Imaging Diagnosis of Hepatocellular Carcinoma

The Liver Imaging Reporting and Data System, Why and How?

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KEYWORDS

• Liver • Hepatocellular carcinoma • Imaging diagnosis

KEY POINTS

- Imaging modalities carry high specificity for the diagnosis of hepatocellular carcinoma (HCC) when stringent criteria are applied in at-risk patients, thus enabling many HCCs to be diagnosed without biopsy.
- The Liver Imaging Reporting and Data System (LI-RADS) aims to standardize the lexicon, technique, interpretation, and reporting of liver imaging in patients at risk for HCC.
- For diagnosis, 2 LI-RADS algorithms are available covering cross-sectional imaging techniques (CT/MRI LI-RADS) and contrast-enhanced ultrasound (CEUS LI-RADS).
- Although both algorithms provide high positive predictive value (PPV) and high specificity in the diagnosis of HCC, the algorithms are not identical, reflecting intrinsic differences between imaging modalities.
- Users should be aware of and consider the unique advantages and disadvantages of CEUS, CT, and MRI when deciding which imaging method to use.

INTRODUCTION

Approximately 90% of hepatocellular carcinomas (HCCs) develop in people with risk factors such as cirrhosis or noncirrhotic chronic hepatitis B infection.[1] In patients with chronic hepatitis B infection without cirrhosis, the 5-year cumulative risk of HCC is up to 3%, whereas in patients with liver cirrhosis the 5-year cumulative risk can reach up to 30%.[2–6] Tumors detected at early stages are amenable to curative therapies such

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as surgical resection, thermal ablation, and liver transplantation, resulting in 5-year survival rates of 80%.[7] Patients with advanced-stage disease have fewer options and poor prognosis. Imaging plays a crucial role in the management of HCC. Given the benefit of early detection, high-risk individuals are recommended to undergo HCC surveillance, typically with ultrasound with or without serum alpha fetoprotein measurement.[8] When a nodule is detected on screening, patients should undergo diagnostic imaging with either contrast-enhanced computed tomography (CT), contrast-enhanced MRI or contrast-enhanced ultrasound (CEUS). All 3 imaging modalities carry high specificity for the diagnosis of HCC when stringent criteria are applied in at-risk patients, thus enabling many HCCs to be diagnosed without biopsy (ie, by imaging alone).

Different imaging diagnostic systems for HCC have been proposed worldwide. The Liver Imaging Reporting and Data System (LI-RADS), the most comprehensive of these, aims to standardize the lexicon, technique, interpretation, and reporting of liver imaging in at-risk patients. LI-RADS is updated by an international and multispecialty consortium informed by evidence and expertise. LI-RADS comprises 4 different imaging modalities, covering 3 imaging contexts (screening/surveillance, diagnosis, and treatment response) with algorithms for each:

1. US LI-RADS for screening ultrasound
2. CEUS LI-RADS for diagnosis
3. CT/MRI LI-RADS for diagnosis and staging
4. TR LI-RADS for locoregional treatment response assessment (a systemic treatment response algorithm has not yet been developed)

Currently, LI-RADS does not apply to nuclear imaging modalities (ie, positron emission tomography), as the benefits of these techniques for HCC diagnosis, particularly in early disease, are unclear.[9]

In 2018, LI-RADS ultrasound and CT/MRI algorithms were incorporated by the American Association for the Study of Liver Diseases (AASLD) into the 2018 practice guidance for HCC, promoting a unified approach for diagnostic, staging, and management recommendations.[10] The AASLD has not yet adopted the CEUS algorithm for diagnosis of HCC or the LI-RADS TR algorithm for treatment response, but the authors anticipate it might do so in the future as evidence continues to accrue and these algorithms mature.

This article focuses on similarities and differences between the CT/MRI diagnostic algorithm (CT/MRI LI-RADS) and the CEUS diagnostic algorithm (CEUS LI-RADS). Both algorithms rely on the dynamic postcontrast imaging features of HCC, leverage the high pretest probability of HCC in at-risk patients, and provide high positive predictive value (PPV) and high specificity in the noninvasive diagnosis of HCC. However, reflecting intrinsic differences between the applied modalities and corresponding contrast agents, the algorithms are not identical. Users should be aware of and consider the unique advantages and disadvantages of CEUS, CT, and MRI when deciding which imaging method to use.

KEY CONCEPTS

Imaging Algorithms Must Be Applied Only in the Appropriate Population

In order to achieve the desired high PPV, LI-RADS should be applied only in a population with high pretest probability of HCC. This at-risk population (ie, LI-RADS population) includes patients with cirrhosis, chronic hepatitis B viral infection, or current/prior HCC. LI-RADS should not be applied to children (<18 years old) or

patients with vascular etiologies of cirrhosis (eg, Budd-Chiari syndrome or cardiac congestion) or congenital hepatic fibrosis.[11] In these circumstances, the pre-test probability for HCC is not as well established and likely lower. For instance, in patients with Budd-Chiari and congenital hepatic fibrosis, the presence of benign hypervascular nodules that resemble HCC at imaging may reduce the specificity of the diagnosis. Ultimately, in the LI-RADS population, PPV for HCC diagnosis is expected to be greater than 95%. CT/MRI and CEUS LI-RADS apply to the same population.

Although it is plausible that the LI-RADS criteria could provide high PPV in populations with less elevated risk, such as patients with longstanding NAFLD (non-alcoholic fatty liver disease) or patients with stage 2 or 3 fibrosis caused by viral hepatitis,[12] there is currently insufficient literature on the diagnostic performance of LI-RADS to recommend widespread application in such populations. From the radiologist's perspective, the diagnosis of cirrhosis for defining an at-risk patient is based on information provided by the referring physician. A complete discussion of how clinicians make the diagnosis of cirrhosis is beyond the scope of this article, but this determination is usually based on clinical context, histology findings (when available), and clinical indicators of advanced liver disease. Quantitative imaging methods such as transient elastography (TE), ultrasound shear wave elastography (SWE), and magnetic resonance elastography (MRE) can assist in the diagnosis of cirrhosis[13,14] by informing the decision to perform liver biopsy, but these technologies usually do not have sufficient PPV to diagnose cirrhosis reliably in the absence of confirmatory biopsy or other findings.

Imaging Studies Must Meet Technical Standards to Yield Desired Results

Although detailed technical descriptions are reserved for the radiology audience, clinicians should be aware of basic technical differences between CT/MRI and CEUS that are relevant for daily clinical practice. CEUS is an advanced form of ultrasound that uses intravenous blood pool microbubble contrast agents for the dynamic characterization of hepatic observations with high temporal resolution. CEUS requires an ultrasound scanner with contrast-specific imaging capability to visualize signals specific to microbubbles, a feature available on most modern commercially available machines. Of note, the addition of contrast to a standard ultrasound examination requires some preparation, including the placement of an intravenous catheter, which is not otherwise needed for ultrasound. Additionally, the coding and billing of standard ultrasound and CEUS differ, requiring separate orders and insurance authorization in the United States. Because the contrast used in CEUS does not impose any nephrotoxic risk, there is no need for renal function testing prior to administration. It is important to note that perfluorobutane, a contrast agent that has prolonged liver uptake because of greater stability and Kupffer cell phagocytosis, has not yet been adopted by CEUS LI-RADS and is not yet approved for use in the United States. Further details on CEUS LI-RADS technical standards, including imaging protocols and techniques, are described elsewhere.[15,16]

CT/MRI examinations also must be performed according to technical standards. Administration of intravenous contrast and acquisition of a multiphase liver protocol (eg, before contrast, late hepatic arterial phase, portal venous phase, and delayed phase images) is mandatory to allow for diagnosis of HCC.[1,17–19] For CT, multidetector CT ($\geq$8 detectors) is a requisite, whereas for MRI, 1.5 or 3 T magnets are required, according to LI-RADS. For additional description of the technical standards, the interested reader is referred to https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/LI-RADS.[20]

Differences Between Contrast Agents Used in Contrast-Enhanced Ultrasound and Computed Tomography/MRI

CEUS contrast agents are considered blood pool (intravascular) agents that do not diffuse out into tissues. CT/MRI contrast agents transition from the intravascular space to the interstitial and/or intracellular space of tissues. MRI contrast agents are divided in 2 major classes based on the ability to be taken up by hepatocytes (extracellular contrast agents [ECAs] and hepatobiliary agents [HBAs]). This difference in the distribution of the contrast agents results in specific imaging features. Most importantly, the feature washout is characterized differently on CEUS than on CT/MRI. The characterization of washout appearance helps in the imaging differentiation between HCC and non-HCC malignancies. The high temporal resolution of CEUS allows for differentiation between early versus late washout, an important distinction to achieve a specific diagnosis. With CEUS, washout is classified into 2 subtypes based on onset and degree. One subtype (early or marked washout) is suggestive of cholangiocarcinoma and other non-HCC malignancies (LR-M), while the other subtype (late and mild washout) indicates HCC (LR-5). Conversely, on CT and MRI with ECA, washout is classified based on morphology. One subtype (peripheral washout) is suggestive of cholangiocarcinoma and other non-HCC malignancies, while the other subtype (nonperipheral) is suggestive of HCC in particular (**Fig. 1** shows an example of LR-5 observation on CEUS and contrast-enhanced CT). On MRI with HBA, washout is characterized based on morphology and onset. Similar to CT and MRI with ECA, peripheral versus nonperipheral washout distinguishes LR-M versus LR-5 observations, but for nonperipheral washout to be considered a feature of HCC, the onset needs to be in the PVP. On CT/MRI, the degree of washout is not taken into account.

Beyond the differences in imaging appearance between CEUS and CT/MRI contrast agents, there are practical considerations also. Microbubble contrast agents used in CEUS have virtually no adverse reactions. Therefore, they can be used for lesion characterization in patients with contraindications to gadolinium-based and iodine-based contrast agents such as allergies or renal dysfunction. Additionally, CEUS is real-time imaging, which eliminates the risk of arterial phase misiming and may be useful to characterize arterial phase hyperenhancement (APHE) deemed equivocal on CT or MRI. CEUS is also useful in differentiating true nodules from pseudolesions such as arterio-portal (AP) shunts encountered on CT and MRI. For these reasons, CEUS is often used as a problem-solving tool for indeterminate lesions on CT or MRI. On the other hand, CEUS requires separate injections for each lesion evaluated, and so is less well suited to patients with multifocal disease or those who require staging of intrahepatic tumor burden and/or extrahepatic spread. CT and MRI allow for assessment of the whole liver and adjacent anatomic structures and are preferred for assessing tumor extent (ie, staging).[10] Finally, CEUS is not currently recognized by the organ procurement and transplantation network (OPTN) and so cannot be used for establishing automatic transplant eligibility, which will be discussed further.

Diagnostic Algorithms Provide Hierarchical Features for Assigning Categories

In LI-RADS, to assign a diagnostic category that reflects the risk of benignity, malignancy or HCC, radiologists appraise combinations of imaging features in accordance to the diagnostic algorithms. On CT/MRI, LI-RADS major imaging criteria for the diagnosis of HCC are size, in combination with nonrim arterial phase hyperenhancement (APHE), enhancing capsule appearance, washout appearance, and threshold growth. For CEUS LI-RADS, major imaging features are size, APHE, and washout (onset and degree). In addition, both CT/MRI and CEUS algorithms list ancillary imaging features

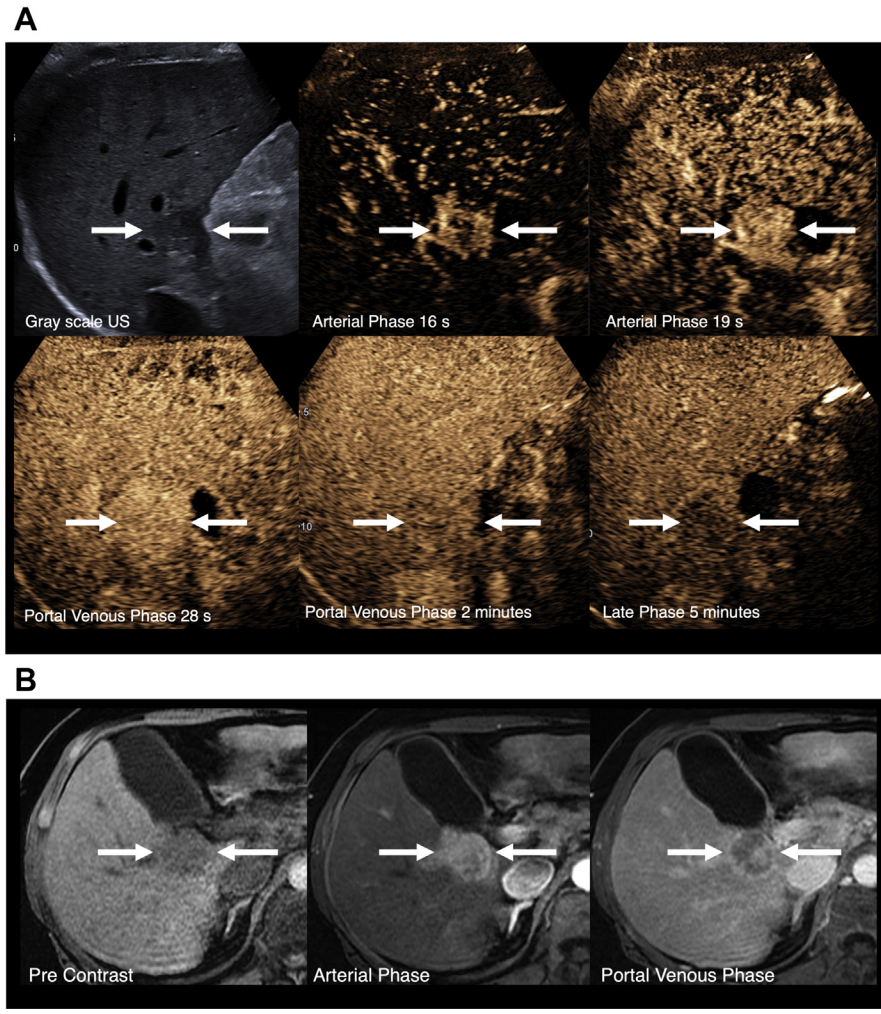

Fig. 1. 62-year-old woman with cirrhosis secondary to chronic hepatitis C viral infection and alcohol abuse. (*A*) Precontrast ultrasound and CEUS images show a 3.0 cm hypoechoic nodule in segment 5. The combination of size ≥10 mm and major features (*arrows*: non rim APHE, late and mild washout at 5 minutes) indicates a CEUS LR-5 lesion (definite HCC). (*B*) Same observation on pre- and postcontrast MRI. The presence of nonrim APHE, washout appearance, capsule appearance (*arrows*), and ≥20 mm are major features of definite HCC (LR-5).

that can be used to increase confidence or adjust the final diagnostic category. These ancillary features (AFs) may favor benignity, malignancy in general, or HCC in particular. For the latter, although AFs can be used to upgrade observations to a higher probability of HCC (ie, LR-4 vs LR-3), they are not specific enough to allow for observations to be upgraded from probably HCC (LR-4) to definite HCC (LR-5) based on their presence. Finally, if the user is still unsure between 2 categories, a tie-breaking rule is applied, whereby the category with lower certainty between the two should be chosen. All these steps are intended to assure the highest possible specificity

for HCC in both algorithms. Fig. 2 shows an LR-5 observation with CT/MRI LI-RADS major imaging features of HCC; the observation also has ancillary features favoring HCC, but these do not contribute to the category assignment in this case.

Diagnostic Algorithms Provide Probabilistic Categories for Diagnosing Hepatocellular Carcinoma

The CT/MRI and CEUS algorithms define 8 diagnostic categories to reflect the relative probability of HCC. Although not identical, each algorithm is applied at the individual observation level and starts with a stepwise decision tree designed to narrow in on nodules of hepatocellular origin that may represent HCC.[11,16] In brief, this stepwise process comprises the following

1. Determine if the imaging study is adequate for categorizing a particular observation that is devoid of significant artifact or technical failure. An observation is categorized as LR-NC (not categorizable) if image omissions or degradation precludes the assessment of its imaging features such that it is not possible to determine if it is more likely benign (ie, should be categorized LR-1 or LR-2) or more likely malignant (ie, should be categorized LR-4, LR-5, or LR-M).
2. The presence of tumor in vein (TIV) should be ruled out. If a positive finding of tumor in vein is detected, an LR-TIV category should be assigned and whenever possible its most likely etiology (due to HCC or non-HCC malignancy) specified.
3. Benign lesions should be recognized. Definitely or probably benign observations are categorized as LR-1 or LR-2, respectively.
4. Observations suspicious for malignancy but not specific for HCC, are assigned LR-M.

If an observation(s) does not fit into one of these categories, it should be assessed using the diagnostic table. The diagnostic table uses the major imaging features of

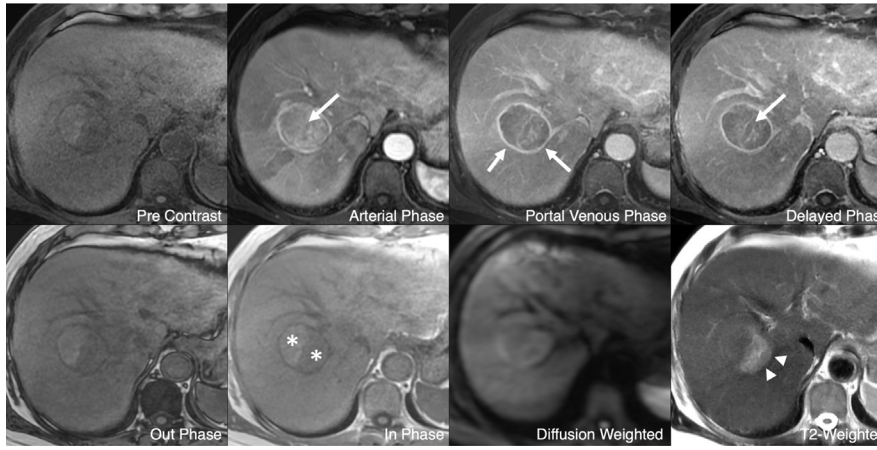

Fig. 2. 67-year-old man, chronic hepatitis C viral infection, pre- and postcontrast MRI. The combination of size ≥20 mm and major features (*arrows*: APHE, washout appearance, and capsule appearance) indicates an LR-5 mass (definite HCC). Incidentally, the mass also shows ancillary features favoring malignancy (*arrowheads*: mild-moderate T2 hyperintensity) and HCC in particular (*asterisks*: mosaic appearance), but these ancillary features do not contribute to the category assignment in this case. The mass would be LR-5 even if all these ancillary features were absent.

HCC to assign categories ranging from intermediate probability to definite HCC (LR-3, LR-4, LR-5). The diagnostic table differs between CT/MRI LI-RADS and CEUS LI-RADS accounting for the different imaging features observed in each modality. Importantly, no single major imaging feature in the diagnostic table is specific enough to categorize an observation as LR-5 (definite HCC)l rather the combination of features stratifies the risk between intermediate, probable or definite. **Fig. 3** shows CT/MRI and CEUS LI-RADS diagnostic algorithms and corresponding tables.

On both CEUS and CT/MRI, the categories LR-3 to LR-5 have increasing probability for being malignant and HCC. Hence, LR-3 observations may be benign or malignant. The LR-4 category implies an observation is highly suspicious for HCC, but there is not 100% certainty. These are often distinctive nodules or masses with imaging features of HCC but lacking a combination of findings that confers high specificity to the diagnosis. LR-5 observations meet criteria for definite HCC, and patients should be assessed for treatment options, usually without need for histologic confirmation.

The CT/MRI criteria for definite HCC are identical between LI-RADS and AASLD, and except for minor differences, are consistent with the European Association of Study of the Liver (EASL) and the Organ Procurement and Transplantation Network (OPTN).[1,17,18] Several publications have shown that CEUS provides high PPV and specificity for the diagnosis of HCC.[21–23] The advances in knowledge led to the endorsement of CEUS for the diagnosis of HCC by the American College of Radiology (ACR), EASL, European guidelines, and various individual countries,[1,19,20,24] although it has not been adopted by AASLD at the time of publication of this article.[10] Current OPTN policies have no mention on the use of CEUS for HCC diagnosis.

The diagnostic performance of the outermost categories (definitely benign [LR-1] and definitely HCC [LR-5]) is extremely high, with reported percentage of HCC in the LR-1 category of 0% and 94% in the LR-5.[21,25] In CT/MRI LI-RADS, the LR-5 category provides high specificity and PPV for the diagnosis of HCC.[26–28] **Table 1** shows

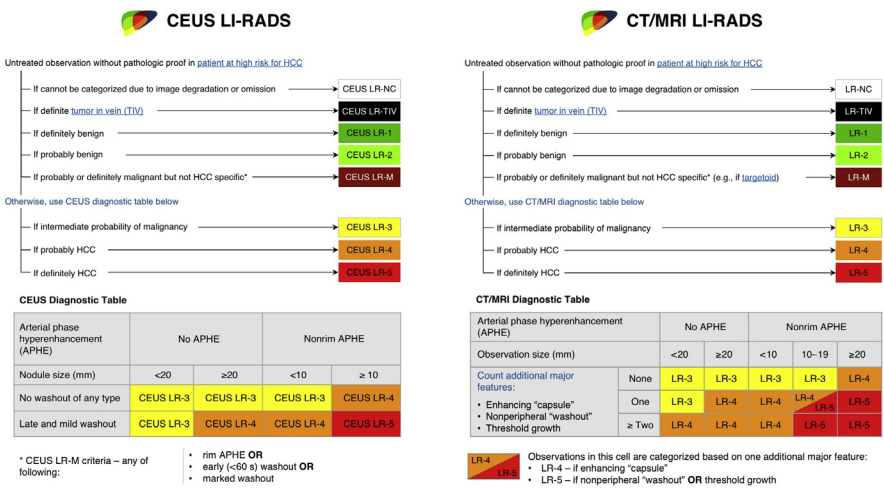

Fig. 3. CT/MRI and CEUS LI-RADS algorithms and diagnostic tables. Both algorithms similarly, although not identically, start with a stepwise decision tree until determining the probability of HCC. Greater differences are noted in the diagnostic table because of differences in imaging features for the diagnosis of HCC. (*From* https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/LI-RADS Accessed Dec 10, 2019; with permission.)

Table 1
Performance of the LR-5 category for the diagnosis of hepatocellular carcinoma in studies using computed tomography/MRI Liver Imaging Reporting and Data System v2018 and contrast-enhanced ultrasound Liver Imaging Reporting and Data System v2017

LI-RADS Algorithm	Specificity	Sensitivity	PPV	NPV	Modality/Contrast
CT/MRI	.	.	88%	.	CT
CT/MRI	90%	78%–80%	94%–96%	58%–69%	MRI/ECA
CT/MRI	89%–98%	67%–81%	92%–99%	50%–79%	MRI/EOB
CEUS	96%–97%	57%–73%	94%–99%	70%	CEUS

Data from Refs.[21,23,28,29]

the reported performance of the CT/MRI and CEUS LR-5 for the diagnosis of HCC. Percentages of HCCs described in prior studies using CT or MRI in the remaining categories are: 0% to 14.8% for LR-2, 16.7% to 40.5% for LR-3, and 47.6% to 74% for LR-4.[23,27,29] Some studies have demonstrated a slightly higher sensitivity of MRI compared with CT, especially for observations less than 20 mm, with HBA-enhanced MRI having the highest sensitivity.[30] Nevertheless, LI-RADS provides 1 single diagnostic algorithm (CT/MRI LI-RADS) and does not recommend 1 cross-sectional method over another, recognizing that the choice of imaging techniques and contrast agents may depend on clinical and institutional factors and the radiologist's expertise. For CEUS LI-RADS, in 2 large studies with more than 1000 observations each, the rates of HCC in the LR-1, LR-2, LR-3, LR-4, and LR-5 categories were 0%, 0%, 11.5% to 47%, 72.3% to 86.0%, and 93.3% to 98.5%, respectively.[21,22]

Not all Malignancies Are Hepatocellular Carcinoma–the Role of LR-M

The LR-M category (probably or definitely malignant, not specific for HCC) describes an observation that is highly suspicious for malignancy but cannot be definitively categorized as HCC. The LR-M category was designed to preserve the specificity of the LI-RADS algorithm for diagnosis of HCC while not losing sensitivity for the diagnosis of malignancy.[31] Accordingly, the LR-M category has high sensitivity for liver malignancies overall, although the performance parameters for this category may vary because of different study designs and populations, and percentages of combined tumors (cHCC-CCA) that impose a diagnostic challenge on imaging.[32–34] The imaging features of LR-M differ between CEUS and CT/MRI. CT/MRI imaging features of LR-M dominantly are described with targetoid morphology or nontargetoid masses that do not meet LR-5 criteria but have infiltrative appearance, marked diffusion restriction, or necrosis. Targetoid appearance includes rim enhancement in the arterial phase (rim APHE), peripheral washout, and progressive central enhancement on delayed phases.[11] Of note, any of these features may be seen in isolation and are sufficient for assigning LR-M categorization. CEUS LI-RADS features of LR-M also include a targetoid appearance (ie, rim APHE). However, unlike CT/MRI, the assessment of washout is based on the time of onset and degree and not morphology. The presence of early (within 60 seconds) and marked washout (observations becoming very dark) are features of LR-M on CEUS.[16] **Fig. 4** shows an example of LR-M observation on CEUS and CT. Conversely, the combination of nonrim APHE with late (onset after 60 seconds) and mild washout permits diagnosis of HCC with almost 99% PPV in the at-risk population.[21]

Almost any liver malignancy can show features of LR-M, although the most common entities in the population of patients at risk for HCC are intrahepatic

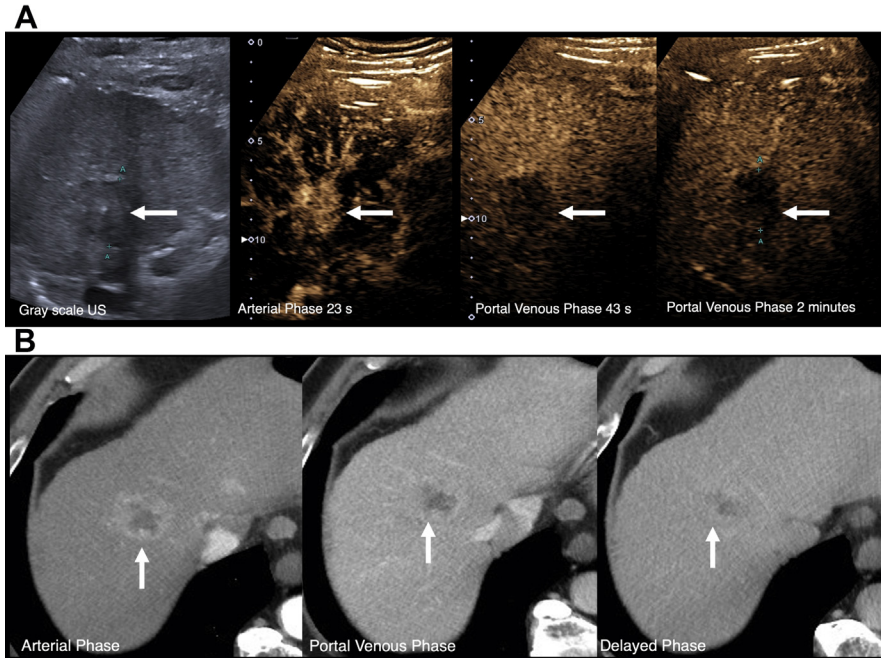

Fig. 4. 62-year-old man with cirrhosis secondary to chronic hepatitis C viral infection and alcohol abuse. (*A*) Gray scale ultrasound and CEUS showing a 32 mm hypoechoic nodule in the right liver lobe. The nodule shows nonrim APHE and early (<1 min) and marked washout. Both early and marked washout is a major feature for CEUS LR-M and typical washout pattern for nonhepatocellular malignancy. (*B*) Pre- and post-contrast CT images show major features for LR-M (*arrows*). Rim APHE and progressive central enhancement with peripheral washout. Histology results showed an intrahepatic cholangiocarcinoma. Different washout pattern is seen between the pure intravascular microbubble contrast agent for CEUS and small molecular contrast agent for CT (and MRI).

cholangiocarcinoma (ICC), combined tumors (cHCC-CCA), and atypical HCC. A common misconception is that LR-M means non-HCC malignancy. Rather, LR-M may still be HCC. The true percentage of LR-M lesions that are subsequently proven to be HCC on biopsy is not fully understood. In a meta-analysis, CT/MRI LR-M observations revealed 36% were HCC (95% confidence interval [CI]: 26%–48%), and 93% overall were malignant (95% CI 87%–97%).[25] An analysis of 288 CEUS LR-M lesions showed 59.7% (172/288) were HCCs; 33% (95/288) were non-HCC malignancies, and 7.3% (21/288) were benign.[22] Hence, LR-M observations should undergo multidisciplinary discussion of diagnostic and treatment options.

The differentiation between HCC from other malignancies in patients with cirrhosis has critical management and prognostic implications. Patients with HCC within stage T2 are eligible for curative treatment through transplantation, but transplantation is often contraindicated in patients with non-HCC malignancies because of the poor long-term survival and high recurrence rates.[35] LI-RADS aims to achieve a very high specificity/PPV for HCC to avoid transplantation misallocation. It is important to note, however, that because of the stringent nature of the LI-RADS criteria, not all HCCs are categorized as LR-5, and some may be categorized as LR-3, LR-4 ,or LR-M.[28] Rarely, other malignancies may potentially be categorized as LR-5; cHCC-

CCA may have imaging features from both lineages, and up to 54% of these lesions may be categorized LR-5.[32]

Emerging data suggest that imaging features and the final LI-RADS category may correlate with biologic behavior and provide prognostic information, regardless of the pathologic diagnosis. Choi and colleagues[33] described that among HCCs, tumors exhibiting imaging features of LR-M had worse overall survival and recurrence-free survival than tumors categorized as LR-4 or LR-5. In a study by Jeon and colleagues[34] cHCC-CCA categorized as LR-M on imaging showed higher recurrence rates than cHCC-CCA categorized as LR-4 or LR-5. Although these retrospective studies suggest that imaging information might have prognostic value, prospective trials are needed to determine how this information should be used in guiding management decisions.

MANAGEMENT TAILORED TO CATEGORY

The management of observations detected on imaging in patients at risk for HCC usually follows guidelines proposed by individual medical societies. These guidelines are often broad to accommodate institutional practices, clinical scenarios, and treatment options inherent to certain geographic regions or populations. In 2018, CT/MRI LI-RADS was incorporated into the AASLD practice guidelines for HCC, leading to a unified management algorithm.[17] Nevertheless, it is important to note that these are informative recommendations, and the AASLD/LI-RADS algorithm does not dictate management. Management decisions should incorporate other clinically available information and institutional practices, ideally supported by multidisciplinary discussions. **Fig. 5** illustrates AASLD-LI-RADS unified management algorithm (CT/MRI) and CEUS LI-RADS management recommendations, which are not currently endorsed by AASLD.

Observations categorized as LR-5 are considered definite HCC, and therefore, staging and treatment planning are recommended without the need of additional imaging or invasive tests. Eventually, biopsy can be pursued in certain scenarios, such as the need for molecular profiling to determine systemic therapy options or in clinical trials.

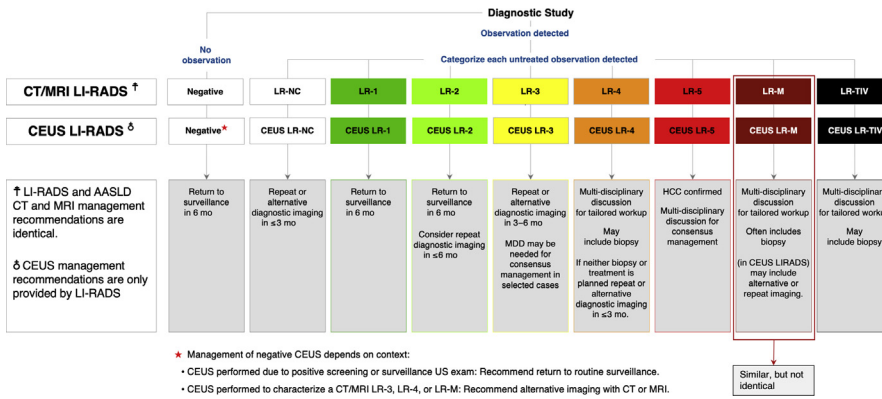

Fig. 5. CT/MRI AASLD-LI-RADS and CEUS LIRADS management recommendations condensed. Both algorithms are similar with minor differences noticed for negative studies and in the LR-M category. (*Adapted from* https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/LI-RADS. Accessed Dec 10, 2019; with permission.)

CT/MRI LR-5 observations count toward T staging to determine patient eligibility for transplantation. In the United States, OPTN is the organization that regulates organ allocation for transplantation. The criteria for definite HCC are similar between LI-RADS and OPTN, with the exception of observations 10 to 19 mm in size, with APHE and washout appearance. According to LI-RADS, these observations meet criteria for LR-5, whereas they are not considered definite HCC by OPTN (OPTN Class 5), and hence, do not count toward T staging.[36] Additionally, OPTN does not routinely recognize CEUS LR-5 for transplantation eligibility.

Management of observations with high probability of malignancy but not definite HCCs (LR-4 and LR-M observations) should be individualized based on specific patient factors and multidisciplinary discussions. Biopsy may be recommended for LR-4 observations when it is critical to obtain a definitive HCC diagnosis for transplant eligibility or resection. LR-M observations are commonly biopsied to dictate appropriate therapy for the underlying malignancy. For observations categorized as LR-NC, both algorithms recommend repeat or alternative imaging within 3 months. LR-1 and LR-2 observations should return to routine surveillance at 6-month intervals, while LR-3 observations should undergo short follow-up imaging in 3 to 6 months.[17]

Selection of Modality: Contrast-Enhanced Ultrasound or Computed Tomography/MRI

Institutional, societal, or geographic practices and recommendations affect the choice of imaging modality. Currently, US guidelines only recognize CEUS as a problem-solving tool and recommend CT/MRI for characterizing liver lesions.[17]

At this time, AASLD and OPTN have not adopted CEUS as a tool for the definitive diagnosis of HCC. EASL and the Asian Pacific Association for the Study of the Liver Disease (APASL) recommend CEUS,[1,19] contrast-enhanced CT, or MRI for characterizing nodules detected during surveillance. CEUS for noncardiac applications was introduced in the United States much later than in Asian and European countries because of its late approval by the US Food and Drug Administration (FDA) in April 2016. As a result, the availability and recognition of CEUS in the United States remain low.

In addition to societal and local practices, modality selection should also take into account the advantages and limitations of each individual method. For example, CEUS can immediately characterize an observation after it is located on surveillance ultrasound, a potential cost- and time-effective approach that minimizes loss to follow-up. Its use over more expensive cross-sectional modalities could also be favored in patients with risk factors other than cirrhosis, as less heterogeneous background liver parenchyma could yield higher diagnostic accuracy to this imaging modality. Recent studies have shown that CEUS may provide improved visibility and higher effectiveness for imaging-guided ablation therapies for primary liver tumors.[37] Conversely, in the setting of tumor resection or transplantation, CT/MRI would likely be preferred to concurrently diagnose and stage the malignancy. Additional research is required to assess the preferred use of HBA to provide balance between sensitivity and specificity ECA in specific clinical scenarios as recommended by some medical societies.[19]

SUMMARY

LI-RADS provides a standardized and rigorous imaging system that aims to improve clinical practice for the care of patients with or at risk for HCC. Although CT/MRI and

CEUS LI-RADS diagnose HCC in at-risk patients with comparably high specificity and PPV, clinicians should be aware of the inherent advantages and limitations of the individual modalities to maximize the utility of the algorithms. Familiarity with the similarities and differences between CT/MRI LI-RADS and CEUS LI-RADS will allow for efficient and appropriate clinical decisions based on individualized patient factors.

In conclusion, the adoption of LI-RADS improves the communication among health care professionals and researchers participating in the care of patients with or at risk for HCC. Its probabilistic rather than binary approach provides clear, granular information to guide personalized management strategies. Additionally, the standardization of many aspects of HCC imaging not only results in increased accuracy of the current methods, but also facilitates the use of clinical data for further refinements and improvements, as well as the development of new clinical practices.

DISCLOSURE

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