phase.



CEUS AF favoring malignancy	CEUS AF favoring benignity
Favoring malignancy in general, not HCC in particular • Definite growth **Favoring HCC in particular** • Nodule-in-nodule architecture • Mosaic architecture	• Size stability ≥ 2 years • Size reduction

If unsure about presence of any ancillary feature: characterize that feature as absent

Fig. 14. Ancillary features and tie-breaking rules of CEUS LI-RADS (Image reproduced with permission from the ACR).

Tie-breaking rules

If after full categorization there is a dilemma between two categories, always choose the category reflecting lower certainty as below (Fig. 15).

Final check

Upon completion of the categorization of the nodule, consider its reasonability and accuracy. If the category seems appropriate, then you are done. If not, reevaluate.

Discussion

CEUS is a new addition to LI-RADS. Although it is very similar to the original LI-RADS for CT and MRI, CEUS has distinct differences. It is important to understand the difference of CEUS from CT and MRI, and its advantages and limitations not only to interpret and use CEUS correctly, but also to take advantage of the unique capabilities of CEUS. Key differences of CEUS from CT and MRI are summarized in this article.

In a meta-analysis evaluating the test performance of imaging modalities for HCC, Chou et al. concluded that there were no differences in sensitivity among CEUS, CT, and MRI [6]. In a meta-analysis assessing the accuracy of diagnosis of small HCC by CEUS [21], we evaluated 6 references which had less stringent criteria than current CEUS LI-RADS, as they included only identification of washout, without consideration of timing or degree. However, these less stringent criteria still provided high specificity (99%) and PPV (97%) for 1- to 2-cm HCC. Sensitivity for smaller HCC was 62%. False-positive diagnosis of ICC as HCC was rare. However, the described studies include only 2 ICCs.

The data from Terzi, E., et al., suggest that the probability of HCC for each CEUS LR category fits

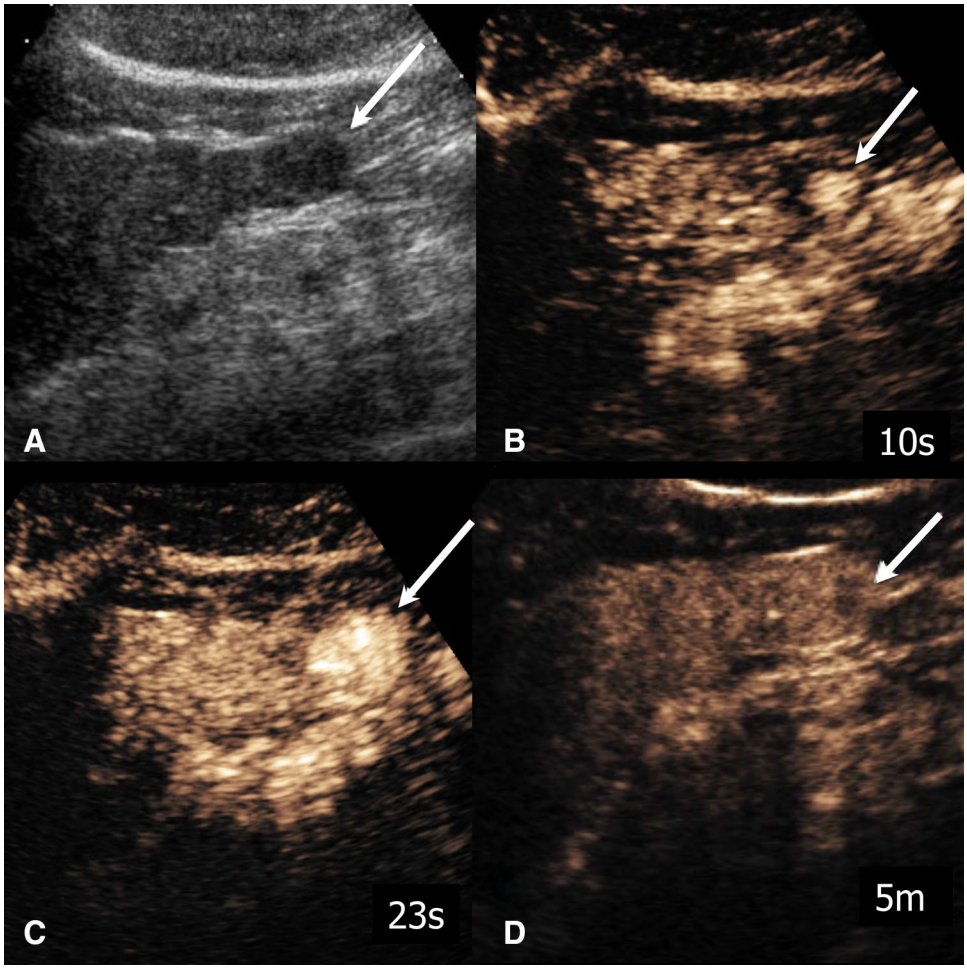


Fig. 15. Ancillary Feature of CEUS LI-RADS, nodule-in-nodule architecture. A 54-year-old male with HCV cirrhosis. **A** A surveillance US shows an exophytic nodule (*arrow*) at the tip of the left lobe. **B** In the early AP of CEUS, there is a small hypervascular nodule (*arrow*) within a larger hypoechoic nodule, appearing *black*. **C** By 23 s, the entire nodule is hyperenhanced. **D** At 5 min, there is washout corresponding with the initial hypervascular nodule. The remainder of the nodule remains isoenhanced. Although the area of initial hyperenhancement and late and mild washout is small and less than 1 cm, the entire nodule is greater than 1 cm. This is "APHE in part", as well as "washout in part", major features for LR-5. Therefore, this is a CEUS LI-RADS 5 lesion, confirmed HCC by biopsy at RFA (Image reproduced with permission from the ACR).

within the intended probability of HCC: LR-1 0%, LR-2 <20%, LR-3 20–70%, LR-4 70–95%, and LR-5 100% [17]. Management suggestions for CEUS are the same in all categories with CT and MRI except for the category CEUS LR-3. Currently, HCC probability of CEUS LR-3 seems to be higher than that of CT and MRI, with LR-3, 45/75 (60%) in the Terzi study. When nodules are seen by ultrasound, they are true nodules and, therefore, the pretest probability of HCC is high. Multicenter, prospective studies are needed to validate CEUS LI-RADS criteria.

We present several important indications of CEUS for characterizing nodules in a cirrhotic liver. CEUS can be used as the first step to characterize nodule(s) detected on HCC surveillance US, which will allow prompt evaluation of the nodule(s), avoiding misregistration. Further, it will avoid unnecessary further imaging for benign lesions. CEUS will also add complementary or additional information to CT or MRI for suspect APS, and CEUS, performed for negative or indeterminate nodules from CT or MR imaging, provides more non-invasive diagnoses prior to consideration of biopsy [22].

Limitations of CEUS include unsuitability for HCC staging. Therefore, once a patient is diagnosed with a malignant lesion(s), either HCC or other malignancy, a CECT or CEMRI is necessary for staging disease. Further, inaccessibility of subdiaphragmatic or deep lesions, limited penetration in large patients, and signal attenuation in patients with severe hepatic steatosis, and infrequent interference of bowel or gastric gas may also limit the success of CEUS.

Although CEUS has been used for liver lesion characterization and for other indications for many years

worldwide, it is fairly new in the United States. CEUS LI-RADS will improve the integration of CEUS into the multimodality approach for the study of the liver at risk for HCC, providing unique and complimentary information to CT and MRI.

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