The Gray Zone: LR3, LR-M, and LR-TIV

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Abstract

The goal of Liver Imaging Reporting and Data System (LI-RADS) is to standardize the lexicon, imaging techniques, interpretation, and reporting of observations in patients with a potential risk for developing hepatocellular carcinoma (HCC), and, consequently, improve communication between radiologists and physicians. LI-RADS diagnostic algorithms are applied to a population “at risk,” follow a stepwise algorithmic approach which categorize and stratify individual observations as HCC, and also assess the likelihood of non-HCC malignancies and tumor in vein. Risk factors for developing HCC have geographical variations, which significantly impact diagnostic and management strategies; however, these variations are not considered in the LI-RADS v2018 version. Further, the diagnostic algorithm includes several major and ancillary features, and, tie-breaking rules, which result in numerous probable combinations by which a plausible observation could be assigned a particular category, inherently increasing its complexity. Heterogeneity of the diagnostic algorithm results in certain imaging pitfalls and poses challenges in the precise characterization of observations, complicating its use in routine clinical practice. This article reviews the gray zones which may be encountered in the evaluation of LR-3, LR-M, and LR-TIV observations during routine clinical imaging with contrast-enhanced computed tomography and magnetic resonance imaging.

Keywords

► CT
► LI-RADS v2018
► LR-3
► LR-M
► LR-TIV
► MRI

Introduction

Liver Imaging Reporting and Data System (LI-RADS) v2018 is the newest version of LI-RADS, representing the unification of the LI-RADS diagnostic criteria with the American Association for the Study of Liver Diseases (AASLD) guidelines.1 LI-RADS categorizes observations into ordinal categories based on their probability of being hepatocellular carcinoma (HCC); LR-1 (definitely benign observation), LR-2 (probably benign), LR-3 (intermediate probability for malignancy), LR-4 (probably HCC), and LR-5 (definitely HCC), and also differentiates HCC from non-HCC malignancies (LR-M) and tumor in vein (TIV). LR-3 observations have an intermediate probability of malignancy, with imaging follow-up preferred over active therapeutic intervention of these observations. LR-4 observations are considered as probable HCC (not a 100% certainty); however, the Asian Pacific Association for the Study of the Liver or Korean Liver Cancer Association–National Cancer Center guidelines consider LR-4 observations as HCCs,2,3 and a multidisciplinary approach is recommended to manage such lesions, which can vary based on institutional practices. Radiological differentiation of HCC from non-HCC malignancies is critical, as the presence of a non-HCC malignancy may preclude the patient from liver transplantation. LR-M observations represent a heterogeneous milieu, and comprise of both atypical HCCs and non-HCC malignancies. TIV is a separate category in the current version of LI-RADS, is an imaging biomarker of biological aggressiveness and invasiveness, correlates with overall poor clinical outcomes, and is an absolute contraindication for liver transplantation. Appropriate assignment of LR-3, LR-M, and LR-TIV categories is critical in a setting of chronic liver disease to minimize the

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number of biopsies, and to guide precise patient management. The purpose of this article is to review the multimodal imaging features of LR-3, LR-M, and LR-TIV observations, discuss the potential gray zones, and therapeutic implications of these observations.

**LR-3**

Development of HCC is a multistep carcinogenesis process. Early detection of HCC (< 10 mm) is vital, as these have a limited propensity to be angioinvasive, and are therefore amenable to early intervention with a curative intent. Focal observations < 10 mm in size are categorized as either LR-3 (intermediate probability of malignancy) or LR-4 (probably HCCs; ► Fig. 1A–D). LR-3 category indicates an intermediate probability of malignancy, so as to warrant routine surveillance with an imaging follow-up rather than active treatment. The AASLD guidelines of 2018 have proposed a 10-mm threshold (subthreshold HCCs), as these lesions are challenging to diagnose and characterize reliably due to their small size, and are less likely to be malignant. In clinical practice, an increasing number of subcentimeter size hypervascular observations are observed on contrast-enhanced computed tomography (CECT) and magnetic resonance (MR) imaging (MRI), with the cumulative risk of HCC progression in these observations being higher than in hypovascular nodules. Ranathunga et al showed that the rate of progression from LR-3 to LR-4 was 22.22% (► Fig. 2A–F) and from LR-3 to LR-5 was 11.1% at least 12 months after the initial observation was detected. Studies evaluating subcentimeter size observations showing typical imaging features of HCC on gadoxetic acid-enhanced MRI and diffusion-weighted imaging (DWI) showed that all nodules (100%) > 5.5 mm progressed to overt HCC within a year in patients with a history of HCC and 89.9 to 100% of the nodules progress to overt HCCs (≥ 1 cm) within 12 months. Diagnostic efficacy and sensitivity of CECT and dynamic contrast-enhanced MRI for detecting early HCCs is based on the observation size, and both modalities have a low sensitivity in diagnosing subthreshold HCCs. Based on the AASLD LI-RADS v2018 guidelines, current noninvasive diagnostic criteria do not allow for characterization of a subcentimeter size observation as LR-5. Subset of subcentimeter size observations demonstrate arterial phase hyperenhancement (APHE), with either one of the following including nonperipheral washout, enhancing capsule, or threshold growth and are categorized as LR-4 observations.

**Gray Zones in the Assessment of LR-3 Observations**

1. Background liver may limit the detection of LR-3 observations: The presence of transient hepatic attenuation/intensity differences (THADs/THIDs) in the liver parenchyma due to inflammation, arterioportal shunts or fistulas, portal vein thrombosis, and posttreatment sequelae can lead to either a false-positive interpretation or false-negative interpretation due to obscuration of LR-3 observations. Background iron overload or steatosis may cause the liver to appear darker than usual, limiting the ability to detect washout resulting in a false negative. On the contrary, the presence of fibrosis, may lead to a false impression of washout with a capsule resulting in a false positive and upgrading of a LR-3 observation to LR-4. Radiologists must note that differentiating fibrosis from

![Fig. 1](image-url) (A–D) LR-3 observation: Axial 3-dimensional T1-weighted (T1-w) fast spoiled gradient-echo (FSPGR) sequences reveal a 3-mm observation in the subcapsular location of segment VI of right lobe of liver, which appears isointense to the parenchyma on the precontrast (A) images, reveals non-rim-like arterial phase hyperenhancement (APHE) (yellow arrow) on the arterial phase (B), without washout on the portal (C) and venous (D) phase images.
capsule is extremely challenging and may lead to miscalcategorization.

2. Limited detection and characterization of subcentimeter size observations on CT: Both LR-3 and LR-4 categories are heterogeneous entities, each assignable by different combinations of imaging features, which may be further adjusted by the application of ancillary features (AFs) and tie-breaking rules. Introduction of AFs and tie-breaking rules introduces interreader variability, which results in lower agreement among radiologists when assigning LR-3 or LR-4 categories. Due to inherent differences in imaging techniques, MR tends to detect benign pseudo-lesions which are categorized as LR-2 or LR-3 more often, which may remain undetected or uncategorized on CT. Presently, there is no consensus on a particular choice of modality within the technical recommendations of LI-RADS. Unlike MR, contrast CT protocols including rate of injection of contrast are not optimized, which further contributes to the diagnostic dilemma. Limited soft tissue resolution of CT precludes definitive assessment of washout or enhancing capsule in subcentimeter size observations. Majority of the AFs are applicable only to MR, and CT is incapable of assessing these features, which precludes accurate upgrading or downgrading of these observations. Early HCC is categorized LR-4 more frequently on extracellular contrast-enhanced MRI than on CT due to the presence of intratumoral fat\textsuperscript{13} and due to the presence of hepatobiliary phase (HBP) hypointensity on gadoxetate-enhanced MRI.\textsuperscript{14}

3. Hypoenhancing observations on the arterial phase (< 20 mm): Nonhypervascular observations detected on multiphasic CT and MR pose a diagnostic challenge (\textit{\textbf{Fig. 3A–H}}). Very little is known and understood about these nodules. Agnello et al\textsuperscript{15} assessed the outcome of LR-3 observations without APHE and showed that 17 out of 55 (31\%) LR-3 observations progressed to LR-5 at follow-up. A baseline diameter of 10 mm significantly increased the risk for LR-5 progression of LR-3 observations in their study. The authors inferred that the hypoenhancing LR-3 observations could represent precancerous lesions (dysplastic nodules or early HCCs) that develop hypervascularization and progress to classic HCC during multistep hepatocarcinogenesis process.\textsuperscript{16–18} HBP hypointensity is an AF and is related to a decreased or absent expression of OATP receptors. LR-3 observations with HBP hypointensity and a baseline diameter of 15 mm have an increased risk of developing APHE.\textsuperscript{16} However, many observations which are stable or are downgraded also show this feature and hence category upgrade only based on this AF should be determined with caution. PEARL: We believe that hypoenhancing LR-3 observations with a baseline diameter of 10 mm or greater should be closely followed-up because of an increased risk of progression to LR-5. The use of ancillary criteria to upgrade or downgrade a hypoenhancing observation requires a cautious approach, and more refinement of the guidelines for the use of AFs in clinical practice is needed.

4. Ancillary features: Changes in hemodynamics of HCC vis-\textit{a}-vis the background “At-Risk” liver is the key to making an accurate diagnosis. However, this approach may not be appropriate in certain populations, inherently reducing the sensitivity for detection of early HCCs, which is attributable to incomplete neoangiogenesis. AFs favoring malignancy in general include mild to moderate T2 hyperintensity, fat sparing in solid mass, iron sparing in solid mass, corona enhancement, transitional phase...
hypointensity, HBP hypointensity, and restricted diffusion. Of these, HBP hypointensity, and DWI contribute to higher sensitivity for HCCs on MRI. On the contrary, Shropshire et al assessed 141 LR-3 observations and showed that ancillary criteria did not contribute to LR-3 observation category changes on follow-up studies. In their study, 40% (57/141) of baseline LR-3 observations remained LR-3, 8% (11/141) were downgraded to LR-2, and 42% (59/141) were downgraded to LR-1. Two percent were upgraded to LR-4 (3/141) or 8% to LR-5 (11/141). In the setting of a new LR-3 observation, AFs such as mild-to-moderate T2-weighted (T2-w) hyperintensity, restricted diffusion, or HBP hypointensity may upgrade an observation to LR-4. In our experience, we do not recommend to upstage observations based on ancillary criteria alone as AFs would need to be weighted appropriately for each LI-RADS category adjustment, and refinement of the ancillary criteria and LI-RADS guidelines may be warranted to reduce interobserver variability to improve categorization of subcentimeter size hypervascular nodules.

5. Imaging follow-up versus biopsy versus immediate therapy: Management of subcentimeter size hypervascular nodules is highly debatable and varies between different institutions. As per the LI-RADS v2018 guidelines, LR-3 observations may undergo follow-up imaging at 3 to 6 months' interval (►Fig. 4A, B), whereas LR-4 observations would require a multidisciplinary approach to decide an individualized management, which may include close follow-up imaging at < 3 months, biopsy, or in few cases a therapeutic intervention. Biopsy of observations (< 1 cm) is challenging, may not be technically feasible, and possesses an inherent risk of sampling bias, with a potential risk of tract seeding. However, if subcentimeter observations are pathologically confirmed to be HCC on biopsy, immediate treatment is recommended. Due to these factors, a follow-up strategy based on threshold growth criteria is clinically more feasible and agreeable to clinicians. Threshold growth is defined as > 50% increase in diameter in < 6 months, represents a surrogate imaging biomarker for progression to HCC, is a “major diagnostic criterion” in the LI-RADS v2018 and Organ Procurement and Transplantation Network-United Network for Organ Sharing guidelines, and, therefore, allows for the diagnosis of early HCCs (10–19 mm). Lastly, there is no specific recommendation on prioritizing strategy for the therapeutic management of these indeterminate nodules, as precise colocalization of such nodules is a technical challenge. There are no studies comparing the clinical outcomes of subcentimeter nodules which have features suspicious for HCC between immediate treatment and follow-up imaging, and there is insufficient clinical evidence to recommend a standardized strategy for monitoring LR-3 observations. Based on the current evidence, an interval of 6 months is optimal and cost-effective, as a short-interval follow-up could increase treatment costs, whereas a longer interval could increase the risk of diagnosing HCC when it is already untreatable.22–24

LR-M

LI-RADS is a probabilistic scale developed primarily for the Western population. The goal of LI-RADS Category 5 is to have a high specificity and positive predictive value (PPV) for the diagnosis of HCC, to negate the need for histopathological diagnosis. The major imaging criteria including observation size, non-rim-like APHE, nonperipheral washout, capsule appearance, and threshold growth are intended to emphasize this high specificity.25,26 Majority of malignant
observations that arise in an "At-Risk" liver are HCCs, which could then be graded using the probabilistic scale of LR-1 to LR-5. However, in routine clinical practice, many HCCs do not meet these stringent criteria. Further, non-HCC malignant tumors deviate from the standardized probabilistic scale of LR-1 to LR-5, as they demonstrate imaging features which are indicative of their non-hepatocellular origin. As a diagnostic algorithm, LI-RADS is unique in that it provides a specific category, namely, LR-M, for defining observations that are definitely or probably malignant, but are not specific for the diagnosis of HCC. The imaging differentials for LR-M observations include intrahepatic cholangiocarcinoma (IH-CCA), combined tumors such as hepatocellular carcinoma (HCC), metastasis, lymphoma, and atypical HCC. Even few benign entities such as atypical abscesses or sclerosing hemangiomas are also included in the LR-M category. It is critical that radiologists must remember that LR-M category does not exclude the diagnosis of HCC,27–29 and the imaging features of such HCCs may have prognostic implication and could imply poor clinical outcomes.30 In this regard, though LI-RADS was principally developed as a diagnostic scale, we do feel it may have prognostic implications which requires validation. LR-M category observations are subcategorized as a targetoid mass or a non-targetoid mass (Illustration 1).

**Fig. 4** (A, B) Stability of LR-3 observation: magnetic resonance imaging (MRI) dated March 22, 2022 shows a 3-mm observation demonstrating non-rim-like arterial phase hyperenhancement (APHE) in the subcapsular location of segment VI of right lobe of liver (yellow arrow), which has remained stable on the follow-up MRI performed on September 9, 2022.
**LR-M: Targetoid Appearance**

Imaging appearance of a targetoid mass is closely associated with the imaging appearance of IH-CCA, as this is the most common non-hepatocellular primary malignant hepatic neoplasm. Histologically, IH-CCA reveals a peripheral hypercellular rim (representing viable tumor) and a central core of desmoplasia or ischemia. Temporal enhancement features (► Fig. 5A–F) of these targetoid observations mirror tumoral histology and include rim-like APHE (enhancement in the observation periphery), peripheral washout on the venous phase (washout is most pronounced in the observation periphery), and delayed central enhancement (core of the observation enhances the late venous phases). Observations which demonstrate rim-like APHE with or without progressive concentric enhancement are reported to be biologically

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**Fig. 5** (A–F) LR-M observation. A 63-year old male with chronic liver disease and portal hypertension with elevated CA 19–9 (67.52 U/mL). A 34-mm observation (yellow arrows) in segment VIII of right lobe of liver which appears hypointense to the background parenchyma on the precontrast (A) three-dimensional T1-weighted fast spoiled gradient-echo (FSPGR) sequence, and demonstrates rim-like arterial phase hyperenhancement (APHE) (B) with peripheral washout and progressive enhancement of the core on the venous phases (C–F).

**Fig. 6** (A–C) Targetoid morphology of LR-M observation in a 63-year-old male with chronic liver disease and portal hypertension with elevated CA 19–9 (67.52 U/mL). On the hepatobiliary phase (A), there is retention of contrast within its core (red arrow) surrounded by a thin hypointense rim (dotted yellow arrows). On the T2-weighted (T2-w) image (B), the observation reveals a hyperintense core (red arrow) surrounded by a thick irregular intermediate signal outer rind (dotted yellow arrows). On the diffusion-weighted (DW) image (C), the core reveals facilitated diffusivity (red arrow) whereas the rind reveals restricted diffusion (dotted yellow arrows).
aggressive and have worse prognosis.\textsuperscript{31–33} On the transitional phase or HBP, these observations reveal moderate to marked hypointense periphery surrounding a milder hypointense core (\textsuperscript{►}Fig. 6A–C). Hepatobiliary-specific gadolinium agents are absorbed by hepatocytes via the OATP1 transported mechanism, including gadobenate disodium (Gd-BOPTA) and gadoxetate disodium (Gd-EOB-DTPA), of which only gadobenate disodium is available for clinical use in India. Radiologists must note that only 2 to 4% of gadoxetate disodium is absorbed by hepatocytes and excreted in the biliary tree between 60 and 120 minutes' interval. Quantum of biliary excretion is dependent on the liver function status, with poor or nonexcretion seen in severe hepatocellular dysfunction or obstructive biliopathy with elevated bilirubin levels, and therefore impacts the appearance of the observation on the HBP. In our experience, a majority of these targetoid observations on HBP reveal a relatively mild hypointense core, the intensity of which is less or nearly isointense to the background hepatic parenchyma but more than the intensity of the spleen, reflecting contrast retention within the extracellular desmoplastic core. Appearance of these targetoid observations on DW and T2-w sequences parallel the temporal enhancement features and reveal a concentric morphology, comprising of moderate to marked hypointense (restricted diffusivity) periphery with milder hypointensity (facilitated diffusivity) in the core (\textsuperscript{►}Fig. 6A–C).

\textbf{LR-M: Nontargetoid Appearance}

Less common clinical scenarios which would necessitate the radiologist in applying the LR-M category would include infiltrative masses without TIV, marked diffusion restriction, necrosis, or severe ischemia, each in the absence of other features of an LR-5 observation. Few AFs which could be suggestive of a non-HCC malignancy include biliary dilatation, capsular retraction, and multiplicity. There is a relative paucity of data on these imaging criteria and would require validation both in the research and clinical setting.

\textbf{Gray Zones in the Assessment of LR-M Observation}

\textbf{Observation Size}

Unlike LR-4 and LR-5 observations, there are no specific size criteria defined for LR-M observations and smaller observations are known to be diagnostically challenging. Small IH-CCAs in an “at-risk” liver may show features that are indistinguishable from HCCs, including non-rim APHE with nonperipheral washout,\textsuperscript{34} and may lack the typical targetoid morphology on the AFs on the T2-w and DW, and HBP.\textsuperscript{35} In our experience, such observations are discussed in the multidisciplinary tumor boards and we recommend either close follow-up imaging at 1 to 2 months' interval or alternatively a percutaneous biopsy if technically feasible, an approach that is similar to LR-4 observations.

\textbf{Combined Neoplasm (HepatoCholangiocarcinoma)}

H-ChC are biphenotypic tumors which reveal overlapping features of HCC and IH-CCA.\textsuperscript{36,37} These observations pose a diagnostic challenge and in a small minority of cases may be classified as LR-5. The presence of even one targetoid LR-M feature (rim-like APHE or peripheral washout on the venous phase or delayed central enhancement) is sufficient to classify the observation as LR-M. If unequivocally present, rim-like APHE in only a part of the observation would require the observation to be categorized as LR-M. If there is a diagnostic dilemma between rim APHE and non-rim APHE, the radiologist should err on...
Multifocality
LR-M observations may be multifocal in an “at-risk” liver. Multifocal LR-Ms (► Fig. 7A–D) generally would be expected to demonstrate identical morphology and temporal enhancement features, which would imply similar histology and biological aggressiveness. Occasionally, LR-Ms may occur synchronously with observations which may be subclassified either as LR-3, LR-4, or LR-5, and this is where the diagnostic conundrum lies (► Fig. 8A–D). In such a clinical context, these observations are reviewed in a multidisciplinary tumor board. Based on the multidisciplinary team (MDT) recommendations, a fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT is the side of reporting rim APHE and assign an LR-M category to the observation.

Fig. 8 (A–D) LR-M observations in association with LR-3 and LR-5 observations. Treated c/o hepatocellular carcinoma (HCC) in a hepatitis B virus (HBV)–induced chronic liver disease. Underwent liver donor liver transplant (LDLT). On routine ultrasonographic surveillance, detected to have few focal liver lesions in the transplant graft. On the axial three-dimensional T1-weighted fast spoiled gradient-echo (FSPGR) sequence acquired during the late arterial phase (A–D), two discrete observations demonstrating rim-like arterial phase hyperenhancement (APHE) (A, B; yellow arrows) are seen in the transplant graft liver, the larger observation in panel A revealing capsular retraction. Note a concomitant LR-5 observation (> 10 mm) revealing a nodule-in-nodule appearance (C; red arrow) and a subcentimeter size (< 10 mm) LR-3 observation in the graft liver.

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Fig. 9 (A–C) LR-M observation. LR-M observation (yellow arrow) in the posterior subcapsular aspect of the transplant graft liver demonstrates rim-like arterial phase hyperenhancement (APHE) (A), and increased metabolic activity (black arrows) on the 18-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) (B, C) images.
usually performed to assess FDG uptake in the observations, the presence of extrahepatic disease, and aid in tissue sampling. Alternatively, due to cost constraints, a percutaneous biopsy may be performed without a FDG PET/CT to obtain histological proof of either a non-HCC or HCC malignancy in view of the impact of tissue diagnosis on therapy and long-term outcomes.

**Role of Positron Emission Tomography/Computed Tomography in LR-M observations**

FDG PET/CT is not recommended for the detection of HCC due to its low sensitivity. Increased uptake of FDG in HCC has been reported to be a surrogate imaging biomarker of biological aggressiveness and has also been associated with poor outcomes (<Fig. 9A–C>). Newer PET tracers such

![Fig. 10](image-url-1) (A–D) Positron emission tomography (PET)/computed tomography (CT) and biopsy of LR-M observation. A 34-mm observation (yellow arrow) in segment VIII of right lobe of liver which demonstrates rim-like arterial phase hyperenhancement (APHE) (A), and a targetoid morphology on the PET/CT (B, C) images comprising of a metabolically active outer rind (black arrows) surrounding a relatively nonactive core (mimicking the appearance on the T2-weighted [T2-w] and diffusion-weighted [DW] images). Axial CT (D) image shows a Trucut biopsy needle traversing the segment VIII observation.

![Fig. 11](image-url-2) (A–F) Histopathology and immunohistochemistry (IHC) of the biopsied LR-M observation in Fig. 10 revealed an intrahepatic cholangiocarcinoma (IH-CCA). Hematoxylin and eosin (H&E) (A) shows an infiltrative neoplasm composed of atypical cells arranged in nests and irregular anastomosing glands set in a fibrotic stroma. Tumor cells are diffusely and strongly positive for PanCK (B), CK7 (D), and CK19 (E) and negative for Hepar1 (C) and synaptophysin (F), chromogranin and arginase (not shown). Images contributed by Dr. Toshi Mishra.
as $^{11}$C-acetate have a higher sensitivity for HCC detection and monitoring the response to locoregional therapies. PET/CT with $^{11}$C-choline overcomes the limitations of $^{11}$C-acetate, and is useful in the therapeutic management of patients with HCC. Further studies are required to clearly define the clinical impact of dual-tracer PET/CT in patients with HCC. In our setting of live liver donor transplants, PET/CT may be used as single imaging tool to exclude extrahepatic disease (nodes, adrenal, pulmonary, or skeletal metastases) and to assess the quantum of FDG uptake in patients with HCC beyond the University of California, San Francisco criteria or with a suspected TIV prior to down-staging. Anecdotally, we have seen that PET/CT may be useful in determining biologic aggressiveness of LR-Ms, which would allow the interventional radiologist to biopsy the observation with the highest maximum standardized uptake value (SUVmax) to obtain maximum diagnostic yield.

**Biopsy**

LR-M observations invariably undergo targeted percutaneous biopsy (►Fig. 10A–D), at our institution, unless the biopsy is not technically feasible, or there are specific contraindications to performing a biopsy (coagulopathy, patient is on blood thinners, observations are in close proximity to critical vascular structures). Biopsy of LR-Ms is imperative, as the presence of pathologically proven non-HCC malignancy precludes the patient from transplantation (►Fig. 11A–F). Alternatively, if an LR-M observation is sampled and pathologically proven to be an HCC, there is a growing need for molecular and immune classification of HCCs. In our experience, the cutting edge of the biopsy needle must traverse the peripheral enhancing rim of the observation to obtain an optimum diagnostic yield. Follow-up imaging is not recommended, unless the observation cannot be biopsied or the biopsy is negative. Duration between the interval follow-up is decided as per MDT recommendations and is individualized.

**ExtraHepatic Findings in LR-M**

As LR-M observations are considered to be biologically more aggressive, it would be pertinent to look for extrahepatic metastatic disease. The common sites would include regional (porta, periportal, common hepatic, retroportal-precaval), retroperitoneal, or lower thoracic adenopathy, or organ-based disease such as adrenal, pulmonary, or skeletal metastases (►Fig. 12A–C). At our institution, either a CT scan of the chest, abdomen, and pelvis along with a bone scan may be performed, or alternatively a whole body FDG PET/CT scan may be performed to assess for extrahepatic disease. If extrahepatic disease is detected, tissue sampling is pertinent prior to strategizing therapeutic options (►Fig. 13 A–F).

**Other Causes of LR-M**

Occasionally, an “at-risk” liver may develop hypervascular metastases from an extrahepatic primary, which could be erroneously categorized as LR-4 or LR-5 observations. Presently, there is no clinical data available which discusses the incidence of APHE metastases in an “at-risk” liver and the frequency of misinterpretation using the LI-RADS probabilistic categorization scale. LR-M category also includes few benign lesions such as abscesses or sclerosis hemangiomas. Categorization of benign lesions as LR-M by the radiologist is a major clinical problem, especially if these patients undergo surgical intervention without prior histological proof. Noninvasive imaging biomarkers have yet to be devised and validated to clearly differentiate probably or definitely malignant LR-M
observations. Further, when in doubt, these observations would always need to be biopsied for histological proof.

**LR-TIV**

Vascular invasion is defined as the presence of tumor within the branches of the portal or hepatic veins, and can be subclassified as either microvascular or macrovascular. Microvascular invasion is observed on histological examination, the current gold standard. Macrovascular invasion is observed on gross examination or imaging and is referred to as TIV in LI-RADS. In a setting of HCC, the reported prevalence of TIV is approximately 6.5 to 44.0%.\(^{38-42}\) Portal vein tumor thrombus in HCC indicates the invasive nature and biological aggressiveness of the neoplasm, corresponds to reduced tolerance to chemotherapy and rapid deterioration of liver function due to decreased reserve, and is associated with poor clinical outcomes.\(^{43}\) Presence of TIV is an absolute contraindication for liver transplantation,\(^{44,45}\) and hence accurate diagnosis of this entity and understanding the pitfalls in assessment of TIV are critical to patient management.

Absence of a parenchymal observation does not preclude the LR-TIV category. However, as a standalone imaging feature, the presence of TIV is not sufficient to classify an observation as an HCC with vascular invasion, as other non-HCC malignancies may also present with TIV. A systematic

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**Table 1** Definitive and suggestive features of LR-TIV as per CT/MRI LI-RADS v2018

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<thead>
<tr>
<th>Definition</th>
<th>Imaging features diagnostic of TIV</th>
<th>Imaging features suggestive of TIV</th>
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<td>Unequivocal presence of enhancing soft tissue in vein, regardless of presence of parenchymal mass</td>
<td>• Occluded vein with ill-defined walls</td>
<td>Presence of these features prompt careful scrutiny for the presence of enhancing soft tissue in the vein</td>
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<tr>
<td>Occluded vein with restricted diffusion</td>
<td>• Occluded or obscured vein in contiguity with malignant parenchymal mass</td>
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<tr>
<td>Occluded or obscured vein in contiguity with malignant parenchymal mass</td>
<td>• Heterogeneous vein enhancement</td>
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<td>Heterogeneous vein enhancement</td>
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**Applicable modalities**

CT, MRI, CEUS

CT, MRI

**Categorization**

LR-TIV

Presence of these features prompt careful scrutiny for the presence of enhancing soft tissue in the vein

**Comments**

CT/MRI - characterize TIV on any phase CEUS—early arrival (same as hepatic arterial opacification) helps differentiate from bland thrombus

Abbreviations: CEUS, contrast-enhanced ultrasound; CT, computed tomography; LI-RADS, Liver Imaging Reporting and Data System; MRI, magnetic resonance imaging; TIV, tumor in vein.
review and meta-analysis of 17 studies by Van der Pol et al reported pooled percentages of HCC for all observations categorized as TIV of 79%.\textsuperscript{46} In another meta-analytic study, Kim et al\textsuperscript{47} observed the pooled percentages of HCC and non-HCC in LR-TIV were 70.9% (95% confidence interval [CI], 55.7–82.5%; $I^2 = 59\%$) and 29.2% (95% CI, 17.5–44.4%; $I^2 = 59\%$), respectively.

As per LI-RADS v2018, the LR-TIV category (\textsuperscript{- Table 1}) can only be applied in the unequivocal presence of enhancing soft tissue within the vein, regardless of the presence of a parenchymal observation.\textsuperscript{48} Presence of enhancement within the thrombus is a definitive feature (\textsuperscript{- Fig. 14A–E}), and is aimed to attain a high specificity toward the diagnosis of TIV which would imply a 100% accuracy in detecting the presence of vascular invasion.

There are few imaging features which are suggestive but not definitive for the diagnosis of TIV on CT/MRI, and are hence not specific enough to classify an observation as LR-TIV. These include an occluded vein with indistinct walls, occluded vein with restricted diffusion, occluded or obscured parenchymal observation.\textsuperscript{48}
vein in contiguity with malignant parenchymal mass, and heterogeneous enhancement (► Fig. 15A–C). Thompson et al.\(^49\) reported that obscuration or poor delineation of the walls of a vein are considered a feature associated with TIV rather than a bland thrombus. DW images may aid in differentiating bland thrombus from TIV. LI-RADS v2018 recommends that DWI sequences should be acquired with \(\geq 2\) b values (including \(b = 50\) and \(b = 400–1000\) second mm\(^2\)). Based on these parameters, an occluded vein has a higher likelihood of representing TIV if it reveals true restricted diffusion unequivocally higher DWI signal compared with hepatic parenchyma and/or apparent diffusion coefficient (ADC) value unequivocally lower than parenchyma. Though studies\(^50\) have reported high sensitivities and specificities of DW-ADC for the detection of TIV, there is considerable overlap between the ADC values of TIV and

**Fig. 16** (A–F) LR-TIV (tumor in vein) versus bland thrombus: Axial T2-weighted (T2-w) (A), diffusion-weighted (DW) (B; b-value 1,000), and portal venous phase (C) images acquired at the level of the porta reveal an expansile enhancing soft tissue (yellow arrows; C) within the right portal vein and its anterior and posterior divisions extending into the main portal vein, which reveals mild to moderate hyperintense signal on the T2-w images (A) and restricted diffusivity (B). Axial T2-w (A), DW (B; b-value 1,000), and portal venous phase (C) images acquired at the level of portomesenteric confluence reveal a nonenhancing intraluminal filling defect within the confluence (F) representing a bland thrombus (white arrows) which reveals moderate to marked hyperintense signal on the T2-w images (D) and restricted diffusivity (E), suggesting considerable overlap in the T2-w and DW signal changes in TIV and bland thrombus. Enhancing soft tissue within a vein is the ONLY unequivocal finding of LR-TIV.

**Fig. 17** (A–D) A 70-year-old man with an infiltrative LR-M observation. Axial three-dimensional T1-weighted fast spoiled gradient-echo (FSPGR) sequences acquired during the late arterial (B) phase reveal a heterogeneously enhancing observation demonstrating nodular or miliary morphology (black arrows in B) in the right lobe of liver. Washout is challenging to detect on the portal (C) and hepatic venous (D) phases images as it mimics the background fibrosis. Few discrete subcentimeter size observations with rim-like arterial phase hyperenhancement (APHE) yellow arrows in B–D) are seen within this large observation, which persist on the portal and hepatic venous phases.
bland thrombus, and hence DW is not that accurate to differentiate the two entities. Heterogeneous enhancement within an occluded vein is highly suspicious for vascular invasion; however, the presence of collaterals in a thrombus may mimic enhancement. Further, the readers must be aware of flow-related artifacts which may mimic enhancement and represents a potential pitfall. In this context, CE ultrasound has a higher sensitivity in detecting TIV as compared with CT/MRI, and may be used as a problem-solving tool to differentiate TIV from bland thrombus.

Gray Zones in the Assessment of LR-TIV Observation

High Specificity and Lower Sensitivity

Goal of LI-RADS category LR-TIV is to have a high specificity and PPV toward the diagnosis of TIV. However, this results in an inherently lower sensitivity, and not all cases of TIV would be accurately classified as LR-TIV. This is especially true when the observations reveal an infiltrative or permeative growth pattern, such as those observed
with diffuse infiltrative HCCs. Infiltrative HCCs often do not reveal the characteristic non-rim-like APHE and the arterial enhancement may be very heterogeneous, patchy, nodular, or miliary, and washout is challenging to detect as it may mimic the background fibrosis (►Fig. 17A–D). TIV is often associated with diffuse infiltrative HCC. In equivocal cases, subtraction images may help detect subtle enhancement in cases of TIV. Occasionally, TIV can be present in the absence of a definitive parenchymal mass lesion (►Fig. 18A–F).

LR-TIV in Non-HCC Malignancies
Non-HCC malignancies (LR-M) may present with TIV in cirrhotic patients, which can easily be misinterpreted as HCC. Van der Pol et al observed that among the non-HCC LR-TIV observations, 37% were combined HCC-CCA, 25% were IH-CCA, 6% were sarcomatoid carcinoma, and 32% remained undetermined. The presence of imaging clues such as rim-like APHE or peripheral washout should alert the reader to the presence of a LR-M observation (►Fig. 19A, B).

Expansion of an Occluded Vein
Band thrombosis of the portosplanchnic veins occurs in cirrhotic patients due to portal hypertension, reduced/sluggish portal flow, or the presence of a malignancy. Expansion of a vein is considered a sign of vascular invasion; however, this sign is also seen during acute thrombosis of a vein.

T1 Hyperintense Signal of a Thrombus
Occasionally, the presence of hemorrhagic component within a thrombus may appear hyperintense on the unenhanced T1-w images, and mimic enhancement (►Fig. 20A–C). In such cases, subtraction images will differentiate pseudoenhancement from true enhancement.

Enhancement within a Thrombus
If the clot is not dissolved, numerous collateral vessels develop around an occluded vein which may mimic enhancement. Further, serpiginous vessels do develop in cases of recanalization which also mimic enhancement and may lead to a spurious diagnosis of LR-TIV.

Necrosis with the TIV
Necrosis of the intraluminal tumor within an expanded and occluded vein, may lead to absence of intraluminal enhancement; however, this would not rule out the presence of TIV.

Conclusion
This article reviews the potential gray zones in applying major features and AFs in assigning LR-3, LR-4, and LR-M categories on CT and MRI in routine clinical practice, with potential solutions to these diagnostic challenges. In-depth understanding and knowledge of the diagnostic algorithm, its gray zones and potential pitfalls, and regional practice variations are pertinent for the precise diagnosis of these entities and to guide patient management.

Conflict of Interest
None declared.

References
LR3, LR-M, and LR-TIV


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