# HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

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## Current Status of the Liver Imaging Reporting and Data System in Hepatocellular Carcinoma

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**G&H** What are the current uses of the Liver Imaging Reporting and Data System in hepatocellular carcinoma, and what are its main categories?

**VC** There are currently 3 main contexts of use for the Liver Imaging Reporting and Data System (LI-RADS) in hepatocellular carcinoma (HCC). One is surveillance, for which there is an ultrasound algorithm. Another is diagnosis, which can be performed with either computed tomography (CT)/magnetic resonance imaging (MRI) or contrast-enhanced ultrasound (CEUS), each of which has an algorithm. The third use is treatment-response assessment, which currently can be done with CT/MRI following nonradiation-based locoregional therapies. In the next several months, CEUS assessment following nonradiation-based locoregional therapies and CT/MRI assessment for postradiation treatment will be released.

The LI-RADS categories for HCC are specific to the 2 diagnostic algorithms. The categories for the CT/MRI algorithm are the same as those for the CEUS algorithm. The categories range from LR-1 to LR-5, in which LR-1 is definitely benign observation and LR-5 is definite HCC. Additional categories include LR-M (probably or definitely malignant, not HCC specific), LR-TIV (definite tumor in vein), and LR-NC (noncategorizable, meaning that technical limitations prevent assessment). Each category reflects the probability a lesion is malignant and the probability it is HCC.

**G&H** How have the algorithms been integrated into guidance from other organizations?

**VC** The American Association for the Study of Liver Diseases (AASLD) initially adopted LI-RADS in 2018, when LI-RADS updated its LR-5 category. The edits to LR-5 category criteria were approved by the LI-RADS Steering Committee, and then the CT/MRI algorithm was adopted by AASLD guidance. Thus, the AASLD's 2018 guidance does not specify its own diagnostic criteria, but rather refers to the LI-RADS 2018 CT/MRI diagnostic criteria.

AASLD guidance was updated in 2023, and the management schema became slightly more involved and complex, including features other than just imaging. The updated ultrasound LI-RADS surveillance algorithm was just published on the American College of Radiology (ACR) website in February 2024, and now it is congruent with last year's AASLD guidance in terms of incorporating visualization scores into a management schema.

In addition, there had been slight differences between the definite HCC criteria used by LI-RADS and the United Network for Organ Sharing (UNOS). Some transplant centers resisted adopting LI-RADS, as they believed they had to be committed to using UNOS definitions. As of 2023, UNOS has fully adopted the LR-5 (definite HCC) category definitions of LI-RADS for Organ Procurement and Transplantation Network (OPTN) Class 5 so that all LR-5 observations are now OPTN-5 observations.

**G&H** What were the most important changes introduced in the last version of LI-RADS, and what further changes are expected soon?

**VC** The last update to the CT/MRI diagnostic algorithm

was in 2018. The main change was removing the requirement for ultrasound visualization to categorize a 10- to 19-mm observation with nonrim arterial phase hyperenhancement and washout as LR-5 in order to mirror the criteria set forth by the AASLD. An additional small change was the simplification of the definition of threshold growth. Now only a size increase of 50% or greater in 6 months or less is considered to be threshold growth; all other changes in size are considered to be subthreshold growth. Previously, there had been 2 additional ways to define threshold growth—100% size increase in 12 months or new observation of more than 10 mm. These now meet the criteria for subthreshold growth, which is an ancillary feature of malignancy.

LI-RADS has several updates coming in the pipeline. New algorithms for treatment response assessment of lesions managed with radiation-based therapy and for assessment using CEUS are coming imminently. These algorithms, as well as an updated algorithm for CT/MRI treatment response assessment following nonradiation locoregional treatments, were approved by the LI-RADS Steering Committee. The core documents will soon be published on the ACR website (https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/LI-RADS).

### G&H What is the probability of an LR-3 or LR-4 being or developing HCC in the future?

**VC** This is an important but complex topic of much investigation. Large meta-analyses have demonstrated the proportions of lesions in each category that are HCC. Looking at a group of LR-3s, at that particular moment approximately 31% are HCC and 36% are malignant. For LR-4s, 64% are HCC and 65% are malignant.

In terms of outcomes, the data for LR-3 are somewhat messy because different studies have different inclusion criteria, follow-ups, and so on. According to data from several retrospective studies, within 12 to 24 months 23% to 60% will remain LR-3, 15% to 68% will decrease in category, and 7% to 24% will progress to either LR-5 or LR-M. According to similar retrospective studies for LR-4, within 6 to 12 months approximately 44% will remain LR-4, 13% will be down-categorized to LR-3, and 33% and 38% will become LR-5 or LR-M, respectively.

Only 1 prospective study and a few retrospective but longitudinal studies have assessed the cumulative incidence of HCC over time. The cumulative incidence of *classic* HCC in LR-4 is a nearly straight line. By 48 months of follow-up, approximately 85% of LR-4s will become hypervascular HCCs, meeting the criteria for LR-5. For LR-3s, the cumulative incidence within the first 36 months is also a relatively straight line but with a much lower slope. Approximately 20% will become HCCs by 36 months. The slope of the line changes dramatically at this point, and by 48 months the cumulative incidence of HCC is just over 60%. Thus, it all depends on how long patients are followed.

Another study looked at cumulative progression of LR-3 to LR-5 and followed patients just less than 36 months. In that data set, the cumulative incidence was just under 40% by 30 months, and it did not matter whether CT or MRI was used; the cumulative incidence was fairly the same.

### G&H What are the positive likelihood ratio, positive predictive value, and specificity of LR-5 for diagnosing HCC?

**VC** The positive likelihood ratio of LR-5 is between 10 and 17, and the positive predictive value is consistently between 92% and 98% in studies. A meta-analysis of all versions of the LI-RADS CT/MRI diagnostic algorithm found that the positive predictive value for HCC for the LR-5 category is 95%. Interestingly, that is independent of modality. These data are very stable and mean that a lesion detected on any modality (CT or MRI with extracellular contrast agent or MRI with gadoxetate disodium) meeting the criteria for LR-5 has a 95% probability of being HCC.

Sensitivity is a different story. The criteria for LR-5 are fairly stringent; only 50% to 70% of HCCs meet those criteria. That means between 30% and 50% of all HCCs do not meet the criteria for LR-5. Many will fall into the LR-4 category, some will fall into the LR-3 category, and a number of them will fall into the LR-TIV or LR-M categories, the latter of which has prognostic implications.

### G&H How can CEUS currently be used for HCC diagnosis?

**VC** The use of CEUS for HCC diagnosis is well established. According to meta-analyses, the performance of CEUS and CT/MRI is comparable. The categories behave similarly; there are minor differences in terms of positive predictive value for LR-3 depending on modality, as a good number of LR-3s on CT or MRI are atypical vascular shunts, which is not a problem with CEUS. The proportion of HCC in LR-3s found with CEUS is higher than with CT/MRI, but otherwise the categories have very similar proportions of HCC.

### G&H Which MRI sequences are required?

**VC** An entire section of the LI-RADS manual on the ACR website is devoted to optimization of MRI protocols. Required MRI sequences include late arterial phase,

portal venous phase, and delayed phase with extracellular contrast agents, and then late arterial phase, portal venous phase, and hepatobiliary phase with gadoxetate disodium. Also required are in- and out-of-phase images, which are used to detect intracellular fat in the background of the liver and within the lesion itself. T2-weighted sequences are required as well. Those are all needed to meet the technical requirements for LI-RADS. The LI-RADS manual also provides guidance regarding technical parameters (eg, slice thickness), as well as optimization of protocols.

In addition, the diffusion-weighted sequence is optional, although strongly recommended. It is a finicky sequence that requires extra effort for quality optimization, which is why it is recommended but not required. It may be challenging for some centers to put resources into optimizing the sequence, although it can be a tremendous help.

### G&H Does LI-RADS offer any guidance for multifocal HCC?

**VC** For multifocal HCC, it may be detrimental to describe in detail every single of the multitudes of lesions for fear of losing the forest for the trees. The LI-RADS reporting guidance says to report up to 5 lesions with the highest categories individually and report the rest of the lesions in aggregate, including locations, size, imaging features, and category. The reporting guidance for multifocal disease is not as rigid as it is for individual lesions, and there is some room for a radiologist to take a more individualized approach.

### G&H Can LI-RADS be integrated with abnormal laboratory findings (eg, alpha-fetoprotein, des-γ-carboxy prothrombin)?

**VC** At this time, categories are not changed based on any of those laboratory results. Once a patient is diagnosed with LR-4, LR-5, LR-M, or LR-TIV, they are supposed to undergo multidisciplinary discussion. For patient-specific management decisions, the multidisciplinary team will probably take into account any abnormal laboratory findings. For example, my colleagues and I have had patients referred to a tumor board with an LR-M observation and extremely elevated alpha-fetoprotein, and the decision was to assume that this was HCC and not undergo biopsy, even though LR-M observations are usually biopsied because approximately 65% are non-HCC malignancies. However, this decision is up to the multidisciplinary tumor board and patient. Some patients are quite averse to undergoing interventions, so alpha-fetoprotein, des-γ-carboxy prothrombin, and other findings may be integrated to try to avoid biopsy, even when indicated.

### G&H What are the biggest gaps in LI-RADS currently?

**VC** There are a number of gaps, some of which are easily addressable and some of which will require some effort in the coming years. One gap in the latter category involves the use of pathology as a gold standard in literature, even though pathology is imperfect. HCC is heterogeneous, and there may be undersampling or incorrect sampling of lesions. Also, imaging techniques have become so good at diagnosing HCC noninvasively that the majority of LR-5 observations do not get biopsy confirmation. Thus, the studies that do include pathology as a gold standard may include a skewed sample of atypical HCCs selected because they needed a biopsy. Finally, there are recent studies that showed that imaging features, including LI-RADS category, are predictive of outcomes better than histologic diagnosis. All of these issues have been leading to a shift toward focusing on more outcome-based studies instead of using pathology as the final stamp of approval.

An additional gap in current CT/MRI diagnostic LI-RADS is not allowing assessment of transitional- or hepatobiliary-phase hyperintensity as washout. This is a large issue, especially in Eastern populations, which have high proportions of patients with hepatitis B and are more aligned in the use of gadoxetate disodium. Data have shown that allowing transitional- or hepatobiliary-phase hyperintensity as a major feature increases sensitivity of HCC diagnosis. However, it also decreases specificity by 5% to 7%. In Western populations, there is emphasis on specificity because of the need to allocate organs for transplantation, whereas in Eastern populations, sensitivity is of greater importance to allow treatment, such as resection, at an earlier stage. The solution for these competing priorities remains a major gap, and more data are needed to close it. There is some early evidence that allowing washout assessment in transitional or hepatobiliary phases may not impact the specificity of LR-5 as much if the LI-RADS algorithm is followed correctly—that is, when all LR-1, LR-2, and LR-M observations are excluded before the LI-RADS diagnostic table is applied. However, all these studies were performed in Eastern populations, and validation is needed in Western cohorts. Once validated in Western cohorts, transitional-phase and hepatobiliary-phase hyperintensity will probably become major features in future LI-RADS algorithms.

Interreader agreement constitutes another gap, as it is imperfect. Based on meta-analysis, interreader agreement for major features is moderate, with kappas in the 0.7 range. Different readers may choose to compare a lesion to a different part of liver background or focus on a different area of the lesion when comparing it to the

liver background. These differences, along with lesional and background liver heterogeneity commonly seen in patients with parenchymal liver disease, contribute to imperfect interreader agreement. This gap may not be solvable without developing a quantitative assessment for imaging features, for example with artificial intelligence, in addition to qualitative assessment.

Intermodality agreement is another gap. CT and MRI may result in different LI-RADS categories in a fairly substantial number of cases. There are inherent differences between CT and MRI. Additionally, some imaging features can only be assessed on one modality (or are better assessed on one), resulting in categories that may disagree. To close this gap, the goal is to eventually create large multi-institutional data registries, which will allow for precise calculation of HCC risk in a given observation in a given patient on a given modality.

Some HCCs behave more aggressively than others, but only 2 prognostic indicators are currently captured by LI-RADS: LR-TIV, which portends a bad prognosis because of macrovascular invasion, and LR-M, which data have shown is associated with poorer recurrence-free and overall survival compared with LR-5. Work is underway on this issue, and a number of new imaging features that are associated with prognosis (ie, prognostic imaging features) have been established in recent years. It may be possible to integrate them into assessment so that LI-RADS has a prognostic component rather than being a purely diagnostic system. However, the data on how to incorporate these prognostic features and how they should guide management decisions are not yet available.

Finally, the heterogeneity of LR-3s and LR-4s poses management issues, especially LR-3 observations, which need to be followed closely. Because frequent follow-up results in patient anxiety and mounting costs, identifying the subgroup of LR-3s and LR-4s that will progress faster would improve patient care by allowing more nuanced follow-up recommendations. The National Institutes of Health has recognized this important gap in knowledge and published a request in 2022 for proposals of multi-institutional studies to address this issue.

## **G&H** What are the future objectives of LI-RADS?

**VC** Closing the aforementioned gaps is an important objective of LI-RADS in the near future. The overarching long-term goal is to create a system that has more precise prediction of the risks of HCC and malignancy and some component of prognostication. This is a lofty goal, 10 to 20 years down the line, that likely will require the use of artificial intelligence and may incorporate patient-specific factors (eg, smoking or diabetes), lesion-specific factors (eg, major and ancillary features, taking into consideration the modality being used), and liver-specific factors (eg, texture analysis as it may reflect the immune microenvironment of the liver). All of these factors would be integrated into a model, likely using artificial intelligence given its complexity. The result would give the exact probability of a lesion being HCC and the probability of the lesion responding to a particular treatment based on all of the aforementioned factors. This sounds complex, and clearly is not implementable with the tools available right now. However, this is the ultimate goal, where management can be individualized based on factors related to the patient, lesion, and liver for a more precise estimation of HCC probability and prediction of biological behavior and outcomes. More data are needed, in addition to creation of registries and collaboration with colleagues on the clinical side.

***Disclosures***

*Dr Chernyak has served as a consultant for Bayer and Gilead.*

## Suggested Reading


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