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HEPATIC CANCER (A SINGAL AND A MUFTI, SECTION EDITORS)

Understanding LI-RADS, Its Relationship to AASLD and OPTN, and the Challenges of Its Adoption

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Abstract Imaging-based diagnosis of hepatocellular carcinoma (HCC) is incorporated in many clinical guidelines on the management of HCC. However, there is variability in the diagnostic criteria for HCC and lack of precise definitions for imaging characteristics. With the intent of standardization and maintaining compatibility with the American Association for the Study of Liver Diseases (AASLD) and Organ Procurement and Transplantation Network (OPTN), the Liver Imaging Reporting and Data System (LI-RADS) was developed as a system for standardizing the performance, interpretation, and reporting of CT and MRI in patients at high risk of HCC. It precisely defines the terms and imaging features used in the diagnostic algorithm with the aid of a lexicon and illustrative atlas. While it is a comprehensive system, the challenges to its adoption are not trivial and can be controversial. A better understanding of the purpose and the limitation of the system can help in building consensus within and across disciplines. In this paper, we describe LI-RADS and its relationship to AASLD and OPTN guidelines. The LR-5 category is essentially equivalent to OPTN class 5 with few minor exceptions. LR-5 has been expanded to also encompass the AASLD definition of HCC. LR-4, LR-3, and LR-2 allow for more granular classification of indeterminate lesions. We highlight the advantages of the system and try to address the challenges that may impede or delay its adoption. We also review the emerging literature on its validation emphasizing that since LR-5 is designed to be specific, many HCCs will not meet LR-5 criteria and most of them will be LR-4.

Keywords LI-RADS · AASLD · OPTN · Hepatocellular carcinoma · Liver nodules · Diagnostic criteria

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Introduction

The noninvasive diagnosis of hepatocellular carcinoma (HCC) based on imaging is a widely accepted and validated strategy in the management of at risk patients. A large number of clinical guidelines for the management of HCC have emerged since 2001, most of which incorporate an imaging-based diagnosis of HCC [1–4, 5••, 6–10]. While these guidelines represent a remarkable advance in the diagnosis and management of HCC worldwide, their multiplicity and variability highlights some of the challenges in the diagnosis of HCC. Among these challenges is the lack of precise definitions for the imaging characteristics of HCC and variations in these definitions. Furthermore, there is inherent variability in appearance of HCC that may not be captured by the existing criteria. Most of these criteria follow a nearly binary categorization of lesions as either positive or negative for HCC (or indeterminate in some cases), while in clinical practice, the likelihood of a lesion being HCC is often not a binary decision. For example, a lesion suspicious for HCC but not

meeting definitive criteria should be managed differently than a suspected benign lesion. Providing a standardized terminology for communicating these differences would facilitate management decisions as well as potentially allow for validation studies of these management paradigms.

As the management of HCC requires a multidisciplinary approach, the radiologist also faces the challenge of applying multiple criteria concurrently. For instance, both the American Association for the Study of Liver Diseases (AASLD) and Organ Procurement and Transplantation Network (OPTN) guidelines [3, 6] may direct the patient management during different stages of the clinical course. The radiology report therefore has to provide sufficient information to communicate effectively with hepatologists, surgeons, and interventional radiologists as well as radiologists who will read the subsequent imaging. Standardized reporting and consistent guidelines would allow for efficient and consistent multidisciplinary discussion of the imaging findings.

Starting in 2008, a large panel of expert radiologists convened with the goal of developing a comprehensive system for interpreting and reporting CT and MR examinations of the liver in patients at risk for HCC [11••]. This panel, which is endorsed by the American College of Radiology (ACR), launched the Liver Imaging Reporting and Data System (LI-RADS) in March 2011 and continued expanding and updating the system with voluntary input from radiologists, hepatologists, liver surgeons, and pathologists. The LI-RADS algorithm was based on existing evidence, expert opinion, desire of consistency, and existing clinical criteria, namely, AASLD and OPTN guidelines (2014 guidelines available online at http://www.acr.org/Quality-Safety/Resources/LIRADS) [12].

On the one hand, LI-RADS has elegantly tackled many of the challenges of the imaging diagnosis of HCC and has been gaining wide acceptance, but on the other hand, it may still be perceived as a competing paradigm to the established practices at some institutions. Adoption is hampered by the difficulty of building consensus within and across disciplines. Perhaps, one reason for delayed adoption is the lack of large validation studies that leaves unanswered important questions about the 5-point scale probabilistic model of LI-RADS. In this paper, we will describe LI-RADS and its relationship to AASLD and OPTN guidelines. We will highlight the advantages of the system and try to address the challenges that may impede or delay its adoption.

What Is LI-RADS?

LI-RADS is a system for standardizing the performance, interpretation, and reporting of CT and MRI in patients at high risk of HCC. In addition, LI-RADS tries to standardize imaging techniques by listing technical requirements for CT and MRI studies. LI-RADS assigns a relative probability of HCC to an observation in the liver based on a diagnostic algorithm and precisely defines the terms and imaging features used in the algorithm with the aid of a lexicon and illustrative atlas, which are largely missing from other guidelines. The term "observation" is used to refer to any area with imaging features differing from adjacent liver parenchyma and is preferred to the term "lesion" as some of these observations may not represent a true lesion such as a perfusional alteration. LI-RADS includes five main categories with LR-5 indicating a definite HCC, LR-1 indicating a definite benign lesion, and LR-4, LR-3, and LR-2 indicating decreasing likelihood of HCC. Two additional categories cover specific situations which are LR-M indicating a probable malignancy not specific for HCC and LR-treated indicating a loco-regionally treated observation with no implications on the success or failure of the treatment. In assigning LI-RADS categories to at risk patients, the algorithm relies on imaging features only, with no regard to other clinical information that may or may not be available to the radiologists and should be interpreted in this context. The advantages of LI-RADS are listed in Table 1.

What LI-RADS Is Not

It is important to emphasize that LI-RADS is only applicable in high-risk patients, whom the LI-RADS document define as "patients in whom the incidence of HCC is sufficient to justify screening or surveillance according to the AASLD guidelines" [12]. It therefore does not independently define the at-risk patients nor address the frequency or means of surveillance in that population.

LI-RADS is not a management guideline but serves as a tool to standardize the performance, interpretation, and reporting of imaging findings. For LR-5 lesions (definite HCC), clinical guidelines such as the European Association for the Study of the Liver (EASL) and AASLD should address the management of the lesion. For observations in categories LR-2, LR-3, and LR-4, diagnostic recommendations are issued in the radiology report directing the patient toward continued surveillance, accelerated follow-up, alternate imaging, or toward a multidisciplinary discussion. The LI-RADS algorithm states that "a recommendation for biopsy or treatment should not follow directly from an imaging interpretation, but should be the result of multidisciplinary discussion." [12]

LI-RADS Categories

Imaging Features

There are five major imaging features in the LI-RADS algorithm, which are precisely defined and illustrated: arterial

Table 1 Advantages of LI-RADS

Advantages of LI-RADS
- Standardization of interpretation and reporting: LI-RADS offers precise terminology that is clearly defined and illustrated which is largely missing from the other criteria.
- Compatibility with OPTN and AASLD: Radiology reports based on LI-RADS provide sufficient information to make management decisions based on OPTN and AASLD.
- Non-binary system: Whereas other criteria may group all indeterminate lesions in one broad category, LI-RADS makes the indeterminate category more granular and therefore allows for more nuanced management. For instance, other guidelines recommend biopsy more frequently in indeterminate lesions but biopsy may not be warranted in all cases.
- Addresses special situations: LI-RADS addresses major vascular involvement and lesions that are favored to represent malignancies other than HCC.
- Evolving system: The LI-RADS is steadily evolving to incorporate newer imaging techniques (e.g., usage of hepatobiliary agents) and new evidence and to address special situations that are recognized. A major update is expected every 3 years.

phase hyperenhancement (APHE), diameter, washout appearance, capsule appearance, and threshold growth. Version 2014 of LI-RADS also incorporates the presence of a corresponding 10 to 19 mm lesion on antecedent surveillance US. In addition, there are a large number of ancillary imaging features that either favor malignancy (e.g., mild to moderate T2 hyperintensity, restricted diffusion, intralesional fat) or benignity (e.g., homogenous marked T2 hyperintensity, diameter stability ≥2 years). Figure 1 shows the LI-RADS algorithm.

In comparison, the AASLD guidelines only incorporate arterial phase hyperenhancement, washout appearance on

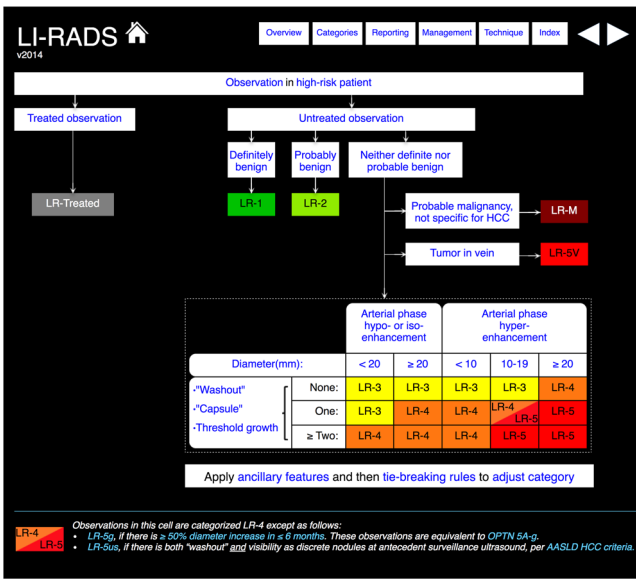

Fig. 1 LI-RADS diagnostic algorithm. The text in *blue* and the *cells* are hyperlinks that provide definitions, explanations, and illustrations (Source: ACR LI-RADS version 2014. Accessed January 2017, from http://www.acr.org/Quality-Safety/Resources/LIRADS)

venous or delayed phase imaging, and diameter that apply only to observations ≥10 mm detected at surveillance US. The OPTN guidelines use the same five major criteria as LI-RADS; however, it applies a stricter definition of threshold growth compared to LI-RADS. Specifically, growth according to OPTN is defined as diameter increase ≥50% on serial exams ≤6 months apart but does not include new lesions or lesions that have grown ≥100% in >6 months, which are both included in the LI-RADS definition of threshold growth.

LI-RADS 5 Category

Striving for high specificity, LR-5 category indicates definite HCC, meaning there is nearly 100% certainty the observation is HCC. Lesions in this category do not need confirmatory imaging or biopsy prior to treatment. LR-5 category is based on major criteria only and does not incorporate ancillary features. Lesions must demonstrate arterial phase hyperenhancement to qualify for LR-5 and therefore the diagnosis of HCC requires an adequate arterial phase.

Per the LI-RADS document, LR-5 is essentially equivalent to OPTN class 5 and may provide HCC exception points for priority on the liver transplantation list [12]. However, since OPTN applies a stricter definition for growth compared to LI-RADS, there are a few situations in which a LR-5 lesion may not meet the strict definition of OPTN class 5. New arterially enhancing lesions ≥10 mm or lesions that have more than doubled in >6 months would qualify as threshold growth that may bring them to LR-5 (if diameter ≥20 mm, or diameter 10 to 19 mm with one additional major criteria); however, their growth would not count toward OPTN class 5 categorization. It is worth noting that LI-RADS version 2014 has eliminated one of the discrepancies between LR-5 and OPTN class 5 by introducing category LR-5g, which corresponds to OPTN class 5g (arterial-enhancing lesion between 10 to 19 mm demonstrating ≥50% diameter increase in ≤6 months).

All lesions diagnosed as HCC on the basis of AASLD would fall within LR-5 category. Specifically, LI-RADS v.2014 introduces the LR-5us category, which applies to arterial-enhancing lesions with washout measuring ≥10 mm seen on prior screening US. However, the reverse is not true since many LR-5 lesions may not fit the AASLD criteria, particularly because AASLD does not consider the capsule appearance or threshold growth. Lesions ≥20 mm with either threshold growth or capsule but no washout would be LR-5, but would be indeterminate according to AASLD. Lesions 10 to 19 mm with both threshold growth and capsule but no washout would also be LR-5, but indeterminate on AASLD. In addition, AASLD requires that the lesion was identified on surveillance ultrasound, and therefore, all LR-5 lesions not seen on surveillance US are not addressed by AASLD. Table 2 compares LI-RADS category 5 with OPTN and AASLD.

Table 2 Comparison of LI-RADS category 5 with OPTN and AASLD (adapted from ACR LI-RADS version 2014. Accessed January 2017, from http://www.acr.org/Quality-Safety/Resources/LIRADS)

	LI-RADS	OPTN	AASLD
Diameter ≥20mm, APHE, +washout, ±capsule, ±threshold growth	LR-5	OPTN-5B (or 5X if > 5cm)	Definite HCC**
Diameter ≥20mm, APHE, no washout, +capsule, ±threshold growth	LR-5	OPTN-5B (or 5X if > 5cm)	Indeterminate**
Diameter ≥20mm, APHE, no washout, no capsule, growth ≥50% in ≤6 month	LR-5	OPTN-5B (or 5X if > 5cm)	Indeterminate**
Diameter ≥20mm, APHE, no washout, no capsule, new or growth ≥100% in >6 month	LR-5	Not categorized*	Indeterminate**
Diameter 10 to 19 mm, APHE, +washout, +capsule, ±threshold growth	LR-5	OPTN-5A	Definite HCC**
Diameter 10 to 19 mm, APHE, +washout, no capsule, growth ≥50% in ≤6 month	LR-5	OPTN 5A-g	Definite HCC**
Diameter 10 to 19 mm, APHE, no washout, no capsule, growth ≥50% in ≤6 month	LR-5g	OPTN 5A-g	Indeterminate**
Diameter 10 to 19 mm, APHE, no washout, +capsule, growth ≥50% in ≤6 month	LR-5	OPTN 5A-g	Indeterminate**
Diameter 10 to 19 mm, APHE, no washout, +capsule, new or growth ≥100% in >6 month	LR-5	Not categorized*	Indeterminate**
Diameter 10 to 19 mm, APHE, +washout, no capsule, new or growth ≥100% in >6 month	LR-5	Not categorized*	Definite HCC**
Diameter 10 to 19 mm, APHE, +washout, no capsule, no threshold	LR-5us	Not categorized*	Definite HCC

APHE arterial phase hyperenhancement

[a] OPTN guidelines defer to LI-RADS for cirrhosis-related nodules not meeting criteria for OPTN class 5 which leaves these scenarios uncategorized due to the discrepancy between LR-5 and OPTN-5

[b] AASLD is only applicable if the lesion was detected as ≥10-mm nodule at antecedent surveillance US

[c] OPTN does not directly address tumor in vein, however, since tumor in vein does not fit within the definition of stage T2 lesion described in OPTN; it can by inference be considered OPTN-5X

Since LR-5 category, OPTN class 5 and AASLD-definite HCC criteria all require arterial hyperenhancement as a criteria; hypovascular HCCs are not included in these categories. Most early HCCs are hypovascular due to incomplete development of the anomalous arterial supply which is characteristic of HCC [13, 14], and therefore, they will be missing from these categories. Similarly, large infiltrative HCCs are not included in any systems due to their variant imaging features.

LI-RADS 5V Category

LR-5V refers to definite tumor in the portal or hepatic vein based on presence of enhancing soft tissue in the vein. LR-5V is not a subgroup of LR-5, but is rather a separate category in the LI-RADS algorithm and may have different management implications. It is considered a contraindication to liver transplantation and may have implications on the eligibility for different types of loco-regional treatment. This situation is not directly addressed in OPTN or AASLD.

LI-RADS 3 and 4 Categories

LR-4 indicates a high probability that the observation is a HCC but without 100% certainty. These observations have features suggestive of HCC but are not definitive HCC and do not match the criteria for HCC on either OPTN or AASLD. Therefore, LR-4 observations may require further evaluation prior to treatment and do not provide HCC exception points for liver transplantation.

LR-3 indicates intermediate probability for HCC. In other words, both HCC and benign entities are considered moderate probability. These observations are less suspicious for HCC than LR-4 lesions, either because of their small size or because of lack of sufficient major features. LR-3 can be a "catch all" category. The LI-RADS algorithm describes "tie-breaking rules" which can be used to assign a final category when an observation has questionable features which place it between two categories. These tie-breaking rules always favor LR-3.

There is no direct correlate to these categories in AASLD and they would all fall under "indeterminate lesions." On the other hand, the latest version of OPTN describes the imaging criteria for class 5 lesion only and in the notes sections defers to LIRADS for description of other cirrhotic liver nodules [1.]

In our experience, LR-3 and LR-4 may cause the most confusion when adopting LI-RADS for multiple reasons:

- For the experienced radiologist, many observations that are categorized as LR-4 may have been simply reported as HCC if LI-RADS was not used. The suspicion for HCC can be based on ancillary features like restricted diffusion, high T2 signal or intralesional fat detected on MRI and clinical context (presence of other convincing lesions, satellite nodules, history of HCC in the same patient, or elevated HCC biomarkers). If LI-RADS is strictly adopted, these observations would have to be labeled as "probable HCC." This limitation is a consequence of trying to eliminate any false positive HCC in the LR-5 category. These cases are, to an extent, an inherent limitation of any reporting system, and neither OPTN nor AASLD offer any advantage. In fact, LI-RADS has avoided using ancillary features in the LR-5 category in part to maintain compatibility with OPTN.
- Some radiologists find LI-RADS too time consuming to learn and apply particularly when distinguishing LR-3 from LR-4 where the application of numerous ancillary features may further complicate the algorithm and may lead to inter-reader variability [15••]. In this view, the increased complexity is not justified since the distinction of LR-2, LR-3, and LR-4 does not directly have defined management implications. The LI-RADS algorithm addresses the increased complexity by making the application of ancillary features to be at the radiologist discretion. This may contribute to increased inter-reader variability, but there is no reason to expect that variability in reporting to be any better in the absence of the standardized LI-RADS terminology and rules.
- Another challenge is that LI-RADS is not a management guideline and intentionally avoids doing so. According to the LI-RADS Management Working Group, LR-2, LR-3, and LR-4 should be issued along with a diagnostic recommendation to help reach greater diagnostic certainty [11••]. These recommendations are limited to alternative imaging, routine surveillance, accelerated follow-up, or multidisciplinary discussion. Recommendation for biopsy or loco-regional treatment should not follow directly from the radiology report according to LI-RADS.
- Radiologists and treating clinicians may have difficulty accepting this categorization due to the lack of validated percentages to back up the terms "probable HCC" and "intermediate probability for HCC."

LI-RADS 1 and 2 Categories

LR-1 refers to definitely benign entity meaning that there is 100% certainty the observation is benign. LR-2 refers to observations with imaging features suggestive but not diagnostic of benign entities. Examples of benign entities that can be categorized as LR-1 or LR-2 are cysts, hemangiomas, vascular anomalies, perfusion alteration, focal steatosis or focal fat sparing, hypertrophic pseudomass, confluent fibrosis, or focal scarring. LR-1 is also assigned to observations that have disappeared on follow-up. Cirrhosis-associated nodules can be categorized as LR-2 when they follow a set of strict criteria, namely diameter

<20 mm and homogenous and isoenhancement on all phases. Otherwise, they should be classified as LR-3 or higher.

In our practice, we seldom use the term LR-1 and uncommonly use the term LR-2 when reporting observations. We label the observation by its diagnosis and if we are less certain, we recommend attention on follow-up imaging. The instances when we use LR-2 are usually when an observation that was previously categorized as LR-3 or higher was downgraded to LR-2 based on ancillary features or stability.

LI-RADS M Category

LR-M is used when an observation is probably malignant, but the imaging features are not specific for HCC. When working through the LI-RADS algorithm, it is important to consider whether an observation has features that may suggest another malignancy before assigning it a LR-4 or LR-5 category. Other systems do not address the increased incidence of intrahepatic cholangiocarcinoma (ICC) seen in cirrhotic livers. These patients with cholangiocarcinoma have potentially different management and outcomes from HCC especially in relationship to transplantation [1].

LI-RADS-Treated Category

LR-treated refers to observation that had undergone locoregional treatment. Up until version 2014, LI-RADS did not offer any guidelines in the assessment of the treated lesions. Ascribing a LR-treated category to an observation does not communicate any information about whether the lesion has shown response to treatment.

Currently, the Treatment Response LI-RADS working group is developing a standardized system for the interpretation, reporting, and data collection for treatment response assessment in patients who undergo liver-directed treatments for known or suspected HCC. The system will be called TR LI-RADS and is expected to be released in 2017 [12].

Compared to LR-treated, OPTN class 5T has a stricter definition as it only refers to lesions previously categorized as OPTN 5 that were subsequently treated. LR-treated, on the other hand, does not explicitly require that the observation be categorized as LR-5 previously. According to OPTN, priority points toward transplant are predicated on the pretreatment categorization of the lesion.

Validation of LI-RADS

Since their release, the AASLD criteria have been validated in a number of studies demonstrating high specificity of >95% and a wide range of sensitivity of 44–79% [16–21]. The latest OPTN guidelines were retrospectively validated in one study demonstrating specificity of 85–93% and sensitivity of 54–61% [22]. A large prospective multicenter trial comparing CT and MRI for HCC diagnosis and transplant allocation based on OPTN is underway by the American College of Radiology Imaging Network [23]. Since the LR-5 category in version 2014, which includes LR-5g and LR-5us, is essentially the combination of OPTN class 5 and AASLD-definite HCC with few uncommon exceptions discussed earlier, it follows that the specificity of LR-5 should be high. However, there are fewer large prospective data that specifically validated LI-RADS than the AASLD criteria and OPTN.

The LI-RADS 5 category is designed to have a very high specificity and intends to eliminate false positives since an imaging diagnosis of HCC is considered final and will dictate the transplant exception model for end-stage liver disease (MELD) score. This comes at the expense of relatively low sensitivity. In few studies that employed a combination of pathology and clinical criteria for the diagnosis of HCC, the sensitivity of the LR-5 ranged from 10 to 64% [24–27]. When assessing the performance of the combined LR-4 and LR-5, the sensitivity ranged from 71 to 91% [24, 25, 28]. Choi et al. validated LR-4 and LR-5 categories of LI-RADS 2014 in 240 liver nodules categorized as LR-4 or LR-5 with histologic diagnosis and reported a PPV of 95% for LR-5 and 82% for LR-4 [26]. Ehman et al. retrospectively assessed the images of 184 histologically proven HCCs. One hundred fourteen of them had adequate imaging, and only 61 of 114 (54%) HCCs were LR-5, 42 (37%) were LR-4, 10 (9%) were LR-3, and 1 (<1%) was LR-2 [25].

It is hard to extrapolate further from these studies given their variable designs and methods; however, the trend emphasizes that a large portion of LR-4 observations are HCCs. Close to half the HCCs in some studies did not meet LR-5 criteria, and most of them were classified as LR-4. The unanswered question remains, what percentage of LR-4 are HCCs compared to the other categories? A prospective study by Darnell et al. included lesions <20 mm detected on screening US. The patients underwent MR imaging and fine-needle biopsy. They found that 24 of 25 (96%) LR-4 observations were HCC. This compares with 44 of 45 (98%) LR-5 observations, 29 of 42 (29%) LR-3 observations, and 3 of 12 (25%) LR-2 observations [29••]. This study used LI-RADS v2013. Of the 25 classified as LR-4 (21 LR-4A and 4 LR-4B) in this study, 19 would be reclassified as LR-5us on LI-RADS v2014. All of those 19 were HCCs. This study supports the new LR-5us classification and the existing AASLD criteria, but does not answer the question about the sensitivity and specificity of the LR-4 category of LI-RADS version 2014.

Perhaps another way to better appreciate the meaning of the LR-4, LR-3, and LR-2 categories is to assess the natural history of these observations. A retrospective study by Burke et al. on the natural history of LR-4 observations followed 181 LR-4 observations by imaging for a median follow-up period of 163 days and found that 31% of the

observations were upgraded to LR-5, 40% remained LR-4, and 29% were downgraded on follow-up imaging [30]. Of the nodules upgraded to LR-5, 75% were upgraded within 6 months. No LR-4 nodules developed venous invasion, satellite nodules, or new intrahepatic or extrahepatic metastatic disease. A study by Choi et al. followed 69 LR-3 observations for a mean interval of 11.2 months [31]: 6% progressed to LR-5 or LR-4 and 94% remained stable or decreased. A larger retrospective study by Tanabe el al. followed LR-2, LR-3, and LR-4 by imaging, with a mean follow-up of 614 days and showed comparable results to the two prior studies [32••]. Of 52 index LR-4 observations, 38% progressed to malignant category (19 progressed to LR-5 and 1 to LR-M) and 44% remained stable. Of those that progressed, 75% progressed within 6 months. Of 166 index LR-3 observations, 4% progressed to LR-5 after >6 months, 5% progressed to LR-4, 23% remained LR-3, and 68% decreased in category. All 63 index LR-2 observations remained stable. A crude summary of these studies would suggest that about a third of LR-4 observations progress to LR-5 usually within 6 months and approximately 5% of LR-3 progress to LR-5. When discussing the natural history of the LI-RADS categories, it is important not to confuse progression of LI-RADS scores with the histological spectrum of HCC. Progression of the LI-RADS score may or may not reflect histological progression.

Another important aspect of validating the LI-RADS algorithm is assessing the inter-reader agreement in LI-RADS as compared to other systems. Davenport et al. [15••] looked at inter-reader agreement for LI-RADS version 2013, OPTN, AASLD, and the major imaging features among ten blinded readers. OPTN class 5, LI-RADS 5, and arterial enhancement had the best inter-reader agreement, which was described as substantial agreement. AASLD-definite HCC category had moderate inter-reader agreement. Washout and pseudocapsule had moderate agreement between readers. However, when evaluating the whole systems, LI-RADS and AASLD had only fair inter-reader agreement, while OPTN had moderate agreement. Overall, experts had better inter-reader agreement than novices. The decreased agreement on LR-4, LR-3, and LR-2 can be attributed in part to the use of ancillary image features to upgrade or downgrade observation within those categories. A study by Bashir et al. evaluated 200 hypervascular nodules >1 cm [33•]. Three radiologists categorized each observation based on OPTN and LI-RADS version 2013 and then applied the Milan criteria. There was strong agreement between category 5 assignments by the OPTN and LI-RADS systems. Inter-reader agreement was moderate for nodule features and nodule classification. The authors concluded that inter-reader variability is much higher than intersystem variability and agreement on patient eligibility for hepatocellular/MELD exception points is very strong. Three other studies have also looked at inter-reader agreement of the major imaging features of LI-RADS and showed a similar pattern of moderate to good agreement for arterial enhancement, washout, and capsule, and excellent agreement for diameter [25, 34, 35]. The study by Zhang et al. showed moderate inter-reader agreement for LI-RADS [35]. The one feature that showed consistently excellent agreement between readers in these studies was the diameter of the hepatic observation [15••, 33•, 35].

The LI-RADS algorithm expresses no preference for either MRI or CT; however, a number of the ancillary features described in the algorithm only apply to MRI. The studies that have compared MRI and CT using LI-RADS showed that MRI upgraded a significant number of observations relative to CT [24, 27, 36]. While ancillary features are a contributing factor to the difference between CT and MRI in LI-RADS scoring, it is probably not the only factor. Older literature suggests improved visualization and detection of arterial hyperenhancement with MRI compared to CT [37–39]. Zhang et al. has shown that there is substantial discordance between CT and MRI in scoring observations based on LI-RADS with CT producing significantly lower accuracy and sensitivity than MRI when using LR >3 as a positive threshold. This was due to improved detection of arterial enhancement, washout, and capsule appearance on MRI relative to CT [24]. It is worth noting that the ACR Appropriateness Criteria for initial characterization of liver lesions rate MRI higher than CT [40].

LI-RADS version 2014 incorporates the use of hepatobiliary contrast agents (HBAs) into the diagnostic algorithm, including gadoxetate disodium and gadobenate dimeglumine. There are three new ancillary features, two of which favor malignancy, hepatobiliary phase (HBP) hypointensity, and HBP hypointense rim. One new feature favors benignity, and HBP isointensity. None of these features contribute to LR-5, since neither OPTN nor AASLD criteria incorporate hepatobiliary agents. Multiple studies have already incorporated hepatobiliary agents in their evaluation of LI-RADS [26–28, 33•, 41]. Joo et al. [27] showed a comparable sensitivity of gadoxetate-enhanced MRI to CT (63 vs. 64%). Ancillary features upgraded 18% of observations on the MRI from LR-3 to LR-4. Washout and capsule appearance were less evident on gadoxetate-enhanced MRI. Hope el al. [41] showed that gadoxetate-enhanced MRI changed the LI-RADS categorization of 52 of 73 observations (71%) compared to CT: 30% were upgraded and 41% were downgraded. Based on clinical follow-up of these observations, the LI-RADS categorization on gadoxetate-enhanced MRI was more

accurate than on CT. These simply show that the use of hepatobiliary contrast agent may alter the LI-RADS categorization as would be expected, but there is no evidence in these studies that hepatobiliary contrast agent are superior to extracellular MRI contrast agents.

Summary

LI-RADS has evolved over the last few years and is gaining increasing recognition among radiologists and multidisciplinary hepatology teams. LI-RADS builds on the existing criteria namely OPTN and AASLD. It goes further by providing a lexicon and precise definitions of imaging of features, which is a major step toward standardization of interpretation and reporting. It deliberately stays away from management decisions that are already addressed by OPTN and AASLD. The LR-5 category is essentially equivalent for OPTN-5 with a few minor exceptions therefore providing sufficient information for transplant exception points. With the addition of LR-5us, the LR-5 category also encompasses the AASLD-definite cancer category. LR-4 is best considered as observations with high suspicion for HCC but not meeting definite criteria. Based on limited available literature, about a third of these will be categorized as LR-5 if followed by imaging, usually within 6 months. The actual percentage of LR-4 observations which are already HCCs is not yet clear from the literature, but it is evident that many HCCs do not meet LR-5 criteria (close to 50% in some studies) and the majority of them will fall under LR-4. LR-3 and LR-2 represent decreasing probability of HCC. The promise of achieving standardization is somewhat curbed by studies showing that only LR-5 category showed substantial inter-reader agreement and the remaining categories had moderate inter-reader agreement at best.

While the challenges to LI-RADS adoption are not trivial, a better understanding of the role and purpose of LI-RADS can facilitate its adoption. The multidisciplinary conference offers the best context for building this common understanding.

Compliance with Ethical Standards

Conflict of Interest Joseph H. Yacoub and Frank H. Miller each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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