Hepatocellular carcinoma: Advances in diagnostic imaging

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Summary	Thanks to the growing knowledge on biological behaviors of hepatocellular carcinomas (HCC), as well as continuous improvement in imaging techniques and experienced interpretation of imaging features of the nodules in cirrhotic liver, the detection and characterization of HCC has improved in the past decade. A number of practice guidelines for imaging diagnosis have been developed to reduce interpretation variability and standardize management of HCC, and they are constantly updated with advances in imaging techniques and evidence based data from clinical series. In this article, we strive to review the imaging techniques and the characteristic features of hepatocellular carcinoma associated with cirrhotic liver, with emphasis on the diagnostic value of advanced magnetic resonance imaging (MRI) techniques and utilization of hepatocyte-specific MRI contrast agents. We also briefly describe the concept of liver imaging reporting and data systems and discuss the consensus and controversy of major practice guidelines.

Keywords: Ultrasonography, tomography, X-Ray computed, magnetic resonance imaging, cirrhosis, diagnostic imaging, contrast media

1. Introduction

The common risk factors for hepatocellular carcinoma (HCC) are hepatitis B virus (HBV) or hepatitis C virus (HCV) infection and alcoholic liver disease. Less common causes include nonalcoholic fatty liver, hereditary hemochromatosis, autoimmune hepatitis, alpha-1 antitrypsin deficiency and Wilson disease, some porphyria and schistosomiasis (*1*). These risk factors can lead to remodel of texture with fibrotic progression of hepatic parenchyma. In patients with cirrhosis, the 5 year cumulative occurrence of HCC is between 5-30% depending on the causes of the disease, and associated cirrhosis is seen in 80-90% of patients with HCC (*2,3*). Due to the growing population of obesity and other metabolic syndromes, there is an increasing incidence of HCC due to non-alcoholic fatty infiltration liver disease; the incidence of HCC continues to grow in spite of the hepatitis B and C viruses' infection being prevented by the development of vaccines and anti-viral therapies (*4,5*). The fact that the classic imaging features

could yield a definite diagnosis and the probability of needle track seeding are limiting the necessity of liver biopsy (*6*). Therefore, HCC is the unique malignancy to be diagnosed by diagnostic imaging, exempting the necessity of a needle biopsy (*7*).

Since imaging plays a decisive role in the diagnosis of HCC, it is critical that imaging examination might be performed according to generalized protocols (including the types of equipment, scanning parameters, administration of contrast agents and timing of acquisition) and the imaging findings might be interpreted and reported following a standardized terminology and categorization.

2. Imaging modalities of HCC

2.1. *Ultrasounography (US)*

US is a non-invasive examination and has no ionic radiation on the human body. It remains inexpensive as well, which is recommended as the first choice for the screening and surveillance of HCC by the guidelines of almost all international societies (*8*). Patients who have risk factors for developing HCC should undergo US surveillance every 3 to 6 months (*9*). However, the sensitivity varies from 58% to 70% and is even poor for small HCC less than 1 cm (*8-10*). Classic findings of

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HCC include hypoechoic nodules or mixed echogenic nodules due to tumor necrosis or fatty metamorphosis or a surrounding thin hypoechoic band indicating a capsule which is characteristic for HCC. Colored doppler flow imaging may show hypervascularity and tumor vascular shunting (*11*). Contrast enhanced ultrasound (CEUS) with microbubble agents could reflect the real time dynamics of blood supply of the lesion, which is helpful in both detection and characterization of HCCs (*12,13*).

2.2. *Multi-phasic enhanced computed tomography*

Multi-phasic enhanced computed tomography (CT) is the most common choice for the diagnosis of HCC. In the past decade, technical advances in CT scanners have yielded considerably faster acquisition time and a dramatically dropped radiation dose. There are technical requirements on the equipment and scanning parameters: at least 8 rows multi detector CT for fast acquisition, scanning with thin collimation not over 5mm, adequate amount of contrast medium used and a bolus injection rate over 3 mL/s (*14*). Accurate timing is critical, at least three phases should be acquired after administration of iodinated contrast agents, namely hepatic arterial phase, portal venous phase and delayed phase (*15*). Precontrast CT is suggested to provide a baseline to demonstrate the level of enhancement, and it may provide information on existence of fat content, iron, calcification, hemorrhage, and iodized oil after transarterial chemoembolization (TACE) treatment (*16*). The arterial phase is a time range with the hepatic artery fully enhanced while hepatic veins are not enhanced yet, it could be divided into early and subsequently late hepatic arterial phase (*17*). Late hepatic arterial phase is strongly recommended, because the hyperenhancement in HCC is more predominant in the late than the early arterial phase, and a majority of HCCs may show hyperenhancement only in the late hepatic arterial phase (*18,19*). Portal venous phase is acquired in which the images have the following characteristics: Portal veins and hepatic parenchyma are maximally enhanced, and hepatic veins are enhanced by antegrade flow as well (*20*). Delayed phase should be acquired at least 3 minutes after the initial of injection when liver parenchyma is less enhanced than in portal venous phase (*21*). The advantage of CT also affords the ability to perform three-dimensional reconstructions that may help with preoperative planning which is superior to MRI. Due to possible complications such as radiation, contrast media leaking, allergic reaction and contrast induced nephropathy, CT is not a choice of repeated surveillance (*22*).

2.3. *Magnetic resonance imaging (MRI)*

MRI is superior in both detection and characterization of HCC and is continuing to improve its performance

and capability. The sensitivity and the specificity of MRI are reported at 91% and 95% as compared to 81% and 93% with MDCT (*23*). The standardized imaging protocol includes T2-weighted sequences to reveal the lesion in high resolution anatomic details, pre-contrast and multi-phasic enhanced 3D T1-weighted gradient echo sequences, and chemical shift in/opposed phase imaging which is sensitive to lipid content (*23,24*). The protocol of contrast examination is similar to contrast CT, and both early and late hepatic arterial phase might be acquired without fear of ionic radiation (*25*). The functional imaging is an added advantage of MRI. Among functional imaging techniques, diffusion weighted imaging (DWI) is the most promising method, it is based on differences of Brownian motion (diffusion) of water molecules within tissues in vivo. For tissues with increased cellularity and destroyed cell integrity such as malignancy, the diffusion of water molecules is restricted, which shows altered signal intensity and parametric changes on DWI (*26*). DWI is useful for detecting small HCC and differentiating compared to benign entities, however, it is not as robust and stable in image quality as T1WI and T2WI sequences and the positive predicting value and negative predicting value are controversial (Figure 1) (*27,28*). Currently, DWI is suggested but not required in most of the institutes.

The contrast medium commonly used for MRI is non-specific gadolinium-based contrast agents, however, hepatocyte specific contrast agents are promising in both detection and characterization of HCC (*29*). Among of several commercially available contrast agents, gadoxetate dimeglumine is a newer agent which enables both dynamic contrast and hepatocyte specific imaging with one administration (*30*). Approximately half of the agent is taken up by hepatocytes and excreted into the bile in about 20 min after routine contrast imaging, which is called hepatobiliary phase (*30*). Typically, HCCs appear hypointense in hepatobiliary phase because of lack of normal hepatocytes, which is a main feature for differentiating HCC from both regenerative nodules and dysplastic nodules which appear isointense
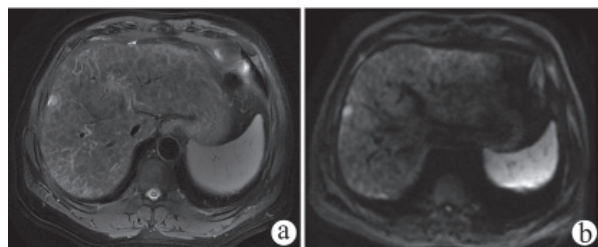

Figure 1. MRI feature of a small HCC associated with liver cirrhosis. (a) A moderate hyperintense nodule was revealed on fast suppressed T2WI sequence in the right margin, many small hypointense nodules could be seen in the background parenchyma suggesting the existence of cirrhosis. **(b)** The small HCC demonstrate remarkably hyperintense on diffusion weighted images, suggesting restriction of water molecule movement in the tumor.

(Figure 2) (*31,32*). However, about 10% of HCCs appear hyperintense compared to background parenchyma in hepatobiliary phase, because of overexpression of organic anion transporter peptide (OATP) proteins that are responsible for the transportation and uptake of the agent (*33*). Gadoxetate dimeglumine has proved its value in distinguishing small HCCs. The major limitation of the agent is lack of pure delayed phase, because the early uptake of the agent in delayed phase might superimpose true delayed enhancement, as a consequence, it might obscure the capsule which is diagnostic for HCC, the accumulation of the agent in the delayed phase might likewise mimic a tumor which is characteristic of delayed enhancement such as cholangiocarcinoma (*34*). Until now, in North America and European countries, gadoxetate dimeglumine is not widely used as compared to its use in East Asia (*35,36*).

3. Characteristics features of HCC

Cirrhotic nodules include regenerative nodules (RN), low-grade dysplastic nodules (LGDN), high-grade dysplastic nodules (HGDN), and HCCs (*37*). While the imaging modalities have greatly evolved and the detection rate of liver nodules has increased in the past decade, characterization of atypical hyperplastic/ dysplastic nodules with small HCCs are still challenging (*38*). The following features are characteristic for HCC, the combination of these features could yield a definite diagnosis in most cases.

3.1. *Cirrhotic liver background*

In developing countries, many cirrhotic patients are unaware of their diseased condition until

developing advanced HCC or liver decompensation or gastrointestinal bleeding, so the radiologist also need to determine the associated cirrhosis in the absence of clinical data (*39*). Therefore, the judgment of liver cirrhosis might also take part in the differential diagnosis of hepatic nodules. The presence of nodular liver contour, atrophy of right lobe and medial segment of left lobe, enlarged caudate lobe and lateral segment of left lobe, widened fissures, heterogeneity of parenchyma with fibrotic and fatty changes, varices, ascites and splenomegaly are indicative of cirrhotic liver (Figure 3a) (*40*). Because many benign entities such as cysts and hemangiomas may present with atypical appearance in cirrhotic liver background, the judgment of cirrhosis helps to distinguishing HCC and benign nodules (*41*).

3.2. *Hypoattenuation and moderate T1hypointense/T2 hyperintensity*

The classical imaging characteristics of HCC are hypoattenuation on precontrast CT and hypointense on T1-weighted images and moderately hyperintense on T2-weighted images (*42*). Low T1 and high T2 intensity represents increased water proton density in the tissue, which is caused by cytotoxic edema, tumor necrosis and hypervascularity (Figure 1a) (*42*). HCC with lower T1 signal and moderate higher signal is often recognized as poorly differentiated (*43*). High T1 intense represents the accumulation of starch, protein, or glycoprotein that is common in RNs and DNs, some of the high differentiation HCC can also have similar high intensity, and HCC with higher T1 intense suggests being well differentiated in classification of
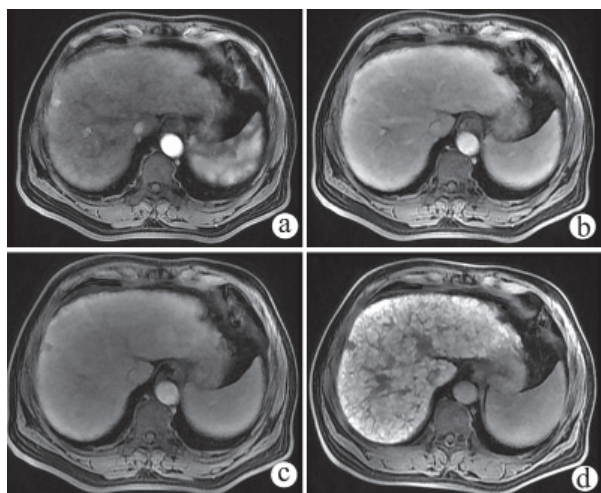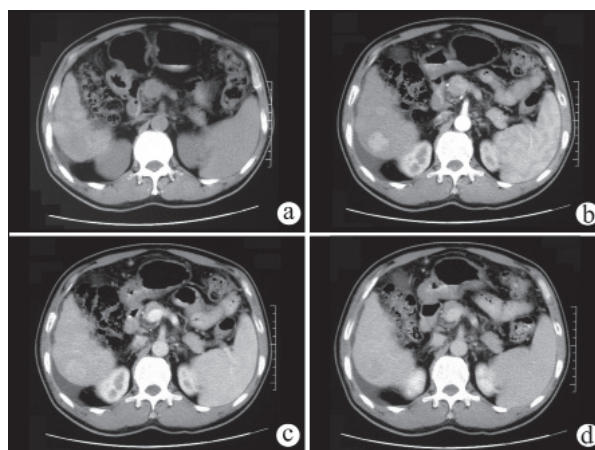

Figure 2. Gadoxetate dimeglumine enhanced T1 weighted MR imaging of a small HCC (the same case as in Figure 1). (a) The nodule shows remarkable hyperenhancement in arterial phase. **(b)** Rapid washout was observed in portal venous phase. **(c)** The nodule showed low intensity in delayed phase. **(d)** There was no uptake in the nodule in hepatobiliary phase.

Figure 3. Multiphasic enhanced CT of a HCC associated with cirrhosis. (a) Precontrast CT showed a hypoattenuation nodule; while the nodular contour, parenchymal heterogeneity in attenuation, ascites and splenomegaly were indicative of cirrhosis. **(b)** In arterial phase, the nodule showed unequivocal hyperenhancement which had much higher enhancement than the adjacent background and precontrast baseline. **(c)** In portal venous phase, the nodule showed less enhancement but still higher than the background liver. **(d)** In delayed phase, the nodule demonstrated unequivocal washout which showed lower attenuation than the adjacent parenchyma.

which the prognosis is relatively good (*44*).

3.3. *Arterial hyperenhancement and washout appearance*

Arterial hyperenhancement is defined as more enhancement than liver parenchyma and higher attenuation/intensity in whole or in part of the lesion in the hepatic arterial phase compared to background liver. Washout is defined as an attenuation/intensity in whole or in part less than the earlier phase during the portal venous or delayed phase following the presence of arterial phase enhancement (*45*). If the lesion is surrounded by dense fibrosis then enhancement of the lesion should be compared to the comprehensive parenchyma. In some instances, delayed phase may be superior to portal venous phase for depicting washout appearance (Figures 3b-3d). Some HCC may show washout appearance only in the delayed phase (*20*). Neither arterial hyperenhancement or washout is characteristic of HCC, however, when combined together, the features are specific for HCC (*46,47*). A large nodule over 1.5-2 cm which appears to have hyperenhancement in the arterial phase and washout in the portal venous or delayed phase could be a diagnosis of HCC near 100% (*48*).

3.4. *Fibrous capsule or pseudocapsule*

The fibrous capsule of HCC consists of a dense fibrous tissue in the inner layer and a peripheral rim of sinusoids and small bile duct, while the pseudocapsule is made up of the dilated blood sinus and fibrous tissue around the tumor (*49,50*). Both fibrous capsule and pseudocapsule appear as slightly low signal on T1 and slightly high
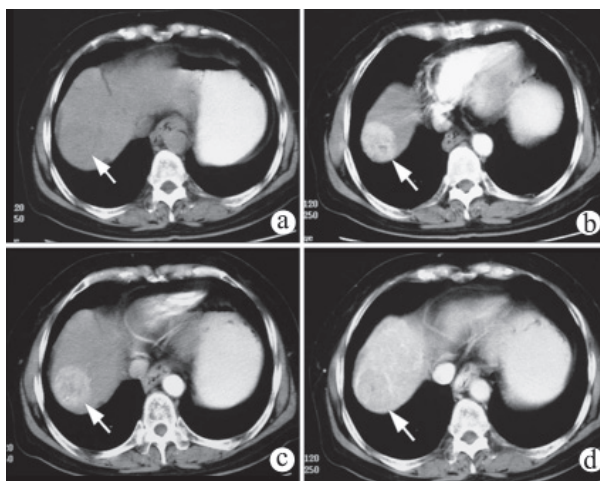
signal on T2 (Figure 4), and show a discrete ring of hyperenhancement along margin of HCC in the portal venous phase or delayed phase, the enhancement usually increases from portal venous phase to delayed phases. Compared to the ring along the margin of regenerative nodules in surrounding liver, capsule appearance is thicker and more conspicuous (*50*). The capsule appearance is characteristic of HCCs, regardless of whether it is tumor capsule or pseudocapsule, and it is also reported to be capable of predicting HCC progression, while HCC with complete capsule lesions has lower recurrence rate after treatment than that of incomplete capsular counterparts, suggesting that the fibrous capsule may be able to prevent the spread of HCC (*51,52*).

3.5. *Intratumoral lipid contents*

Lipid content is often seen in HCCs of 1.5-3 cm in size, and occasionally seen in larger tumors (*53*). On CT examination, a mass may be demonstrated as having intratumoral fat if its attenuation is below 40 Hounsfield units (HU) (Figure 5a). Loss of signal intensity on the opposed-phase T1-weighted images is more sensitive to fat content than CT (Figure 5b) (*54*). HCC with lipid content often shows slow progression and relatively better prognosis (*55*). HCCs with intratumoral lipid content need to be differentiated from angioleiomyolipoma or liposarcoma which is rarely seen in cirrhotic liver.

3.6. *Mosaic architecture*

Mosaic architecture is used to describe appearance consisting of randomly distributed nodules with different appearances in attenuation/intensity and enhancement pattern; it also refers to lesions with internal enhancing septations (*56*). "Nodule-in-nodule" is a subtype of mosaic architecture, which is defined as the presence of a small nodule within a larger nodule or mass, the latter are often DN, especially for HGDN, and it reflects the growth pattern of HCC (Figure 6) (*57*). The internal nodule differs in enhancement or other

Figure 4. Capsule appearance of HCC (Arrow). (a) Precontrast CT showed an equivocal hypoattenuation nodule. **(b)** In early arterial phase, the nodule showed remarkable and heterogeneous hyperenhancement. **(c)** In late arterial phase, the nodule showed less enhancement but still higher than the background liver. **(d)** In portal venous phase, the nodule demonstrated unequivocal washout and a hyperattenuation ring was seen along margin of HCC namely capsule appearance.
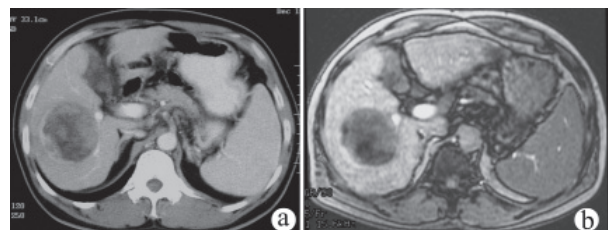

Figure 5. Intratumoral lipid contents in a masslike HCC. (a) Heterogeneous hypo-attenuation area (CT attenuation ranged from 25-38) in the mass on portal venous phase was indicative of intratumoral lipid. **(b)** Opposed phase imaging demonstrated obvious signal loss in the mass, which was specific for lipid content.
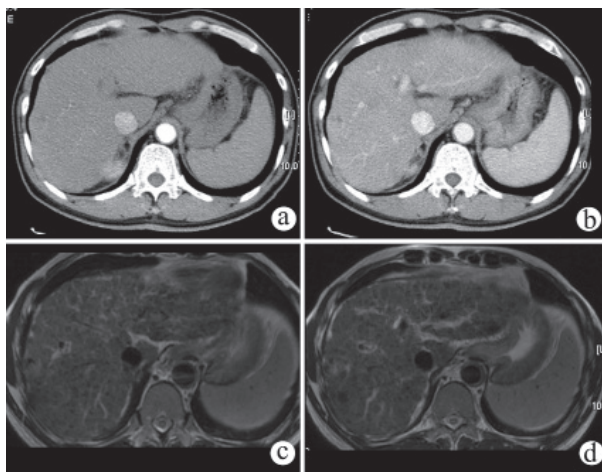
Figure 6. Nodule in nodule appearance in a cirrhotic liver. A heterogeneous enhanced nodule in arterial phase **(a)** and portal venous phase **(b)**. CT could be seen adjacent to the right margin of the liver. **(c and d)** On T2WI sequence, the majority of nodules showed iso- and hypo- intense, there was a smaller nodule with moderately high T2 intense in the center of bigger nodule, histopathological findings had proved it was a small HCC in a high grade dysplastic nodule (HGDN).

Figure 7. Intratumoral hemorrhage in a poorly differentiated HCC. 48-year-old man with sudden abdominal pain and history of hepatitis B virus infection. US revealed a mixed hyperechogenity mass in right lobe. **(a)** Precontrast CT showed a heterogeneous mass with irregular hyperattenuation in the central area. **(b)** Contrast CT demonstrated no enhancement in either hyperattenuation area or the majority of hypoattenueation area which were proved to be blood products in different stages, a small portion of soft tissue with moderate enhancement could be seen in the left margin on portal venous phase, which proved to be poorly differentiated HCC with intratumoral hemorrhage.

features from the larger nodule. Mosaic architecture is a characteristic feature of HCCs (*56*).

3.7. *Hemorrhage*

Hemorrhage refers to presence of intra-tumoral or peritumoral blood products in absence of biopsy, trauma or local-regional treatment, it is an ancillary feature favoring HCC (*58*). On precontrast CT, hemorrhage could manifest as a heterogeneous hyper-attenuation area, but MRI is more sensitive and specific for detection of blood products than CT (Figure 7). On MRI, blood products usually manifest as areas of heterogeneous high T1 signal intensity and low T2 signal intensity due to T2* shortening (*59*).

3.8. *Tumoral thrombus*

Tumoral thrombus is defined when definite enhanced soft tissue is seen in the lumen of portal or hepatic vein. Vein occlusion with arterial phase hyperenhancement and washout within the lumen, lumen expanding, ill-defined walls and arterioles within lumen of vein are suggestive of tumor thrombus (Figure 8) (*60*). Comparatively, non-tumoral thrombus does not enhance and usually does not expand lumen to the same degree as tumor in vein (*61*). Tumor thrombus is a diagnostic feature of HCCs (*61,62*).

4. Imaging-based guidelines of HCC

Currently, there are at least 18 practice guidelines for the diagnosis and management of HCC since 2001. They are: Barcelona (BCLC) staging system; guideline 2010 from American Association for the Study of Liver Disease (AASLD); guideline from European
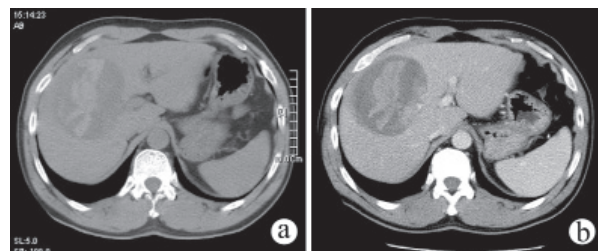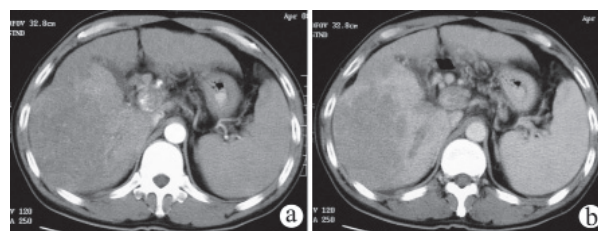

Figure 8. Tumoral thrombus in portal vein from a masslike HCC. (a) Hyperenhancement and arterials could be seen in the expanded but occluded portal vein lumen in arterial phase. **(b)** Rapid washout in vein could be seen in portal venous phase, no antegrade blood flow could be found in branches of the portal vein. A definite diagnosis of HCC with portal vein invasion could be made for the irregular mass in right lobe.

Association for the Study of Liver Disease (EASLD) updated in 2012; guideline from Asian Pacific Association for the Study of Liver Disease (APASL) in 2010, Japan Society of Hepatology (JSH) guideline 2014 and guideline from Korean Liver Cancer Study Group (KLCSG) in 2014 (*9,62-66*). These guidelines were developed to standardize the diagnosis of HCC mainly from the scope of clinical management. In 2011, Liver Imaging Reporting and Data System (LI-RADS) was proposed by American College of Radiology from a committee of radiologists, physicians, surgeons, pathologists and interventional radiologists (*67*).

LI-RADS is a system with a view of diagnostic imaging to provide standardized terminology and criteria for interpreting and reporting findings of CT and MRI in patients with cirrhosis or risk factors for HCC, which will help referring physicians to understand radiologic reports. It has been updated in 2013 and 2014 based on feedbacks from practice (*67*). The lexicon term "Observation" is used in the categorization instead of lesion or nodule, because observation might either be a hispathologically true lesion, perfusion alteration or artifacts. The features of arterial hyperenhancement and washout with size combination, capsule appearance

and interval growth are ancillary findings. LI-RADS categorizes radiological findings into five categorizations ranging from definitely benign to definitely HCC (Table 1) (*67*). LI-RADS is applied only for patients with cirrhosis or at high risk of HCC. Although it has more in common with AASLD compared to other guidelines, LI-RADS classified the "Indeterminate" category into probably benign, intermediate probability for HCC and probably HCC (LR 2, 3 and 4) to facilitate categorizing and reporting, especially for small nodules between 10 mm and 20 mm (*9,67*).

Because of the etiology, the incidence rate as well as treatment policies are different among international societies, and there is lack of consensus in the imaging techniques, diagnostic criteria, staging and treatment of HCCs. Some of the guidelines aim to enable ultimate specificity while others try to achieve higher sensitivity. The diagnostic strategies are different among LI-RADS and other clinical practice guidelines on several aspects: the application of CEUS in detection and characterizing of HCC, the application of specific imaging techniques of CT and MRI, the role of hepatocyte specific contrast agents, the diagnostic criteria of atypical HCC such as hypovascular HCC, diagnosis and management toward very small HCC, and the differential diagnostic spectrum of malignances other than HCC (*68-70*). Table 2 summarizes the controversies of the diagnostic strategy among major practice guidelines toward HCC.

In summary, with the growing knowledge of behavior of HCC, and the continuous improvement in

Table 1. Categories of LI-RADS v2014

LI-RADS	Category	Concept and definition
LR-1	Definitely benign	*Concept*: 100% certainty observation is benign. *Definition*: Observation with imaging features diagnostic of a benign entity, or definite disappearance at follow up in absence of treatment.
LR-2	Probably benign	*Concept*: High probability observation is benign. *Definition*: Observation with imaging features suggestive but not diagnostic of a benign entity.
LR-3	Intermediate probability for HCC	*Concept*: Both HCC and benign entity have moderate probability. *Definition*: Observation that does not meet criteria for other LI-RADS categories.
LR-4	Probably HCC	*Concept*: High probability observation is HCC but there is not 100% certainty. *Definition*: Observation with imaging features suggestive but not diagnostic of HCC.
LR-5[*]	Definitely HCC	*Concept*: 100% certainty observation is HCC. *Definition*: Observation with imaging features diagnostic of HCC or proven to be HCC at histology.
LR-5V	Definitely HCC with tumor in vein	*Concept*: 100% certainty that observation is HCC invading vein. *Definition*: Observation with imaging features diagnostic of HCC invading vein.
LR-5T	Treated observation	*Concept:* A loco-regionally treated HCC. *Definition*: LR5A or 5B observation or biopsy-proven HCC lesion that has undergone loco-regional treatment.
LR-M	Other malinancy	*Concept*: High probability that observation is a malignancy other than HCC. *Definition*: Observation with features suggestive of non-HCC malignancy.

[*]LR-5g, if there is ≥ 50% diameter increase in ≤ 6 months. [*]LR-5us, if there is both "washout" and visibility as discrete nodules at antecedent surveillance ultrasound. Modified from the original table from American College of Radiology. Liver Imaging Reporting and Data System. *http://www.acr.org/Quality-Safety/Resources/LIRADS. html*

Table 2. Major difference on the diagnosis of HCC among six major practice guidelines

Items	AASLD 2010	EASLD 2012	APASL 2010	JSH 2014	KLCSG 2014	LI-RADS 2014
Contrast enhanced ultrasonography	N	N[*]	Y	Y	Y	N
Angiographic assisted CTA/CTAP	N	N	N	Y	N	N
Inclusion of small HCC < 1.0 cm	N	N	Y	Y	Y	N
Diffusion weighted Imaging	N	N	N	N	N	Y
Hepatocyte specific contrast imaging	N	N	Y	Y	Y	Y
Criteria for hypovascular HCC	N	N	Y	Y	N	Y
Consideration of other malignances	N	N	N	N	N	Y

Y: agreed, included or recommended; N: disagreed, excluded or declined. [*] EASLD considers contrast enhanced ultrasonography to be used with caution.

imaging techniques and evidence-based interpretation in cirrhotic liver, the detection and characterization of HCC has improved in the past decade. Besides dynamic enhanced US/CT/MRI, hepatocyte-specific imaging and DWI are showing their potential for diagnosis of early HCCs. A number of practice guidelines for the imaging diagnosis have been developed to reduce interpretation variability and to help standardize management of HCC, and they are constantly updated with advances in imaging techniques and better understanding of features from clinical data.

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