



Pitfalls and problems to be solved in the diagnostic CT/MRI Liver Imaging Reporting and Data System (LI-RADS)

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Abstract

The 2017 Core of the computed tomography (CT)/magnetic resonance imaging (MRI) Liver Imaging Reporting and Data System (LI-RADS) provides clear definitions and concise explanations of the CT/MRI diagnostic algorithm. Nevertheless, there remain some practical and controversial issues that radiologists should be aware of when using the system. This article discusses pitfalls and problems which may be encountered when the version 2017 diagnostic algorithm is used for CT and MRI. The pitfalls include challenges in applying major features and assigning the LR-M category, as well as categorisation discrepancy between CT and MRI. The problems include imprecision of category codes, application of ancillary features, and regional practice variations in hepatocellular carcinoma (HCC) diagnosis. Potential solutions are presented along with these pitfalls and problems.

Key Points

- Although the diagnostic algorithm provides clear and detailed explanations, major feature evaluation can be subject to pitfalls and differentiation of HCC and non-HCC malignancy remains challenging.
- Ancillary features are optional and equally weighted. However, features such as hepatobiliary phase hypointensity and restricted diffusion have greater impact on HCC diagnosis than other ancillary features and may merit greater emphasis or weighting.
- LI-RADS was initially developed from a Western paradigm, which may limit its applicability in the East due to regional practice variations. In Eastern Asia, high sensitivity is prioritised over near-perfect specificity for HCC diagnosis in order to detect tumours at early stages.

Keywords Algorithms · Diagnosis · Liver cancer · Tomography · Magnetic resonance imaging

Abbreviations

APHE	Arterial phase hyperenhancement
ECA	Extracellular contrast agent
HBP	Hepatobiliary phase
HCC	Hepatocellular carcinoma
H-ChC	Hepato-cholangiocarcinoma
ICC	Intrahepatic cholangiocarcinoma

LI-RADS	Liver Imaging Reporting and Data System
PVP	Portal venous phase
TG	Threshold growth
TP	Transitional phase

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Introduction

The Liver Imaging Reporting and Data System (LI-RADS) aims to standardise the terminology, interpretation and reporting of liver imaging in patients at risk for hepatocellular carcinoma (HCC) [1]. LI-RADS has been iteratively refined; an example is the recent clarification on target population [2]. However, practical limitations and controversies still remain in the version 2017. The article discusses pitfalls and problems of the CT/MRI diagnostic algorithm, together with potential solutions.

Pitfalls

Pitfall set 1: characterisation of major features

Arterial phase hyperenhancement (APHE)

LI-RADS defines APHE by comparing an observation with surrounding liver parenchyma, not by comparing it with unenhanced images or using subtraction imaging. The definition requires that at least part of the observation be brighter than the liver in the arterial phase; observations that are hypointense precontrast and isointense in the arterial phase are not considered to have APHE, despite enhancing more than liver. Question remains why such observations, despite the hypervascular nature, do not qualify for APHE in LI-RADS. Similarly, subtraction imaging, when combined with conventional arterial phase images, can help evaluate APHE on MRI and increase the sensitivity of HCC diagnosis [3, 4]. The use of subtraction images is especially helpful in observations with intrinsic T1 hyperintensity. We encourage LI-RADS to standardise the use of subtractions in future versions. Contrast-enhanced ultrasound may also be performed to evaluate hypervascularity in these observations.

In cases of arterial phase mistiming, APHE can manifest after the nominal late arterial phase [5]. Greater awareness of this possibility among LI-RADS users may help. Additionally, since multi-arterial phase imaging can improve the consistency with which APHE is demonstrated [6], future versions of LI-RADS could give guidance to using this emerging technique.

Finally, some large circumscribed HCCs may show iso- or hypoenhancement on the arterial phase except for intratumoural arteries [7] (Fig. 1). The presence of intratumoural arteries, being a “part” of observation, should qualify as APHE. The current definition does not make this as clear as it should. Clarification is needed.

“Washout”

“Washout” is defined as non-peripheral, visually assessed temporal reduction in the degree of enhancement relative to composite liver tissue, resulting in hypoenhancement in the portal venous or delayed phases. There is debate over whether iso- or hypoenhancement in the arterial phase (i.e. no APHE) followed by hypoenhancement in the portal venous or delayed phases should be regarded as “washout”, as indicated in the current definition, because this may result in overcategorisation of some benign lesions, including dysplastic nodules, as LR-4. Another opinion is that hypoenhancement in the portal venous or delayed phases relative to the adjacent liver is an essential component, and temporal reduction in the degree of enhancement throughout dynamic phases may instead be discarded from the definition. Research is needed to examine the validity

of the current definition of “washout” and inform its refinement.

Using gadoxetate disodium, LI-RADS requires that “washout” be assessed only in the portal venous phase (PVP). This is problematic because LI-RADS does not clearly define the end of the PVP with this agent. Defining the end by a fixed time after injection (2 min) when the transitional phase (TP) begins is simplistic. Research is needed to better understand and define the PVP and TP using gadoxetate disodium.

Hypointensity in the TP or hepatobiliary phase (HBP) is considered an ancillary feature as it may result from background parenchymal enhancement rather than lesional de-enhancement, not being specific enough for HCC [8]. However, studies have suggested that in combination with non-rim APHE, HBP hypointensity is highly sensitive and also specific for HCC [9, 10]. As TP hypointensity itself is more specific for HCC than HBP hypointensity alone [9], the combination of non-rim APHE and TP hypointensity might be even more specific for HCC. Further research is needed to determine if TP or HBP hypointensity can be elevated to major features in the context of small lesions with non-rim APHE, especially after excluding haemangioma and intrahepatic cholangiocarcinoma (ICC).

Enhancing “capsule”

Enhancing “capsule” is a smooth enhancing rim around an observation on the portal venous, delayed or transitional phases which is clearly thicker or more conspicuous than the background liver parenchymal fibrosis. This definition is problematic on gadoxetate-enhanced MRI because the enhancing “capsule” can be masked by background parenchymal enhancement. The phenomenon reduces the sensitivity of gadoxetate-enhanced MRI for detecting enhancing “capsule” compared to extracellular agent (ECA)-enhanced MRI or CT. However, the analogous feature on gadoxetate-enhanced MRI—a smooth hypointense rim in the HBP (i.e. non-enhancing “capsule”)—can improve the sensitivity of HCC diagnosis without reducing specificity [11]. We encourage research to examine the diagnostic performance of HBP hypointense rim relative to that of enhancing “capsule” on gadoxetate-enhanced MRI.

Recognising that LI-RADS is constrained by a desire for congruency with Organ Procurement and Transplantation Network (OPTN) policy, which incorporates enhancing “capsule” in its classification system, there is a concern whether enhancing “capsule” should be retained as a major feature. The main reason for retaining enhancing “capsule” as a major feature is that it contributes to the diagnosis of HCC when “washout” is not discernible, especially in 1- to 2-cm-sized observations with APHE [12]. Other considerations suggest its removal, however [13]. For example, the imaging feature may not represent a true tumour capsule and is less

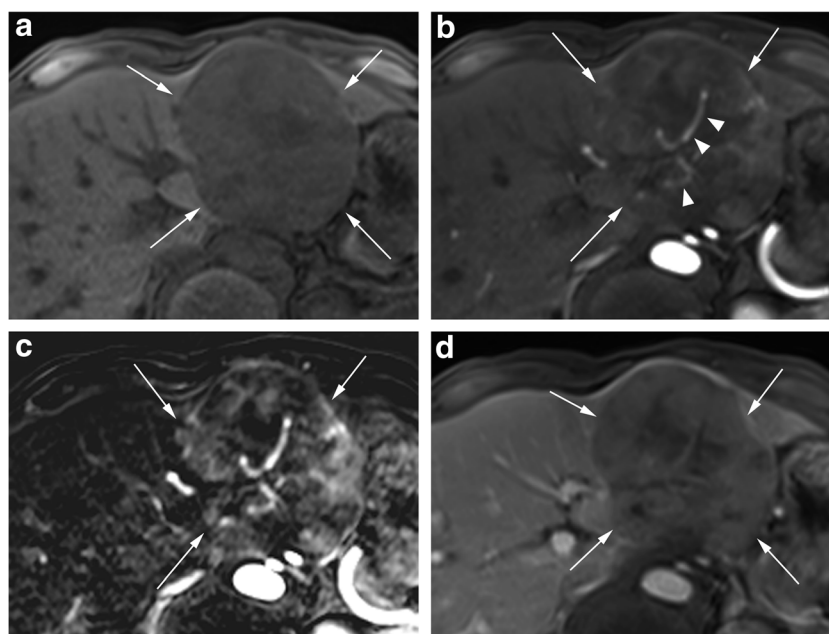


Fig. 1 A 48-year-old man with chronic hepatitis B and a large hepatocellular carcinoma (HCC) containing intratumoural arteries. **a** Axial T1-weighted three-dimensional (3D) gradient-echo unenhanced MR image reveals an 82-mm hypointense mass in the left lateral hepatic section. **b** The mass has scattered areas of vague hyperintensity relative to

the surrounding liver in the arterial phase after gadoxetate disodium administration. Note also intratumoural arteries (*arrowheads*). **c** The arterial phase hyperenhancement (APHE) is subtle and could be missed on the source image but is obvious on the (arterial phase – pre) subtraction image. **d** The mass shows “washout” in the portal venous phase (PVP)

specific for HCC than pathological capsule [14]. Moreover, the feature is relatively infrequent and usually accompanies other major features that permit the diagnosis of HCC anyway [15]. The validity of this latter point needs to be confirmed, however, as it was made prior to the recognition that enhancing “capsule” may create the perception of “washout” [16]. Research is needed to compare the diagnostic performance characteristics of LI-RADS categorisation using versus not using enhancing “capsule” as a major feature.

Threshold growth

Threshold growth (TG), currently a major feature in LI-RADS and OPTN system, represents tumour growth itself, which favours the diagnosis of malignancy over benignity, but per se is not diagnostic of HCC [17]. Moreover, TG cannot be applied in the diagnosis of HCC when previous CT or MRI examinations are unavailable. Finally, TG affects LI-RADS categorisation in only a small proportion of observations [18]. Therefore, contention exists as to whether TG can act as a major criterion for HCC diagnosis. More evidence is needed to validate TG as a major feature.

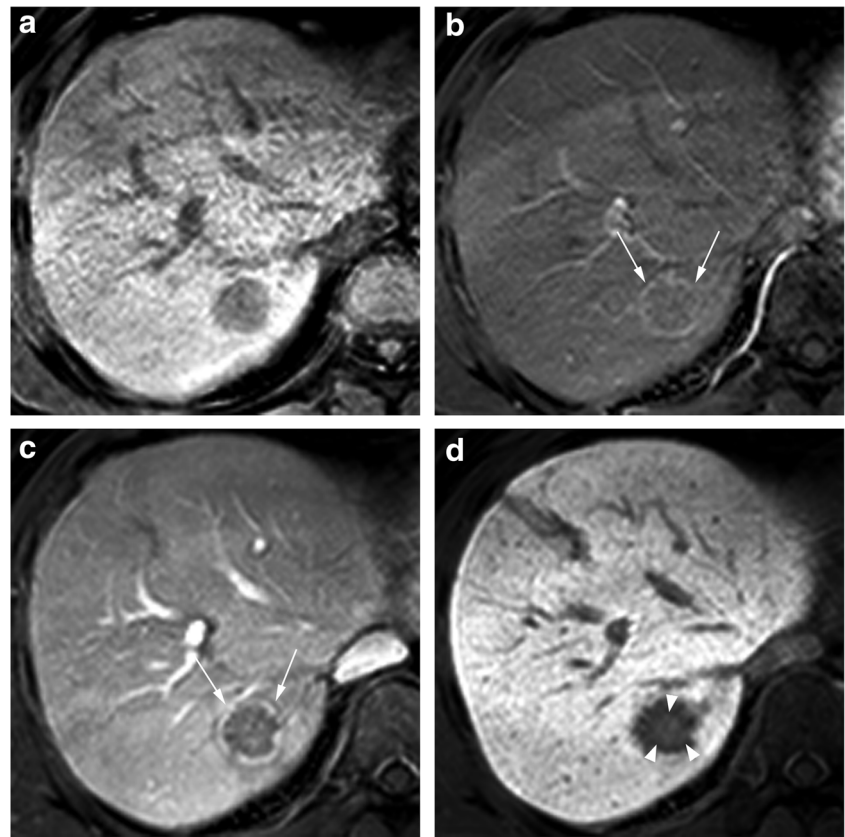
Pitfall set 2: categorisation of LR-M

LR-M is a category for probably or definitely malignant observations which are not specific for HCC. As stated in LI-RADS, the differential diagnosis of LR-M includes ICC,

hepato-cholangiocarcinoma (H-ChC), metastasis, and HCC with atypical imaging features. Thus, users should be aware that in the context of high HCC prevalence, LR-M does not exclude HCC [14, 19, 20]. Interestingly, HCCs which are categorised LR-M may imply worse outcomes than HCCs meeting LR-5 criteria [21] (Fig. 2), suggesting that LR-M features may have prognostic value even for lesions proven to be HCC at biopsy or surgery.

Meanwhile, it is inevitable that some non-HCC malignancies will be incorrectly categorised LR-5 or LR-4 [14, 20, 22, 23] (Fig. 3). In a retrospective analysis, more than half of 61 H-ChCs satisfied the LR-5 criteria for observations 2 cm or larger when LR-M criteria were not considered [24]. The false categorisation was reduced to 6.6% after consideration of ancillary features of version 2014 favouring non-HCC malignancy, suggesting that LR-M features can help differentiate H-ChC from HCC. Nevertheless, since H-ChCs contain HCC components, perfect differentiation from “pure” HCCs is not possible with current imaging technology. In cirrhotic patients, moreover, some small ICCs show non-rim APHE and non-peripheral “washout” and are indistinguishable from HCC based on major features alone. Unfortunately, these small ICCs may lack LR-M features in the HBP or on diffusion-weighted imaging [23]. Further study is needed to identify new imaging features that help discriminate non-HCC malignancy from HCC in order to reduce the rate of miscategorisation and subsequent overtreatment in deceased donor transplantation candidates.

Fig. 2 HCC with the LR-M features in a 60-year-old man with chronic hepatitis B. **a** The axial T1-weighted 3D gradient-echo unenhanced MR image shows a 24-mm hypointense nodule in the hepatic segment VII. **b** The nodule exhibits a targetoid appearance and rim APHE after gadoxetate disodium administration. **c** On the PVP, the nodule shows “washout” and an enhancing “capsule.” **d** On the hepatobiliary phase (HBP), a subtle targetoid appearance is also demonstrated with slightly more pronounced hypointensity in the periphery of the nodule compared to the centre (*arrowheads*). As demonstrated in this case, LR-M does not exclude HCC



Additionally, an extrahepatic primary malignancy can develop hypervascular metastasis to the liver in patients with cirrhosis or chronic hepatitis B. Such metastases may also be inappropriately categorised LR-4 or LR-5 (Fig. 4). Further research is needed to determine the frequency with which hypervascular metastases occur in the LI-RADS diagnostic population as well as the frequency with which these lesions result in diagnostic errors using current LI-RADS criteria.

A final limitation is that LR-M category rarely includes benign entities [14]. For example, sclerosing haemangiomas may manifest rim APHE and be categorised LR-M. The categorisation of benign lesions as LR-M can be problematic in terms of overtreatment when these lesions undergo surgical resection without preoperative biopsy confirmation. The ability to differentiate probably malignant from definitely malignant LR-M observations is an unmet need in these cases.

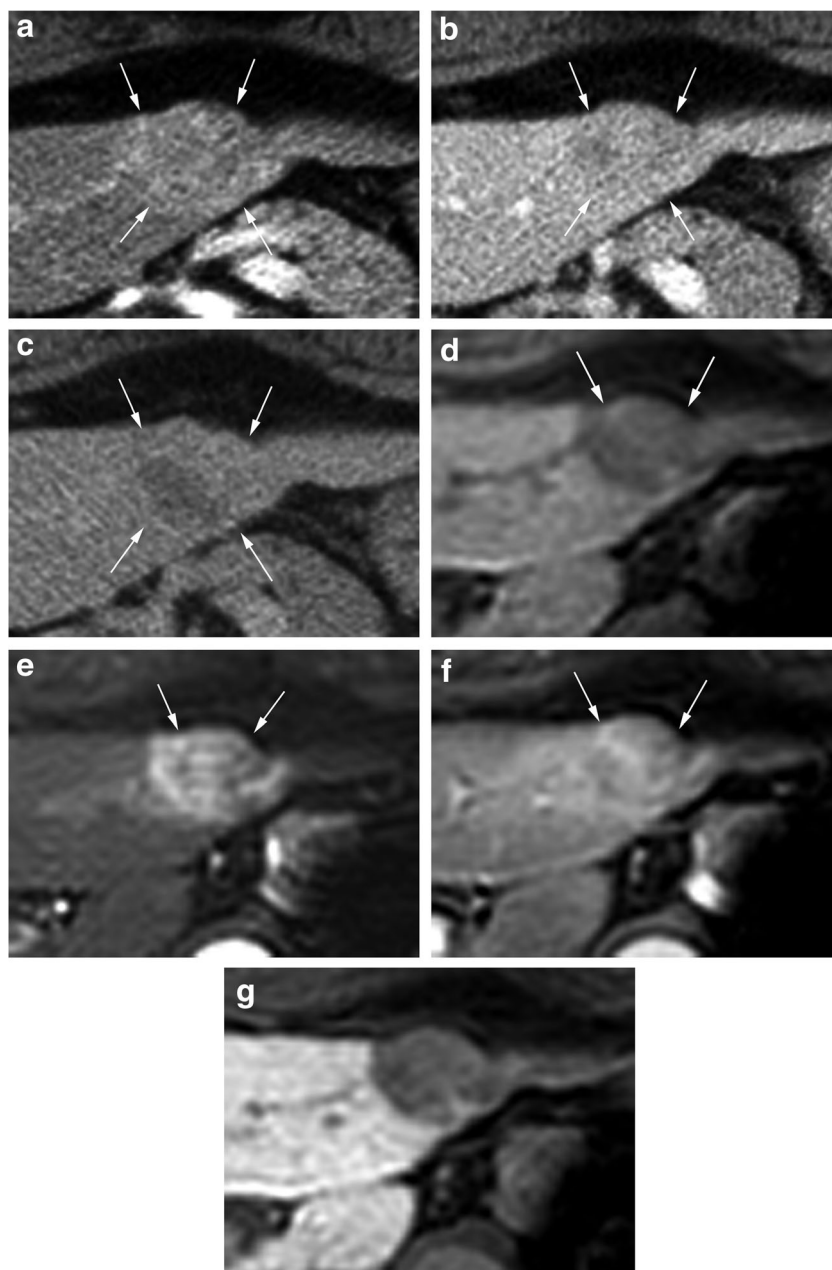
Pitfall set 3: CT-MRI categorisation discrepancy

For simplicity, LI-RADS uses the same basic diagnostic algorithm for CT and MRI, but studies have demonstrated that the LI-RADS categorisation can differ between CT and MRI in 36–77% of observations [25–27]. For example, the frequency of enhancing “capsule” among HCCs was higher in ECA-enhanced MRI than CT (44% vs 17%), leading to a significant increase in the number of 1- to 2-cm-sized LR-5 observations in MRI [12]. In

another study, discordance rates between CT and ECA-enhanced MRI were moderate to high for APHE (57%), “washout” (21%) and enhancing “capsule” (43%); in the discordant cases, these features were demonstrated only in ECA-enhanced MRI, leading to higher category assignments [26]. Discordance also occurs between CT and gadoxetate-enhanced MRI with rates of 7% for APHE, 22% for “washout”, and 33% for enhancing “capsule” [22]; in this study, APHE and enhancing “capsule” were discerned more frequently on gadoxetate-enhanced MRI, while “washout” was seen more frequently on CT.

Similarly, many ancillary features are applicable only to MRI and others only to gadoxetate-enhanced MRI. For example, features of mild to moderate T2 hyperintensity, restricted diffusion, and HBP hypointensity lead to higher category assignment on gadoxetate-enhanced MRI than CT which is incapable of assessing these features [28]. Similarly, early HCC is categorised LR-4 more frequently on gadoxetate-enhanced MRI than on CT because of HBP hypointensity [29], and more frequently on ECA-enhanced MRI than on CT because of intratumoural fat [25]. Meanwhile, marked T2 hyperintensity permits appropriate downgrading to LR-1 or LR-2 of haemangiomas with atypical enhancement profiles [25] (Fig. 5). Conversely, MRI detects benign but potentially confusing vascular pseudolesions more often than CT [25]. Most of these are categorised LR-2 or LR-3 by MRI but, being imperceptible, uncategorised by CT.

Fig. 3 Intrahepatic cholangiocarcinoma (ICC) satisfying the LR-5 criteria in a 77-year-old woman with chronic hepatitis B. **a** The axial CT image shows a 29-mm nodule in the anterior surface of the hepatic segment III with APHE. The nodule shows partial “washout” on the **(b)** portal venous and **(c)** delayed phases. **d** The axial T1-weighted 3D gradient-echo MR image shows a hypointense nodule before contrast enhancement. The nodule depicts **(e)** APHE and **(f)** partial PVP “washout” after gadoxetate disodium administration. **g** On HBP, the nodule is hypointense to the surrounding liver. As illustrated in this case, some ICCs meet LR-5 criteria



Some of these discrepancies may be unavoidable, reflecting inherent differences in the modalities' capabilities. Therefore, some authors suggest combined usage of both modalities under certain circumstances [22, 27]. Further consensus on the choice of modality may be necessary in LI-RADS. In addition, it may be useful to assess the value of ancillary features—which are present mainly on MRI [30]—and if they are really useful.

An additional concern is that contrast administration protocol is less standardised in CT than in MRI. In patients with liver cirrhosis, contrast injection rate and contrast administration dose need to be adjusted in order to yield optimal liver enhancement on CT [31]. Thus, covering the aspect in the LI-

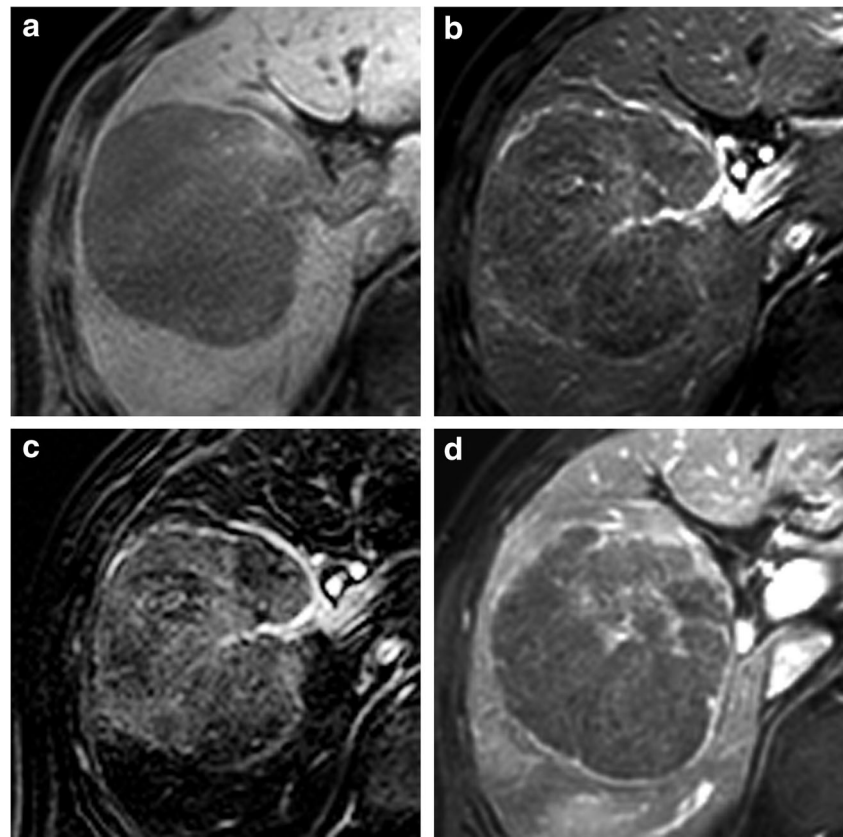
RADS technical recommendations may help decrease the discrepancy between major feature evaluation by CT and MRI.

Problems to be solved

Problem 1: imprecision of category codes

The actual probabilities of HCC associated with LR-3 and LR-4 are not yet well known. Studies suggested that 69–90% of LR-4 observations are HCC [20, 32], but this has not been verified extensively. Interestingly, observations categorised LR-4 based on major features have a higher HCC probability

Fig. 4 Metastasis from thymoma satisfying the LR-5 criteria in a 55-year-old man with chronic hepatitis B. **a** The axial T1-weighted 3D gradient-echo unenhanced MR image shows an 86-mm hypointense mass in the right hemiliver. After gadoterate meglumine administration, the mass depicts hypervascularity on the **(b)** arterial phase image and **(c)** subtraction image. **d** On the PVP, the nodule shows “washout” and an enhancing “capsule”. As illustrated by this case, hypervascular metastasis from an extrahepatic malignancy can satisfy LR-5 criteria, although this is believed to occur only rarely



than those upgraded from LR-3 by HBP hypointensity [32], suggesting that categorisation “pathway” may affect HCC probability. A different study found that 69% of version 2013.1 LR-3 observations discovered initially on surveillance US are HCC [19], but these nodules would be categorised LR-4 using version 2017. Another study showed that 40% of version 2014 LR-3 observations undetected by surveillance US are HCC [20].

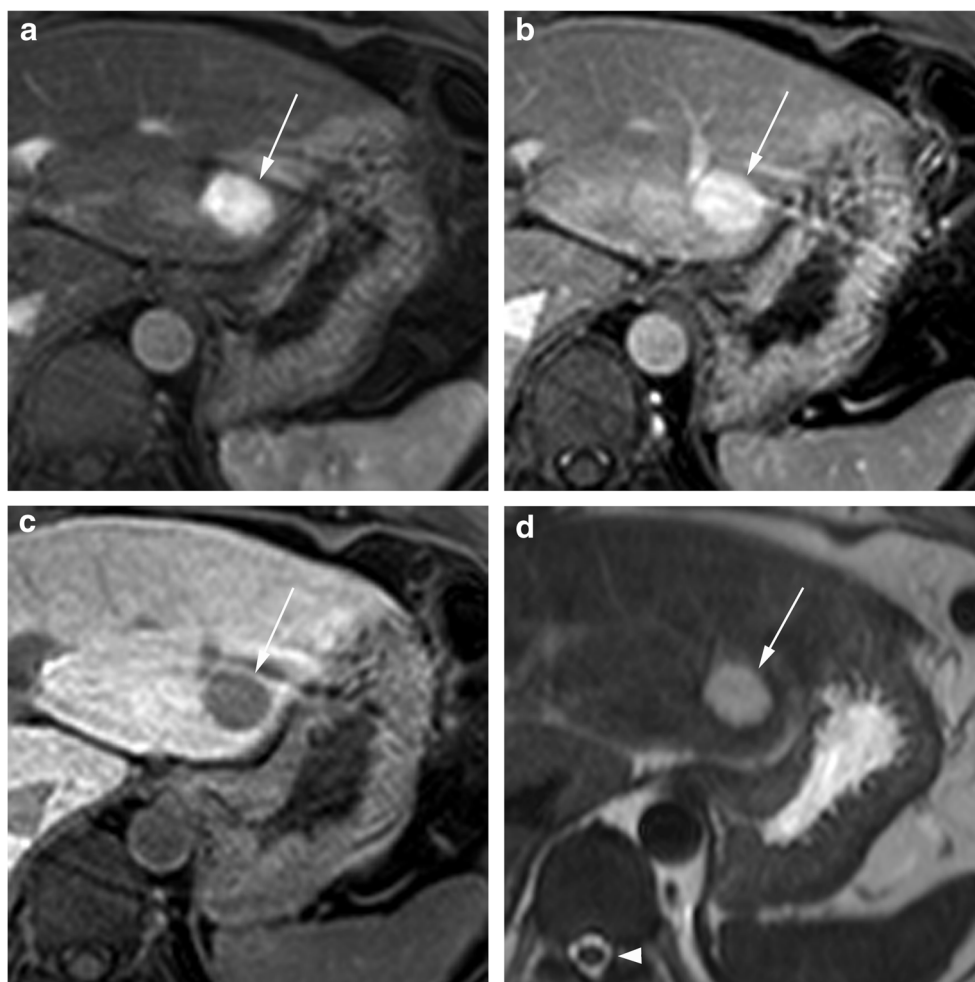
The LR-3, LR-4, and LR-5 categories are heterogeneous, each assignable by several different combinations of features. Contributing to the heterogeneity is that categories may be adjusted by ancillary features and tie-breaking rules. Thus, each category comprises a large and diverse set of observations, each with its own unique categorisation “pathway.” LI-RADS facilitates the diagnosis of high risk borderline lesions, especially with gadoxetate-enhanced MRI [29]. However, the clinical significance of these lesions, mostly categorised LR-3 or LR-4, is still uncertain. Large multicentre studies are needed to define the HCC probability and/or the natural history of common categorisation pathways, especially for LR-3 and LR-4. Such data may eventually permit the assignment of granular probabilities of HCC, which would facilitate application of individualised management strategies and decrease overdiagnosis and overtreatment of borderline lesions.

A related challenge is that reader variability in the characterisation of major and ancillary features can introduce variability in assigning LI-RADS categories. As expected, agreement for assigning LR-2, LR-3 and LR-4 categories is lower than that for assigning LR-1 and LR-5 categories [33]. Meanwhile, assigning LR-M category does not seem to be critically discrepant among readers [30]. A few studies have shown that the inter-reader agreement can be improved in LI-RADS. As diameter measurement tends to be consistent among readers [12, 26, 33, 34], some investigators have proposed a modified algorithm whereby size is the initial node in the decision tree [34].

Problem 2: application of ancillary features

LI-RADS currently includes many ancillary features, although the quality of evidence supporting these features tends to be low. Some ancillary features are rarely used and do not differ in frequency between HCC and non-HCC malignancy [14]. To reduce the perceived complexity of LI-RADS, ancillary features have been made optional. However, this solution is suboptimal as some ancillary features do play important roles in diagnosis. For example, HBP hypointensity and restricted diffusion are strong indicators of malignancy [22]. We anticipate that HBP hypointensity and restricted diffusion could be elevated to major features with appropriate combination of

Fig. 5 Ancillary feature rendering a benign diagnosis in a 41-year-old man with chronic hepatitis B and non-alcoholic steatohepatitis. The axial T1-weighted 3D gradient-echo gadoxetate-enhanced MR images reveal a 20-mm nodule in the hepatic segment III with atypically persistent hyperenhancement throughout the (a) arterial and (b) portal venous phases. c On HBP, the nodule is hypointense to the liver parenchyma. d The signal intensity of the nodule on the heavily T2-weighted image (echo time, 150 ms) is markedly brighter than non-iron-overloaded spleen and close to the brightness of the cerebrospinal fluid (arrowhead), suggesting a diagnosis of haemangioma



other features, based on emerging data [9, 10]. Hierarchical weighting and/or removal of less contributory features may also be beneficial.

Problem 3: regional practice variations

Risk factors and incidence of HCC vary geographically, resulting in different diagnostic and management strategies across the world. For example, whereas hepatitis C virus infection is the most important risk factor in Europe, Japan and North America, hepatitis B virus infection is a major risk factor in the Asia-Pacific region [35–37]. This is important because many patients with HCC due to chronic hepatitis B have no or well-compensated cirrhosis and can be offered curative resection if the cancer is detected in early stages. Thus, in Eastern Asia, where the incidence of HCC is highest [36], early detection of HCC is critical, and high sensitivity for HCC diagnosis is valued even at the expense of an “acceptable” decrease in specificity [13]. By comparison, transplantation is the only curative treatment for patients with HCC developing in the cirrhotic liver. Since deceased donor liver transplantation is the main source of organ procurement in the West, high specificity

for HCC diagnosis is needed to ensure appropriate organ allocation [38]. For this reason, LR-5 category has been designed in LI-RADS to provide a near-perfect specificity for HCC. However, such high specificity may not be as necessary in living donor transplant candidates in Asian countries [39].

Ideally, future versions will consider regional differences in HCC diagnosis and management. For regionally tailored LI-RADS, one proposal is to divide LR-M into LR-4M (probably malignant but not specific for HCC) and LR-5M (definitely malignant but not specific for HCC) [40]. Particularly in Eastern Asia, the most important preoperative goal is to identify definitely malignant lesions (i.e. LR-5 or LR-5M), which also applies to other regional practices in terms of overdiagnosis and overtreatment.

Conclusions

Despite the clear definitions and detailed explanations, there remain some practical and controversial issues regarding the CT/MRI diagnostic algorithm of LI-RADS. Assessment of major features may be subject to several pitfalls, which

indicates the need for continuing refinement of the current system. Refinements are also needed to better discriminate non-HCC malignancy from HCC and to manage the category discrepancy between CT and MRI. Suggestion on granular HCC probability according to categorisation pathway may enable individually tailored management. Some ancillary features merit greater emphasis or weighting. We anticipate that LI-RADS will evolve to integrate regional practice variations and enhance the global influence.

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