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Radiology

REVIEWS AND COMMENTARY • REVIEW

LI-RADS: Looking Back, Looking Forward

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Since its initial release in 2011, the Liver Imaging Reporting and Data System (LI-RADS) has evolved and expanded in scope. It started as a single algorithm for hepatocellular carcinoma (HCC) diagnosis with CT or MRI with extracellular contrast agents and has grown into a multialgorithm network covering all major liver imaging modalities and contexts of use. Furthermore, it has developed its own lexicon, report templates, and supplementary materials. This article highlights the major achievements of LI-RADS in the past 11 years, including adoption in clinical care and research across the globe, and complete unification of HCC diagnostic systems in the United States. Additionally, the authors discuss current gaps in knowledge, which include challenges in surveillance, diagnostic population definition, perceived complexity, limited sensitivity of LR-5 (definite HCC) category, management implications of indeterminate observations, challenges in reporting, and treatment response assessment following radiation-based therapies and systemic treatments. Finally, the authors discuss future directions, which will focus on mitigating the current challenges and incorporating advanced technologies. Tha authors envision that LI-RADS will ultimately transform into a probability-based system for diagnosis and prognostication of liver cancers that will integrate patient characteristics and quantitative imaging features, while accounting for imaging modality and contrast agent.

In 1923, the first issue of *Radiology* had 10 original research articles, three of which were devoted to cancer. In the 100 years since, cancer-related research has continued to dominate the published content, so much so that a separate journal, *Radiology: Imaging Cancer,* was launched in 2019. Medical imaging has become an integral component of oncologic diagnosis, staging, and management. Hepatocellular carcinoma (HCC) diagnosis can be established by imaging alone without biopsy confirmation and epitomizes the importance of imaging in care in patients with cancer (1,2). Increased reliance on imaging and important research over the last 2 decades have spurred the development of multiple imaging systems for HCC diagnosis worldwide (3). The most comprehensive of these, the Liver Imaging Reporting and Data System (LI-RADS), was initially released in 2011 with the support of the American College of Radiology (4). In this article, we summarize LI-RADS development, describe its current structure, discuss current challenges and knowledge gaps, and outline a road map for future refinement.

Overview of LI-RADS History

Primary liver cancer, which is predominantly HCC, can be cured if detected early but is generally fatal if diagnosed at an advanced stage. To enable noninvasive diagnosis and to avoid unnecessary biopsy, diagnostic imaging criteria for HCC were developed in the early 2000s, but these were neither standardized nor part of a comprehensive system with clear and well-defined terminology (3). Creation of LI-RADS filled this gap.

Prototypes of LI-RADS were developed in 2006 in two United States medical centers, the University of California, San Diego, and Thomas Jefferson University, to standardize HCC imaging across institutions (5). The American College of Radiology convened a steering committee 2 years later to further develop LI-RADS into a more universal system. Released in 2011, the first official version of LI-RADS provided criteria for assessing liver observations in high-risk adult patients using CT and MRI with extracellular contrast agents. Modeled on the Breast Imaging Reporting and Data System (hereafter, BI-RADS), LI-RADS provided a framework for reproducible imaging interpretation, actionable communication, and precise terminology, including categorization of probability of HCC.

Differences in the management of liver versus breast malignancies mandated fundamental differences between LI-RADS and BI-RADS. For example, LI-RADS categories are assigned at the observation level, as opposed to the patient-level approach of BI-RADS. Whereas the goal of BI-RADS is to identify high-risk lesions requiring biopsy, LI-RADS aims to achieve near-perfect specificity for HCC diagnosis (LR-5; definite HCC) so that definitive treatment does not require biopsy.

Abbreviations

AASLD = American Association for the Study of Liver Diseases, AF = ancillary feature, CEUS = contrast-enhanced US, HCC = hepatocellular carcinoma, LI-RADS = Liver Imaging Reporting and Data System, PPV = positive predictive value

Summary

Despite the growth and refinement of the Liver Imaging Reporting and Data System, or LI-RADS, since its initial release in 2011, multiple challenges remain and will be addressed in coming years.

Essentials

- Liver Imaging Reporting and Data System (LI-RADS), a comprehensive system for categorizing observations in patients with liver cirrhosis or chronic hepatitis B, includes algorithms for hepatocellular carcinoma (HCC) surveillance, diagnosis, staging, and treatment response assessment following local-regional treatments.
- Since 2011, LI-RADS has evolved, covering all major liver imaging modalities and contexts of use and has developed its own lexicon, report templates, and supplementary materials.
- As scientific evidence accumulates and technological advances are made, LI-RADS will transform into a probability-based system, integrating qualitative and quantitative imaging features and patient characteristics, for diagnosis and prognostication of liver cancers.
- Key remaining gaps in LI-RADS include optimization of surveillance strategies, validation and refinement of US visualization scores, reducing the perceived complexity of the algorithms, improving the sensitivity while maintaining specificity of LR-5 category for HCC, optimization of management of indeterminate observations, global unification of diagnostic systems, development of user-friendly structured reporting, and development of treatment response assessment for radiation-based therapies.

Since 2011, the system has undergone multiple iterations, driven by accumulated data and user feedback, and expanded to include four algorithms: US LI-RADS for HCC surveillance, contrast-enhanced US (CEUS) LI-RADS for HCC diagnosis, CT/MRI Diagnostic LI-RADS for HCC diagnosis and staging, and Treatment Response Assessment LI-RADS (or LI-RADS TRA) for evaluation following local-regional therapy. All LI-RADS algorithms include a set of categories, each reflecting a certain probability of disease (Fig 1) and provide precise criteria for every category. Additionally, LI-RADS released supporting documents to accompany the algorithms (eg, the core materials and manual), as well as a lexicon of liver imaging terminology (6).

In 2018, the algorithms and management recommendations of US and CT/MRI Diagnostic LI-RADS were integrated into the practice guidance of the American Association for the Study of Liver Diseases (AASLD) (1). In 2022, the Organ Procurement and Transplantation Network announced it would update its class 5 criteria to align with the LR-5 (definite HCC) category (7). Landmarks in LI-RADS development are summarized in Figure 2.

Current Status

LI-RADS governance (Fig 3) includes a steering committee that oversees multiple working groups, each tasked with unique and complementary responsibilities and deliverables, and liaises with other clinical organizations, such as the AASLD and Organ Procurement and Transplantation Network. Through education at national and international meetings, publications, and dissemination of free materials on the American College of Radiology website, LI-RADS has established a global influence in clinical care at both academic and community centers (8). To date, LI-RADS materials have been translated into 12 languages (9). In 2022, the use of LI-RADS was included in a set of quality measures for HCC care by the Practice Metrics Committee of the AASLD, solidifying its use for standard of care (10).

In addition to changing clinical radiology practice, LI-RADS has had an important impact in research. From 2017 to 2019, 57% of scientific studies on MRI diagnosis of HCC used LI-RADS terminology, and 61% used LI-RADS diagnostic criteria (11). Before LI-RADS, there was inconsistency in the way imaging features, such as arterial phase hyperenhancement, were defined for each research study. In other words, terms were "study specific" and may or may not have meant the same thing across different studies. A comparison of studies before (2011–2013) and after (2017–2019) the initial release of LI-RADS showed that the use of study-specific definitions for major features has decreased from 80% to 25%, and the use of study-specific imaging diagnostic criteria for HCC has decreased from 69% to 12% (11). This paradigm shift facilitates greater consistency and potential to synthesize data between studies.

The clinical adoption of LI-RADS is supported by extensive validation. To date, PubMed lists more than 650 publications on LI-RADS (43 in *Radiology*), including 36 systematic reviews and/or meta-analyses. These have addressed the diagnostic performance of categories and imaging features, interreader reliability, and intermodality comparison using the various algorithms. CT/MRI Diagnostic LI-RADS is the oldest and most well studied of the algorithms. Recent meta-analyses confirmed the intended probabilities of diagnostic categories, where the probability of HCC increases from LR-1 (definitely benign) to LR-5 (definite HCC), and nearly all observations in LR-M (probably or definitely malignant, not HCC specific) are malignant (Fig 4) (12,13). LR-4 (probable HCC) and LR-5 categories with CEUS and CT/MRI have nearly identical probabilities of HCC and malignancy (14).

Challenges and Gaps in Knowledge

Despite major successes achieved since its initial release, challenges and gaps remain. The following section discusses areas of continued evolution of LI-RADS.

HCC Surveillance

The LI-RADS US algorithm, released in 2017 and integrated into the AASLD HCC practice guidance in 2018 (1), provided the first and only standardized approach for performing, interpreting, and reporting of US for HCC surveillance.

US is the main imaging tool for HCC surveillance across the world. US LI-RADS pioneered a visualization score (A–C), in addition to a detection category, to communicate the quality of obtained images (Fig 1). The visualization score was created by expert opinion and adapted from the breast density assessment in BI-RADS. Supporting evidence is emerging (15,16), and a recent study confirmed that a visualization score of "C" is associated with reduced detection sensitivity for HCC (17). However, visualization score is inherently subjective and has only moderate interreader agreement (18,19). Improved reliability

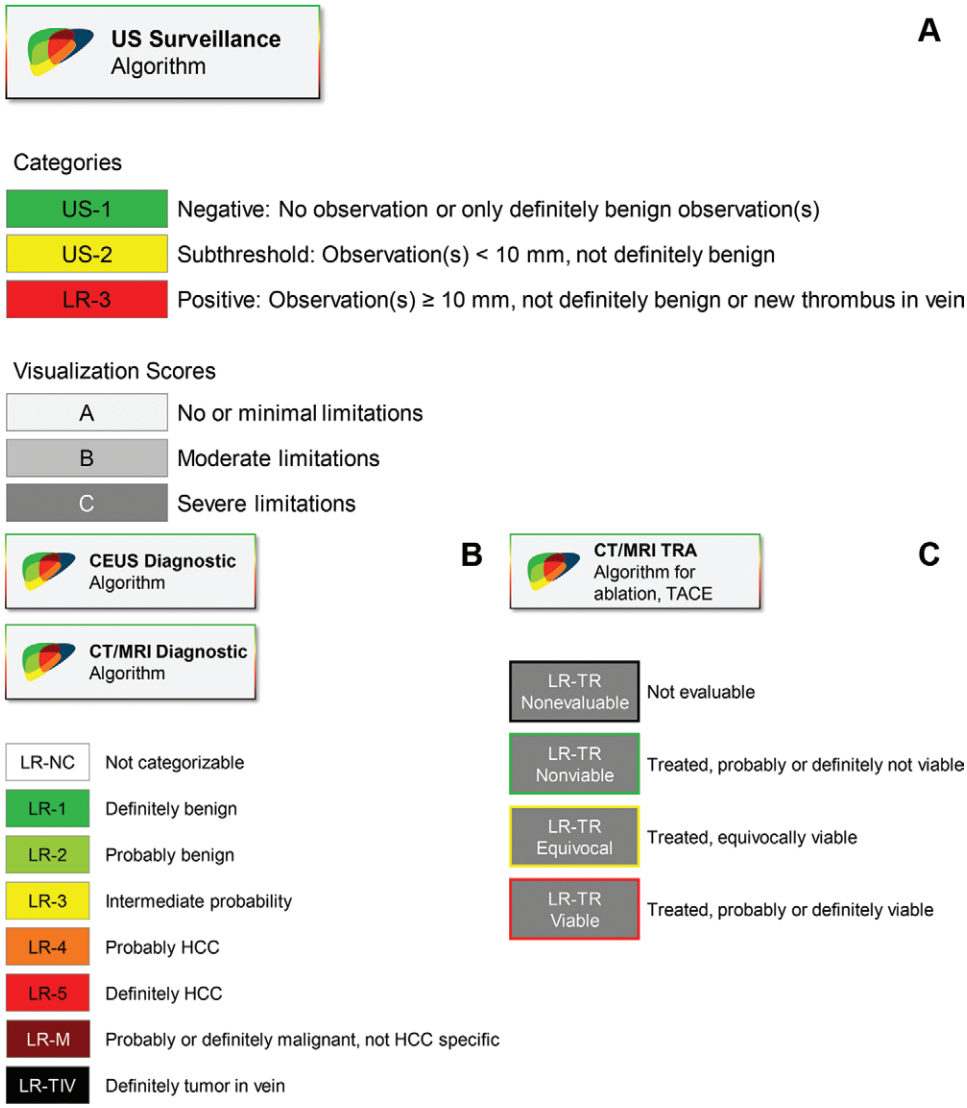

Figure 1: Description of categories included in the Liver Imaging Reporting and Data System algorithms: **(A)** US surveillance, **(B)** CT/MRI and CEUS diagnosis, and **(C)** CT/MRI treatment response assessment. CEUS = contrast-enhanced US, HCC = hepatocellular carcinoma, TACE = transarterial chemoembolization, TRA = treatment response assessment.

is needed and may require quantitative imaging or machine learning–based scoring. Additionally, the management of patients with negative US and limited visualization (score C) is controversial. Some institutions continue with US surveillance, as over 50% of patients with visualization score C at a single surveillance examination will have better liver visualization on follow-up (15), while other centers offer surveillance with an alternative modality (20). Prospective studies are needed to develop optimal surveillance guidelines, potentially including alternative imaging modalities such as abbreviated MRI, in select patients (21). We envision that future versions of LI-RADS, in partnership with AASLD, will provide guidance on when to switch from US to abbreviated MRI surveillance.

Diagnostic LI-RADS: CT/MRI and CEUS Algorithms

Diagnostic population.—To achieve a sufficiently high positive predictive value (PPV) of LR-5 for HCC, LI-RADS restricts the use of the diagnostic algorithms to at-risk populations (ie, adult patients with cirrhosis, chronic hepatitis B viral infection, or personal history of HCC) (2). The diagnostic algorithms do not currently apply to pediatric patients and patients without risk factors, as pretest probability of HCC in these patients is too low to yield the desired posttest probability. Additionally, patients with cardiogenic causes of cirrhosis are excluded from the LI-RADS population, as the high prevalence of hypervascularized benign nodules reduces the PPV of imaging for HCC diagnosis (22).

The definition for the at-risk population was adopted from clinical practice guidelines, which are based on modeling analyses that suggest HCC surveillance is cost effective in patients with cirrhosis and precirrhotic chronic hepatitis B infection (1). Rather than defining the diagnostic population based on cost-effectiveness for surveillance, it would be more accurate to define the diagnostic population based on ability to achieve a high (≥95%) PPV for HCC. Prior studies have shown that

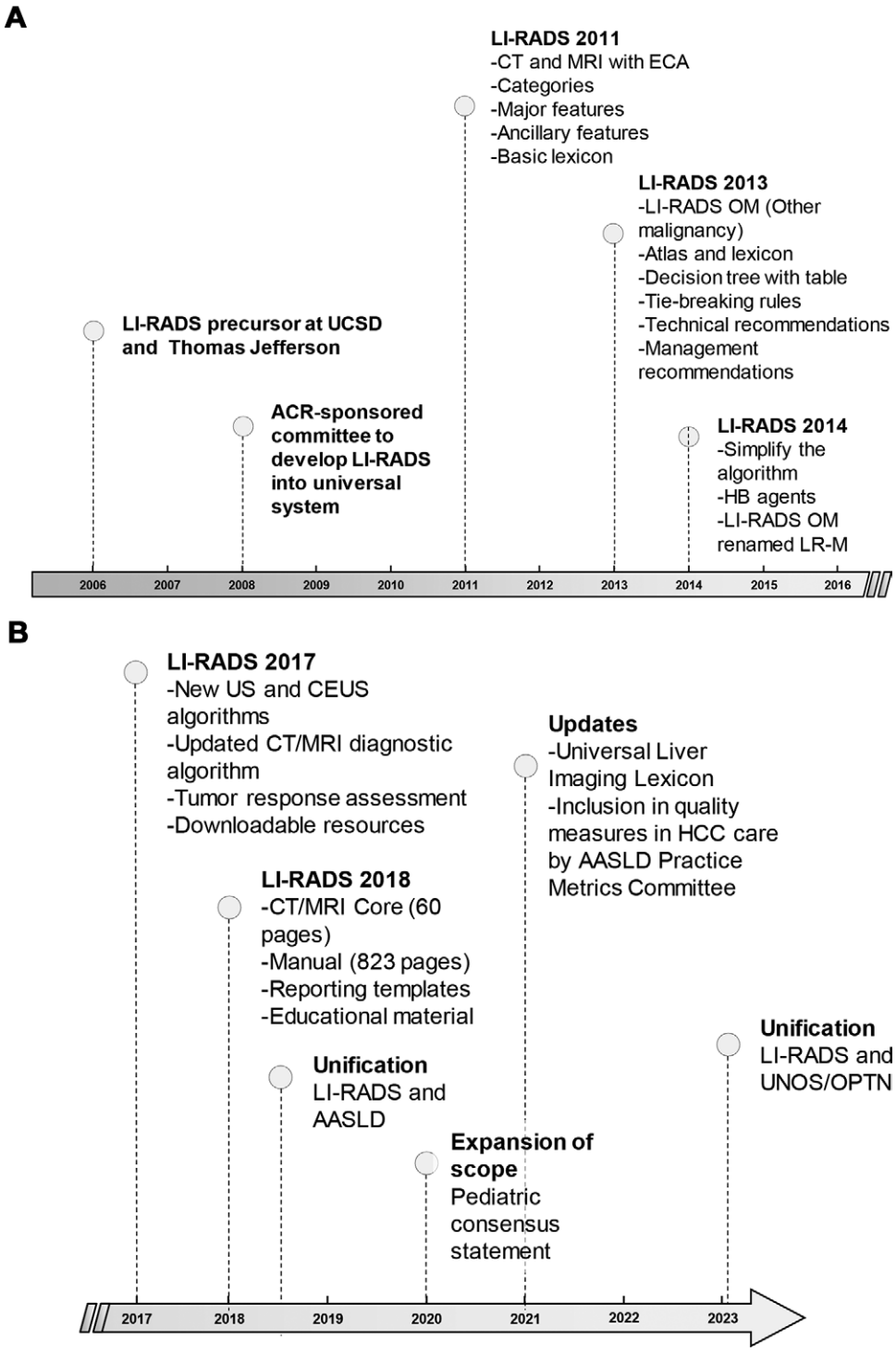

Figure 2: Timelines summarize major achievements of the Liver Imaging Reporting and Data System (LI-RADS) **(A)** 2011–2016 and **(B)** 2017–2023. AASLD = American Association for the Study of Liver Diseases; ACR = American College of Radiology; CEUS = contrast-enhanced US; ECA = extracellular agent; HB = hepatobiliary; HCC = hepatocellular carcinoma; OPTN = Organ Procurement and Transplantation Network; UCSD = University of California, San Diego; UNOS = United Network for Organ Sharing.

LR-5 criteria have a positive likelihood ratio of 17 (23). Thus, according to Bayes theorem, LR-5 can achieve the desired 95% PPV if the conditional pretest probability of HCC (ie, the probability of HCC given the presence of a lesion detected on imaging) is ≥50% (Fig 5). Therefore, research is needed to define the conditional probabilities of HCC based on age, sex, etiology and severity of liver disease, and possibly other factors, such as quantitative imaging and circulating biomarkers. Future machine learning algorithms may enable opportunistic identification of patients at risk through automated detection

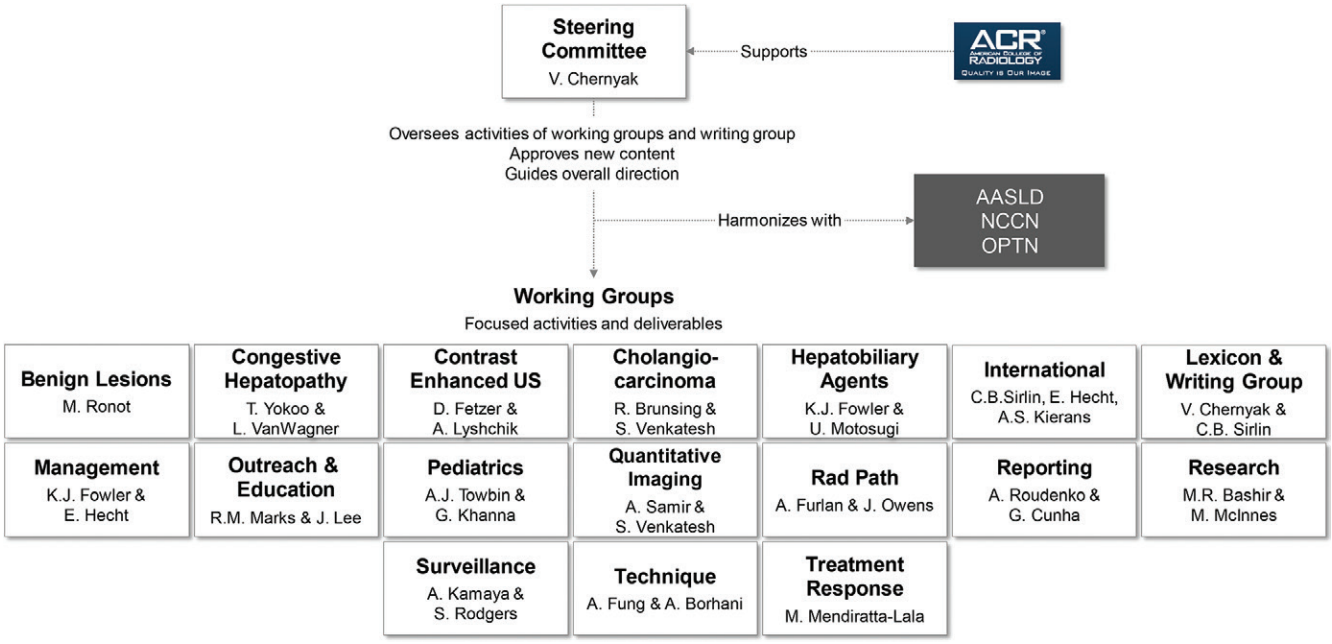

Figure 3: Summary of the Liver Imaging Reporting and Data System governance. AASLD = American Association for Study of Liver Diseases, NCCN = National Comprehensive Cancer Network, OPTN = Organ Procurement and Transplantation Network.

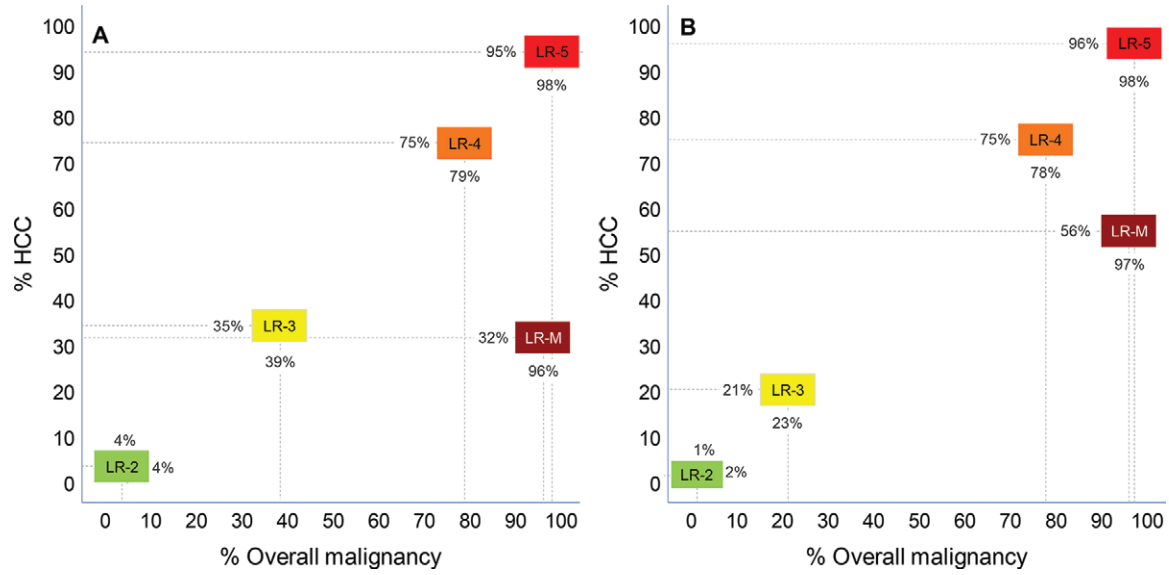

Figure 4: Probabilities of hepatocellular carcinoma (HCC) and overall malignancy per each diagnostic category for **(A)** CT/MRI (2014, 2017, and 2018 versions) and **(B)** contrast-enhanced US (2016 and 2017 versions) diagnostic algorithms. The graphs are based on the data from meta-analysis performed by Zhou et al (14). LR-M = probably or definitely malignant, not HCC specific, LR-2 = probably benign, LR-3 = intermediate probability of malignancy, LR-4 = probable HCC, LR-5 = definite HCC.

of relevant features (eg, surface nodularity) at imaging examinations performed for unrelated reasons. Over the next decade, we anticipate a paradigm shift, where LI-RADS applicability will be determined by individualized conditional probability thresholds derived from clinical factors and biomarkers, rather than on the presence of cirrhosis.

Perceived complexity.—Feedback commonly expressed by users is that LI-RADS algorithms are too complex. For example, the CT/MRI and CEUS algorithms incorporate a decision tree, with stepwise consideration of alternate diagnostic categories, before reaching the diagnostic table, which assigns LR-3, LR-4, or LR-5 categories based on combinations of major features (Fig 6). The granularity of LI-RADS burdens radiologists more than systems that classify observations dichotomously as definite HCC versus not. While dichotomous assessment is easier, it provides no guidance for most observations, which do not meet imaging criteria for definite HCC. These include benign lesions and pseudolesions, dysplastic nodules, early and atypical HCCs, and non-HCC malignancies. Given the wide

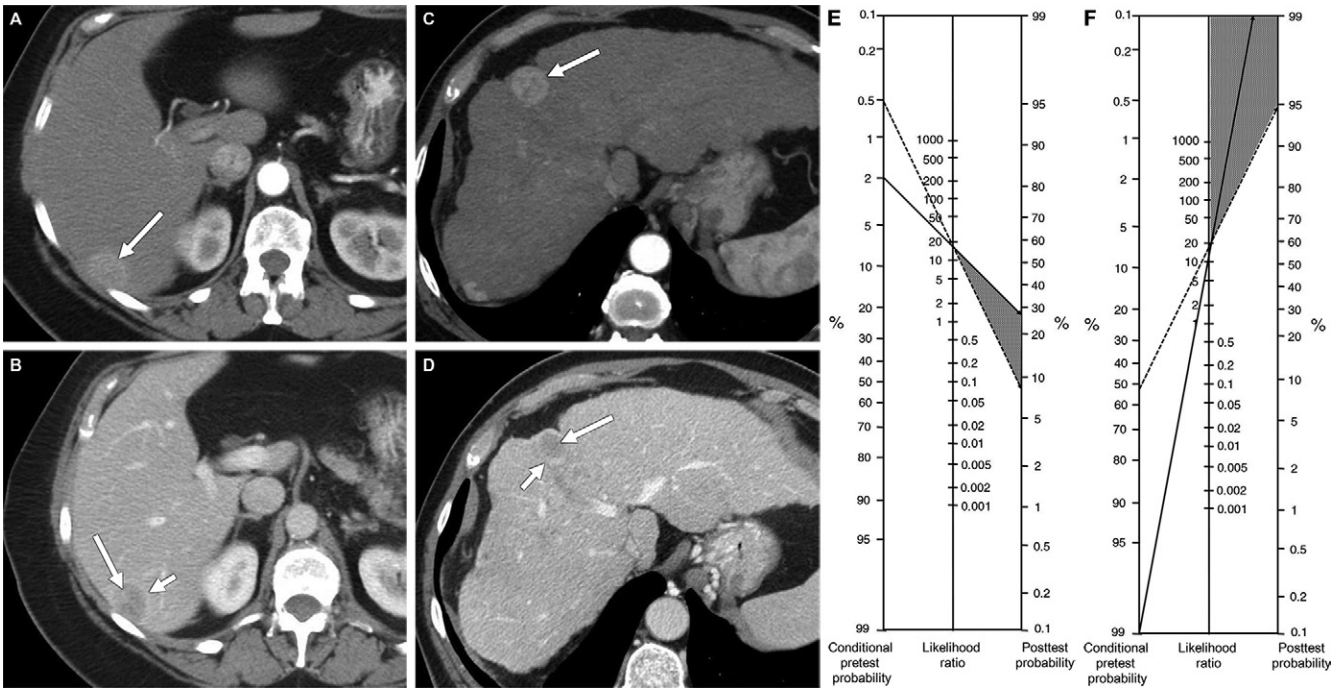

Figure 5: Patient images and Bayes diagrams show the relationship between pretest conditional probability of hepatocellular carcinoma (HCC) and posttest probability (positive predictive value) of HCC. **(A, B)** Patient 1 is a 53-year-old man without a history of parenchymal liver disease. Axial contrast-enhanced CT images show a 23-mm observation with nonrim arterial phase hyperenhancement (arrow, **A**), nonperipheral washout on portal venous phase (long arrow, **B**), and enhancing capsule (short arrow, **B**). **(C, D)** Patient 2 is a 62-year-old man with history of hepatitis C virus cirrhosis. Axial contrast-enhanced CT images show a 24-mm observation with the same imaging features as patient 1, including a nonrim arterial phase hyperenhancement (arrow, **C**), nonperipheral washout on portal venous phase (long arrow, **D**), and enhancing capsule (short arrow, **D**). **(E, F)** Bayes theorem diagrams show conditional pretest and posttest probabilities of HCC in patients 1 and 2. Imaging features for both patients meet criteria for LR-5 (definite HCC), which has positive likelihood ratio of 17 (23). **(E)** Bayes diagram for the patient without parenchymal liver disease (patient 1) demonstrates the patient has a low pretest probability of 0.5%–2% and posttest probability of 7%–28% (shaded area in **E**). **(F)** Bayes diagram for the patient with cirrhosis (patient 2) demonstrates a high pretest probability of ≥50% and a posttest probability of ≥95% (shaded area in **F**). On resection, patient 1 had a neuroendocrine tumor metastasis, and patient 2 had HCC.

range of clinical relevance of such lesions, risk stratification is needed for individualized management of patients, which LI-RADS provides. Nevertheless, simplification of the diagnostic approach remains a goal that is balanced against evidence, comprehensiveness, and precision.

Beyond major features that directly contribute to the diagnosis of HCC, LI-RADS uses two types of additional imaging features: LR-M features and ancillary features (AFs). These features add value, as discussed later, but increase complexity of the system.

Targetoid and nontargetoid LR-M features define the LR-M category and allow categorization of observations that are probably or definitely malignant but not HCC specific. By providing a separate pathway for non-HCC malignancies, the LR-M category helps to preserve the high specificity of LR-5 for HCC (Fig 7). Meta-analyses confirm that a substantial proportion of LR-M observations are non-HCC malignancies (13,14,24–27), justifying the need for this category.

AFs, summarized in the Table 1, can improve detection of observations (Fig 8), increase diagnostic confidence, and permit category adjustment. Although the added value of AFs in combination with major features may be limited for the noninvasive diagnosis of small HCCs (28,29), AFs may improve risk stratification in the indeterminate observations (30–35). For CT/MRI LI-RADS, application of AFs changes the category in 10% of HCCs, and in 86% of such cases the category change is to a more appropriate increased probability category (30). In benign observations, AFs change category in 34%, and in 65% of these observations, the category change is to a more appropriate decreased probability category (30). The LR-3 category is the most affected by the application of AFs, leading to an increased sensitivity for HCC, although with a slight decrease in specificity (31,32). Importantly, for observations categorized as LR-3 based on major features, those with AFs of malignancy demonstrate greater cumulative incidence of progression to HCC than those without AFs (33,34). Additionally, in observations categorized as LR-3 or LR-4 based on major features, every AF of malignancy has a high PPV (85%–100%) for HCC and the presence of ≥3 AFs increases the PPV for HCC to >95% (34). For CEUS LI-RADS, up to 20% of HCCs exhibit AFs, and their use increases sensitivity of LR-4 for HCC diagnosis compared with historical studies neglecting AFs (35).

Emerging data suggest the possibility of reducing the number of AFs, thereby simplifying the system. Studies consistently show that select AFs—mild-moderate T2 hyperintensity, transitional phase hypointensity, and hepatobiliary phase (hereafter, HBP) hypointensity—increase sensitivity for HCC, including those <20 mm, and are independent predictors of HCC (31,34,36–38). The impact of other AFs on diagnostic accuracy is uncertain. For example, mosaic appearance and fat in mass

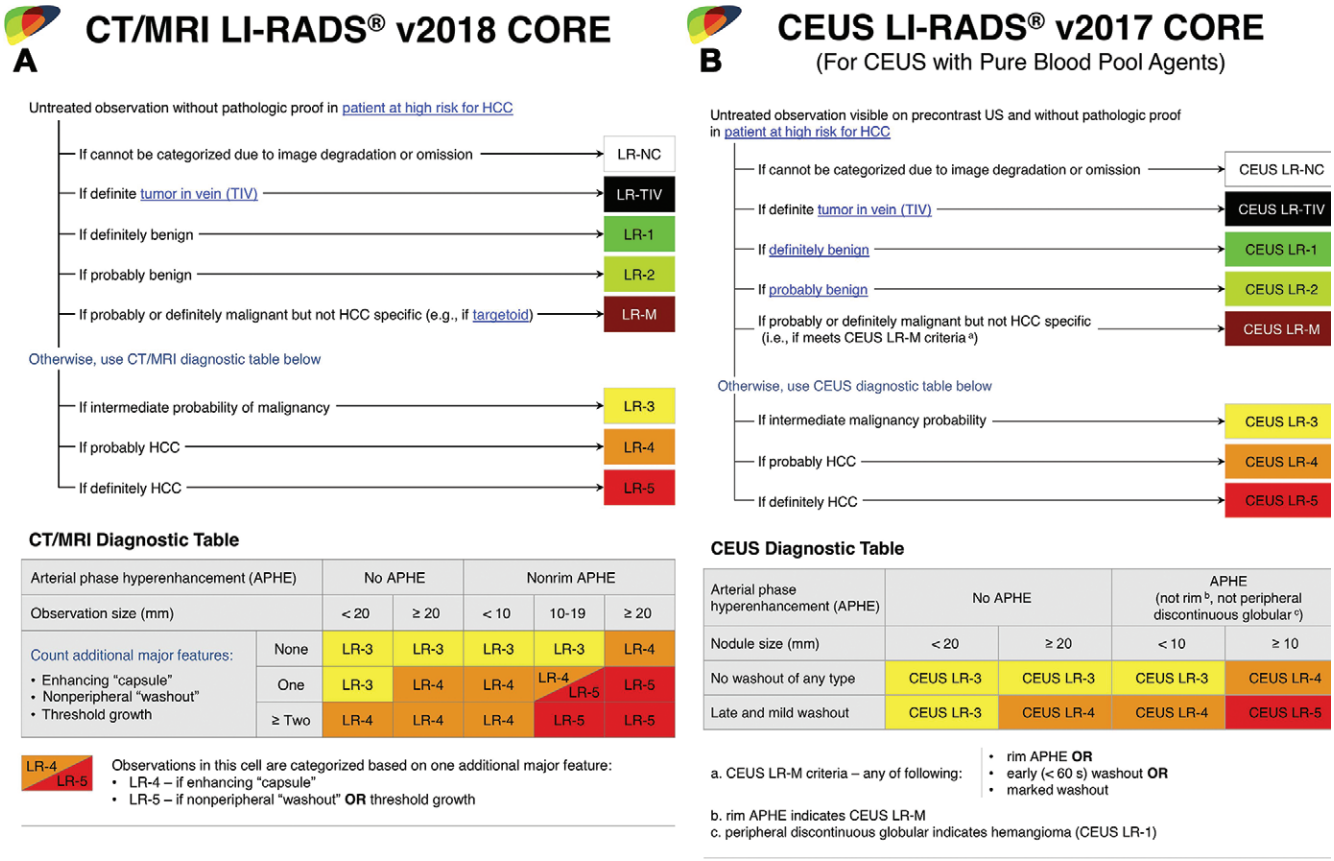

Figure 6: Liver Imaging Reporting and Data System (LI-RADS) diagnostic algorithms for **(A)** CT/MRI (70) and **(B)** contrast-enhanced US (CEUS) (87). HCC = hepatocellular carcinoma.

were shown to increase sensitivity for and be independent predictors of HCC in some studies (29–37), while other investigators found them to be noncontributory (30). Prospective studies are needed to identify the most reliable and discriminatory AFs.

Despite their value, AFs contribute to intermodality and interreader variability. Of all 21 AFs, eight can be assessed only with MRI (Table). As a result, AFs lead to category adjustment more frequently on MRI (56% of observations) than CT (4%) (32,39). Similarly, some AFs are unique to MRI with hepatobiliary agents, leading to discordance based on the administered contrast agent. Some disagreement attributable to modality and contrast agent is inherent to diagnostic imaging technologies and likely to be intractable. Further, the application of AFs is optional, and it can, therefore, be an additional source of interreader variability in practice. Eventually, we envision obligatory use of highly reliable AFs and incorporation of modality and contrast agent into estimating HCC probability as a continuous variable (see Future Directions section).

Limited sensitivity of LR-5 for HCC.—Several preconditions safeguard the high specificity of LR-5 for HCC, at the cost of reduced sensitivity: Only 50%–70% of pathologically proven HCC meet LR-5 criteria (40,41). LI-RADS currently does not permit definitive diagnosis of HCCs without arterial phase hyperenhancement, which comprise 18% of all HCCs <30 mm; these are more likely to be well differentiated and have lower incidence of microvascular invasion (42,43). Defining new LI-RADS criteria for noninvasive diagnosis of HCCs without arterial phase hyperenhancement is an important future direction.

Similarly, LI-RADS currently does not permit definitive diagnosis of subcentimeter HCCs, even for lesions demonstrating all major features. As biopsy is not practical for all small nodules (44), presumed subcentimeter HCCs are usually followed. Supporting this approach, studies have shown similar overall and recurrence-free survival of patients with HCCs <10 mm managed by watchful waiting versus immediate treatment (45–47). Some small HCCs may grow rapidly or metastasize, however, and research is needed to define criteria for these high-risk subcentimeter HCCs.

LI-RADS also requires more stringent LR-5 criteria for observations <20 mm than for those ≥20 mm. Adopted from older diagnostic systems when LI-RADS was first released, the 20-mm size threshold is arbitrary. It is plausible that a lower size threshold (eg, 15 mm) may provide higher sensitivity for HCC without sacrificing specificity.

Hepatobiliary agents such as gadoxetate disodium can identify HCC based on alterations in membrane transporters occurring early in hepatocarcinogenesis, as well as on vascular flow characteristics. Thus, compared with extracellular agents, use of gadoxetate in at-risk patients may improve sensitivity for early HCC (48). When LI-RADS integrated hepatobiliary agents in 2014, it restricted the assessment of washout after gadoxetate disodium administration to the portal venous phase to prevent conflation of tumor washout with pseudowashout (relative lesional hypointensity in the transitional phase due to parenchymal contrast

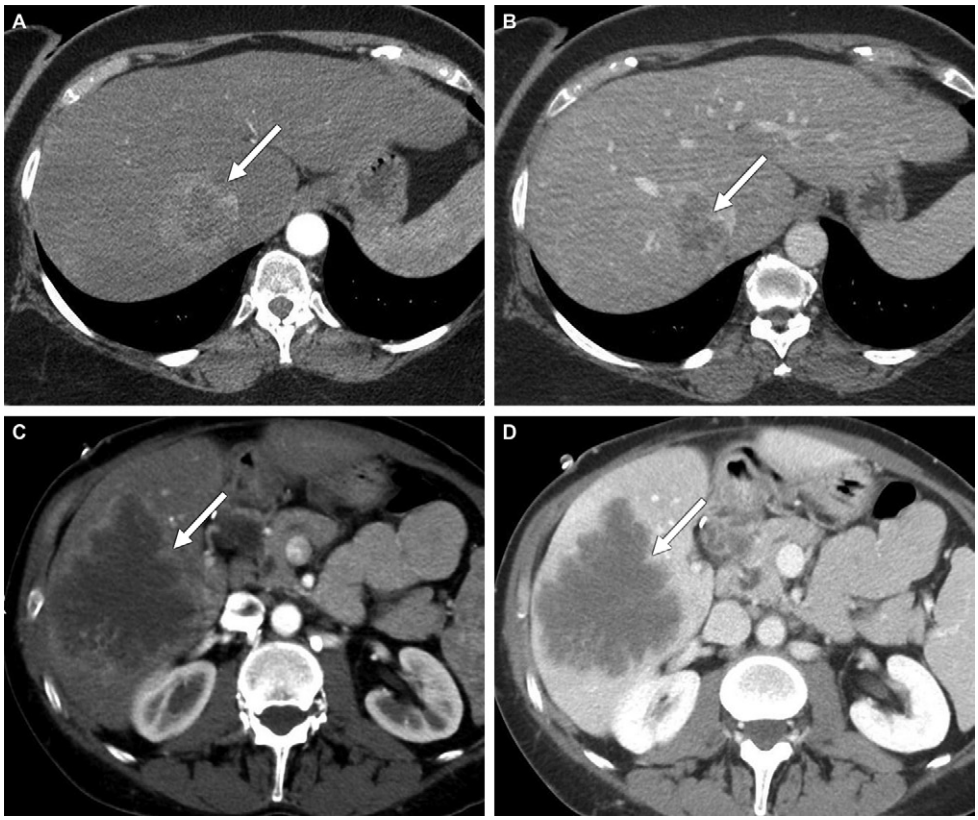

Figure 7: CT images show examples of observations that meet criteria for Liver Imaging Reporting and Data System (LI-RADS) category LR-M (probably or definitely malignant, not hepatocellular carcinoma [HCC] specific). Axial contrast-enhanced CT in **(A)** arterial phase and **(B)** portal venous phase in a 56-year-old woman with nonalcoholic steatohepatitis-induced cirrhosis demonstrates a 36-mm observation (arrow, **B**) with rim arterial phase hyperenhancement (arrow, **A**). Pathology revealed intrahepatic cholangiocarcinoma. Axial contrast-enhanced CT in **(C)** arterial phase and **(D)** portal venous phase in a 63-year-old man with hepatitis C virus cirrhosis demonstrates a 90-mm observation (arrow, **D**) with rim arterial phase hyperenhancement (arrow, **C**). Pathology revealed poorly differentiated HCC with p53 mutation.

uptake) (48). However, 25%–50% of small HCCs fail to show washout until 2–5 minutes after contrast injection (49,50) and, therefore, may not meet criteria for LR-5 with MRI with gadoxetate. As a result, restriction of washout to portal venous phase reduces sensitivity of gadoxetate MRI compared with extracellular contrast agents (51). Initial studies that included transitional phase and HBP hypointensity as major features of HCC reported an unacceptable decrease in specificity from 81%–98% to 58%–86% (52–54). However, these studies did not incorporate LR-1/2 and LR-M observations before diagnostic table application, as required by LI-RADS. Subsequent studies adhered to the LI-RADS algorithm and reported substantial sensitivity improvement (10%–23%) with only modest specificity reduction (3%–5%) (53–55). Future versions of LI-RADS might include transitional phase, and possibly HBP, hypointensity as major features of HCC to improve the sensitivity of LR-5 for HCC, provided maintained specificity is validated in Western cohorts.

Challenges of "indeterminate" observations.—Observations categorized LR-3, LR-4, or LR-M using the CT/MRI or CEUS Diagnostic algorithms impose management dilemmas, as they may be perceived as indeterminate with regard to their probability of HCC. Using CT/MRI Diagnostic LI-RADS, the pooled proportion of HCC are 31% for LR-3 and 64% for LR-4 (13). These percentages are neither low enough (eg, <20%) nor high enough (eg, >80%) to inform clear-cut management decisions, such as follow-up, biopsy, or treatment presumptively as HCC (56). An additional complication is that LR-3 and LR-4 observations have variable natural histories. Several studies found that of all LR-3 observations, 23%–60% remained LR-3, 15%–68% decreased to LR-1/2, 2%–5% progressed to LR-4, and 7%–24% progressed to LR-5/M (57–60). Of all LR-4 observations, 44% remained LR-4 and 33%–38% progressed to LR-5/M in 6–12 months, while a nontrivial minority decreased to LR-3 (13%) or LR1/2 (3%) (59,61).

Prognostic features that can better stratify aggressiveness of LR-3 and LR-4 observations are needed. Some retrospective studies have identified independent predictors of progression, such as hepatitis C virus infection, personal history of HCC, threshold growth, presence of arterial phase hyperenhancement, size >10 mm, T2 hyperintensity, diffusion restriction, and HBP hypointensity, but other studies have failed to show associations of these features with outcomes (61–67). Reliable and accurate stratification of LR-3 and LR-4 observations has been identified as a "major unmet clinical need" by the National Institutes for Health (RFA-CA-22–031).

Ancillary Features Used in CT/MRI Diagnostic Liver Imaging Reporting and Data System (2018 Version)

Ancillary Feature	Applicable Modality
Favoring malignancy in general, not HCC in particular	
US visibility as discrete nodule	CT, MRI-ECA, MRI-HBA
Subthreshold growth	CT, MRI-ECA, MRI-HBA
Diffusion restriction	MRI-ECA, MRI-HBA
Mild-moderate T2 hyperintensity	MRI-ECA, MRI-HBA
Corona enhancement	CT, MRI-ECA, MRI-HBA
Fat sparing in solid mass	CT (±), MRI-ECA, MRI-HBA
Iron sparing in solid mass	MRI-ECA, MRI-HBA
Transitional phase hypointensity	MRI-HBA
Hepatobiliary phase hypointensity	MRI-HBA
Definite growth	CEUS
Favoring HCC in particular	
Nonenhancing capsule	CT, MRI-ECA, MRI-HBA
Nodule-in-nodule appearance	CT, MRI-ECA, MRI-HBA, CEUS
Mosaic appearance	CT, MRI-ECA, MRI-HBA, CEUS
Blood products in mass	CT (±), MRI-ECA, MRI-HBA
Fat in mass, more than adjacent liver	CT (±), MRI-ECA, MRI-HBA
Favoring benignity	
Size stability ≥2 years	CT, MRI-ECA, MRI-HBA, CEUS
Size reduction	CT, MRI-ECA, MRI-HBA, CEUS
Parallels blood pool enhancement	CT, MRI-ECA, MRI-HBA
Undistorted vessels	CT, MRI-ECA, MRI-HBA
Iron in mass, more than liver	CT (±), MRI-ECA, MRI-HBA
Marked T2 hyperintensity	MRI-ECA, MRI-HBA
Hepatobiliary phase isointensity	MRI-HBA

Note.—The symbol "±" is used to denote modalities with which features may or may not be evaluable. CEUS = contrast-enhanced US, ECA = extracellular agent, HBA = hepatobiliary agent, HCC = hepatocellular carcinoma.

The LR-M category was introduced in the 2013 version to codify observations with high probability of malignancy but without features specific to HCC. Almost all LR-M observations are malignant (96% using CT/MRI LI-RADS, 97% using CEUS LI-RADS [14]), and a substantial proportion are HCC (32% using CT/MRI LI-RADS, 56% using CEUS LI-RADS [14]), with the remaining being mostly non-HCC malignancies. Compared with HCC categorized as LR-4 or LR-5, HCC categorized as LR-M may have more aggressive tumor biology and poorer overall and recurrence-free survival (68,69). Accurate differentiation within the LR-M category between HCC and non-HCC malignancies, and stratification between aggressive and nonaggressive HCCs, based on imaging and other noninvasive characteristics (Fig 7) (14), is an area of active investigation.

Finally, the current schematic diagram of the LI-RADS CT/MRI diagnostic algorithm depicts only one of two pathways for LR-M categorization, namely, identification of targetoid features. As described in the CT/MRI version 2018 Core, LR-M can also be assigned to an observation that does not meet criteria for LR-TIV (or tumor in vein) or LR-5, on the basis of nontargetoid LR-M features (Fig 9) (70). This "nontargetoid pathway" could be incorporated schematically into the diagnostic table (Fig 9).

Competing diagnostic systems.—Regional systems elsewhere in the world compete with LI-RADS (3). Geographic differences in tumor biology, available resources, and societal priorities further challenge adoption of a single universal guideline worldwide (71). In the United States and other countries where cirrhosis is the most common underlying cause of HCC, resection is usually prohibited by poor liver reserve, and transplantation is the preferred curative treatment (71,72). This places a premium on high diagnostic specificity to ensure appropriate organ allocation, at the cost of suboptimal sensitivity, as discussed previously. In countries where chronic hepatitis B infection predominates, patients with HCC tend to be younger and have better liver function; hence, resection is preferred, which shifts the emphasis to high sensitivity (72).

Despite such differences, it should be possible to create a single diagnostic system, with management guidelines tailored to different situations. For example, when high sensitivity is desired, practice guidelines could combine LR-4 and LR-5 in their management recommendations. This approach has been shown to increase the sensitivity for HCC by 2%–37% compared with LR-5 alone, while reducing specificity by 0%–54% (23,39,73–77). By comparison, regions requiring maximal specificity would keep the management of LR-4 and LR-5 distinct.

Challenges in reporting.—LI-RADS seeks to provide clear and actionable communication between radiologists, referrers, and patients, but persistent challenges impede the fulfillment of this vision (78,79). The presence of multiple observations constitutes one such challenge. When numerous observations are present, aggregate reporting is preferred over observation-level reporting to avoid losing the forest for the trees. Thus, in patients who present with multiple observations, LI-RADS recommends observation-level reporting for the five observations with highest categories and aggregate reporting for the rest (80). However, patients who present initially with few observations tend to accumulate observations over time, many of which undergo local-regional therapy. Reporting in such cases is difficult and variable. LI-RADS needs to develop clear guidance on when and how to switch to aggregate reporting for such scenarios.

Longitudinal lesion tracking presents an additional difficulty. LI-RADS recommends assigning each observation a unique identifier (eg, observation #1) and to keep identifiers consistent on follow-up (80). In practice, lesion tracking is tedious and subject to human error. Automated lesion tracking software could alleviate this issue.

Reporting rigor is a final complexity. Suggested LI-RADS templates are detailed, requiring explicit accounting for each major feature (79,80). This level of detail increases the burden for the radiologist. User-friendly programs that assist radiologists in LI-RADS category assignment, feature characterization, and standardized report generation could simplify reporting.

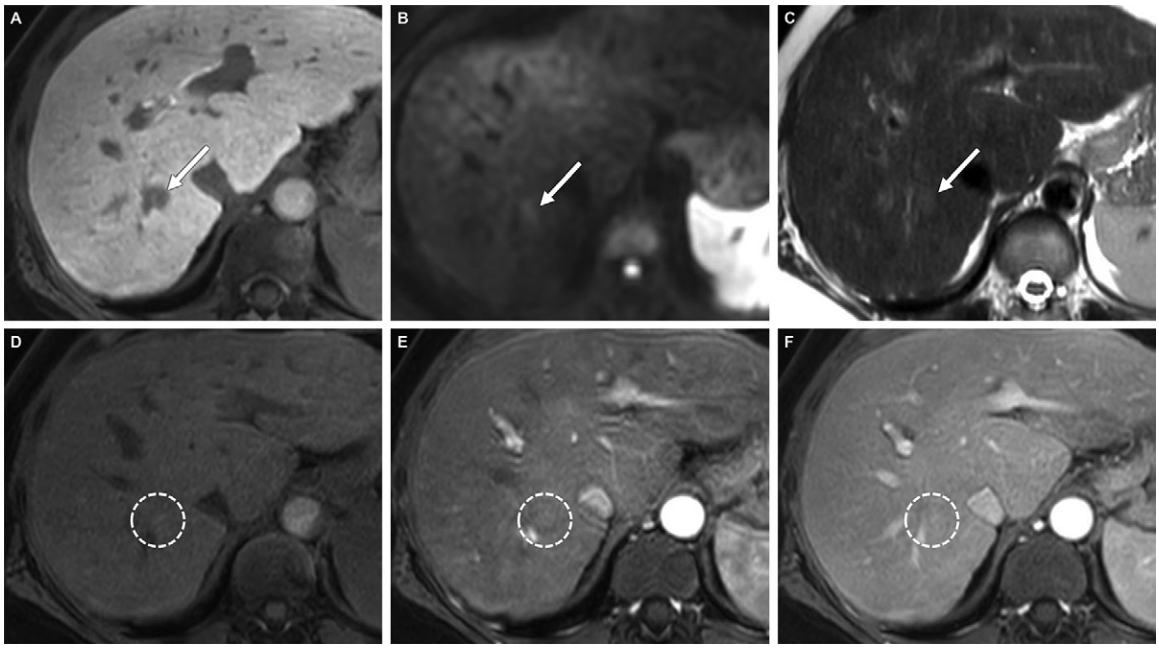

Figure 8: MRI scans with gadoxetate in a 57-year-old woman with hepatitis C virus cirrhosis. MRI scans demonstrate **(A)** a 10-mm observation (arrow) with hepatobiliary phase hypointensity, **(B)** mild diffusion restriction (arrow) with diffusion-weighted image with b = 800 m/sec^2, and **(C)** mild T2-hyperintensity (arrow) with lesional fat sparing (not shown). The observation is not discernable on **(D)** precontrast T1-weighted image, **(E)** arterial phase, or **(F)** portal venous phase (the region of the observation is marked by a circle in **D–F**). The observation progressed to LR-5 (definite hepatocellular carcinoma) in 2 years.

LI-RADS TRA Algorithm

Released in 2017, the LI-RADS TRA provides lesion-level response assessment after local-regional therapy to inform post-treatment management. Using pathology as the reference standard following non–radiation-based therapies, the meta-analytic pooled sensitivity and specificity of LR-TR (or treatment response) Viable category for detecting incomplete necrosis is 56%–63% and 91%–96%, respectively (81,82). Expanding the definition of viable disease to include both LR-TR Viable and Equivocal categories improves sensitivity to 71%–73%, while decreasing specificity to 82%–87% (81,82).

Until now, most studies have not distinguished between microscopic and macroscopic viable disease, thus limiting their interpretability and informing changing LI-RADS TRA. However, imaging cannot detect the microscopic foci of a viable tumor, and the clinical relevance of microscopic viability is unknown. Studies are needed to assess the performance of LI-RADS TRA for detecting clinically meaningful viability. A recent study reported that LR-TR Viable has 10% sensitivity for a viable tumor less than 10 mm and 67% sensitivity for a viable tumor greater than or equal to 10 mm (83). This suggests a need to improve the sensitivity of the LR-TRA for subcentimeter but macroscopic foci of viability. Emerging data suggest that some AFs (transitional phase and HBP hypointensity, T2-hyperintenisty, diffusion restriction) can improve the sensitivity of LR-TR Viable without significantly decreasing specificity (83,84). Thus, AFs might be integrated into the response algorithm.

Currently, TRA only applies to CT and MRI for lesions treated with ablative or embolic local-regional therapies in which the major mechanism of action is tumor necrosis and is not optimized for radiation-based therapies (radioembolization and external beam radiation) that cause tumor death through cell cycle arrest. A new algorithm for radiation-based therapies, including high-dose treatment, is in development. Also forthcoming is a new algorithm for CEUS-based response assessment. Algorithms for systemic therapy assessment are also needed and will be created subsequently.

Future Directions

LI-RADS is dynamic and will continue to evolve in response to new research findings and user feedback. Immediate and longer term goals include filling current gaps in knowledge (such as with the release of the aforementioned algorithms currently in development), producing manuals for surveillance imaging and CEUS, developing guidance on imaging alternatives to US for surveillance (eg, abbreviated MRI), curating definitions for terms missing from the current lexicon, and expanding the scope beyond primary liver cancers. In parallel, outreach efforts will be intensified to promote a more universal adoption of LI-RADS, including the continued translation of LI-RADS into other languages, combined with encouraging critical feedback from regional practitioners.

We anticipate that LI-RADS algorithms will be updated every 5 years or so, balancing the competing demands of stability versus contemporaneity. Some revisions will be straightforward clarifications, such as illustration of the nontargetoid LR-M pathway, while others will be more ambitious endeavors to simplify the algorithms, improve performance, and expand the relevant population. These more ambitious efforts will require

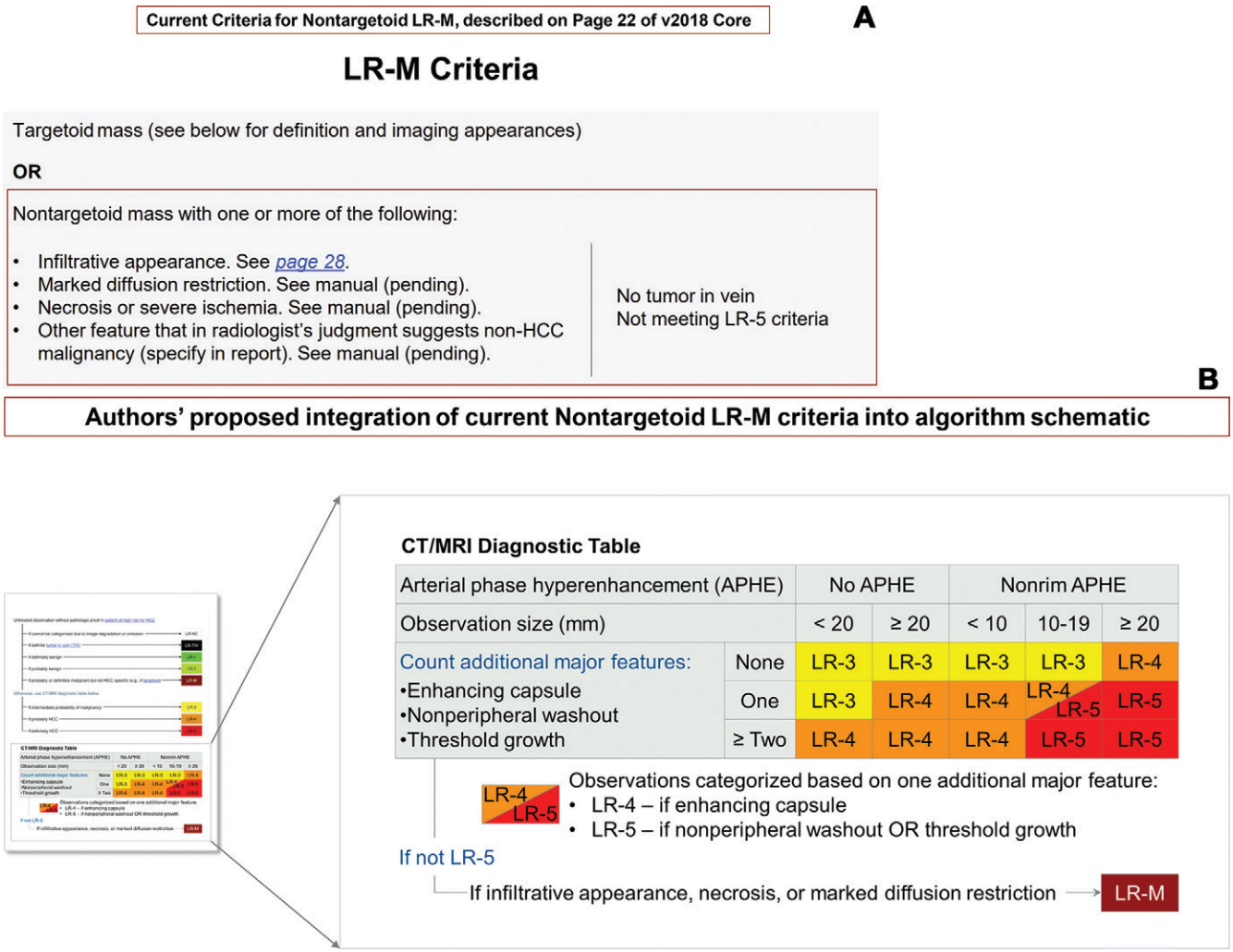

Figure 9: Proposed minor modification to the Liver Imaging Reporting and Data System CT/MRI Diagnostic Table that includes the nontargetoid LR-M category (probably or definitely malignant, not hepatocellular carcinoma specific). **(A)** Current description of the nontargetoid LR-M criteria in version 2018 Core (70). **(B)** Authors' proposed illustration of the nontargetoid LR-M criteria.

scientific evidence, ideally from prospective, multicenter, multinational studies, as well as proactive dialogue with the AASLD and the Organ Procurement and Transplantation Network to maintain unity with other stakeholders.

An inherent and intractable challenge in any radiology system is the subjectivity in interpretation of imaging characteristics. Even features that are reported numerically, such as size, are subject to interreader variability. No degree of training, education, or teaching materials can ever eradicate this challenge. We envision integration of artificial intelligence and other deep learning approaches for more objective and reproducible assessment of observation size and other features.

Expected improvements in reporting technology will streamline the use of LI-RADS in clinical practice. We envision user-friendly reporting software, which integrates natural language processing and artificial intelligence–augmented lesion tracking, to facilitate accurate, consistent, and complete reporting, even in complex cases. The dissemination of such software will enable the formation of curated LI-RADS registries with prospectively collected clinical, imaging, and other data. These registries will facilitate quality assurance and peer learning, enable large-scale observational research, and provide a platform for developing objective and reproducible artificial intelligence– and radiomics-based criteria.

In 10–20 years, we envision a transformation in LI-RADS where probabilities of HCC and posttreatment tumor viability will be assigned as continuous numbers, rather than ordinal categories (85). The future system will integrate patient characteristics, quantitative imaging features, and novel prognostic features (86), while accounting for imaging modality and contrast agent to provide diagnostic, prognostic, and predictive information to individualize patient management (Fig 10). Although a fully integrated system will be more complex, the complexity will be hidden from the user: Computer software will integrate multimodal data and guide the radiologist in characterizing those features that require human interpretation. The transformation to an integrated probability-based system will solve the current regional divide, as regions could select their own probability and predictive/prognostic thresholds for treatment recommendations, while enabling fully personalized precision medicine.

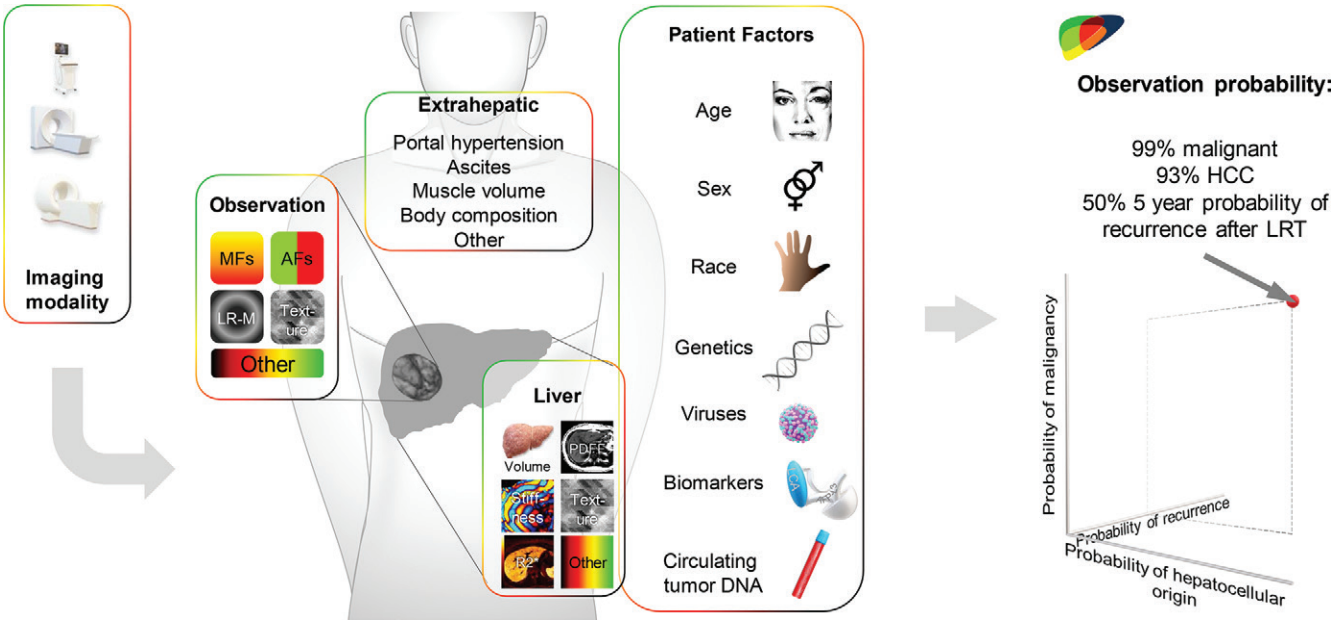

Figure 10: Illustration of the ultimate system for diagnosis and prognostication of liver cancers. A comprehensive probability-based system integrates patient characteristics and quantitative and qualitative imaging features and takes into account imaging modality and contrast agent to arrive at patient-specific probability of hepatocellular carcinoma (HCC) and posttreatment recurrence. AF = ancillary feature, LR-M = Liver Imaging Reporting and Data System category M, probably or definitely malignant, not HCC specific category, LRT = local-regional treatment, MF = major feature, PDFF = proton density fat fraction.

Conclusion

As *Radiology* has grown over the past 100 years and expanded its suite to include journals such as *Radiology: Imaging Cancer*, so too has the Liver Imaging Reporting and Data System (LI-RADS) evolved and expanded in scope since its inception. What began as a single algorithm for hepatocellular carcinoma diagnosis with CT or MRI with extracellular contrast agents has matured into a multialgorithm network covering all major liver imaging modalities and contexts of use. It has also developed its own lexicon, report templates, and supplementary materials. Since its release in 2011, LI-RADS has been refined, expanded, and validated. It has also been adopted by the American Association for the Study of Liver Diseases and the United Network for Organ Sharing and gained popularity across the globe for both clinical care and research. Despite these major achievements, multiple challenges and gaps in knowledge remain and will need to be addressed in coming years.

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