

Radiological Features of Hepatocellular Carcinoma



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Present article is a review of radiological features of hepatocellular carcinoma on various imaging modalities. With the advancement in imaging techniques, biopsy is rarely needed for diagnosis of hepatocellular carcinoma (HCC), unlike other malignancies. Imaging is useful not only for diagnosis but also for surveillance, therapy and assessing response to treatment. The classical and the atypical radiological features of HCC have been described. (J CLIN EXP HEPATOL 2014;4:S63–S66)

Present day radiology plays an essential role in evaluation and treatment together with surveillance of hepatocellular carcinoma. The detailed information regarding the various stages, lesion description, locoregional disease infiltration or distant disease spread can be ascertained. It is essential to use the imaging modalities deliberately and liberally to confidently detect early lesions; thereby allowing effective and curative treatment options for HCC.

CLASSIFICATION OF LIVER LESIONS

The liver lesions are classified into the following as per Liver Imaging Reporting and Data System (LI-RADS).¹

1. Definitely benign (LR1)
2. Definitely HCC (LR5)
3. Probably HCC (LR4)
4. Probably benign (LR2)
5. Indeterminate (LR3) with equivocal imaging features

Smaller lesions (1–2 cm) must meet more stringent imaging criteria than larger lesions (2–5 cm) in order to be

diagnosed as HCC on multiphase contrast enhanced imaging (CT or MRI). Lesions should have following features to meet criteria

Lesions between 1 and 2 cm must be hypervascular on arterial phase imaging, and demonstrate portal vein/delayed phase washout and pseudocapsule enhancement. If both washout and pseudocapsule enhancement are not present, they must demonstrate growth on serial imaging or confirmed on histology.^{2,3}

Lesions between 2 and 5 cm or more must be hypervascular on arterial phase imaging and demonstrate portal vein/delayed phase washout or pseudocapsule enhancement. If no washout or pseudocapsule enhancement, lesion must demonstrate growth on serial imaging.

Lesions less than 1 cm are indeterminate (and thus, not eligible to be considered as HCC).

CHARACTERISTICS OF HEPATOCELLULAR CARCINOMA

Arterial Enhancement

Hepatic artery is the primary feeder to the HCC. It is important to optimize the protocol of imaging based upon the characteristic arterial phase enhancement of HCC. The avid contrast enhancement in arterial phase of the image acquisition is crucial to radiological diagnosis of HCC.⁴

With the evolution of dual source/dual energy and 32 channels MRI imaging, the detection of lesions smaller than even 1.0 cm is possible, especially on arterial phases. If the lesions are larger than 1.0 cm, than in addition to arterial phase imaging, a portal-delayed phase washout can be appreciated and is characteristic of HCC. From the initial three phase imaging (triple phase study) a recommendation of image acquisition for multiple sequences of the arterial phase is important (four-phase CT). This increases the sensitivity for smaller lesions with a profound neovascularization, circumventing the differences in blood flow kinetics and characteristics of the

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Abbreviations: A-P: arterio-portal; CT: computerized tomography; CTAP: CT during arterial portography; CTHA: computerized tomography hepatic angiography; Gd-BOPTA: gadopentetate dimeglumine; Gd-EOB: gadolinium ethoxybenzyl; Gd-EOB-DTPA: gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid; GRE: gradient echo; HCC: hepatocellular carcinoma; LI-RADS: Liver Imaging Reporting and Data System; MDCT: multidetector CT; MRI: magnetic resonance imaging; SPIO: superparamagnetic iron oxide; T1W: T1 weighted; T2W: T2 weighted; TACE: trans-arterial chemo-embolization; TE: time to echo; THAD: transient hepatic attenuation differentiation; THID: transient hepatic intensity differentiation

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tumor. Some large lesions may be hypovascular on arterial phase and may show a heterogenous delayed enhancement.

Washout

The term rapid washout is presence of hypodensity or hypointensity of the lesion as compared to rest of the liver on portovenous or delayed phases, and has a specificity of 95–96% for diagnosis of HCC.^{4,5} Absence of a washout does not exclude HCC as some of these may appear hyperintense or isointense during portovenous phase.⁶

Capsule

About 90% of large HCC (>5 cm) in Asian countries and about 42% of cases in non-Asian countries, have a tumor capsule.⁴ Presence of a capsule or a pseudocapsule differentiates HCC from regenerative and dysplastic nodules. On CT, the capsule usually is hypodense and on MRI hyperintense on T1W and T2W. Some studies suggested that, low-grade HCCs are well encapsulated and the efficacy of TACE treatment is better in HCCs with a capsule.

Vascular Invasion

Vascular invasion is common in large and/or high-grade tumors. Thrombosis of the portal vein, is seen 44–62.8% of large HCC. Thrombosis may be because of the tumor invasion or non-tumoral. The management strategy for the thrombus due to tumor and a bland thrombus are different and critical. Tumor thrombus is usually identified in contiguity of the primary tumor and tends to enlarge the adjacent vessels due to tumor encroachment.

The behavior of the tumor thrombus is identical to that of the parent tumor, exhibiting post contrast enhancement, and a high T2 intensity together with a washout and a restricted diffusion. There is a propensity for a higher ADC (apparent diffusion coefficient) in the bland thrombus than HCC, more than the tumor thrombus itself. The large HCCs have a combination of areas of variable contrast enhancement and inherent signal intensity in T1 and T2 sequences which gives a mosaic appearance. On histopathology, there are multiple confluent areas of tumors, which have a variable cellular differentiation, adja-

cent parenchymal fibrosis, scarring, necrosis together with hemorrhage and septations, which explains the heterogeneous appearance.

IMAGING FEATURES OF VARIANTS OF HEPATOCELLULAR CARCINOMA

Hypervascular Nodules Without Washout

Based upon the nature of contrast uptake in the arterial phase, the liver lesions can be hypovascular and hypervascular in relation to the normal hepatic parenchyma. Sometimes, there is a delayed contrast enhancement, without any washout. Such lesions may be focal nodular hyperplasia, hemangiomas, hepatic adenoma, hypervascular metastases are of transient hepatic enhancement difference. Some HCC may not show washout with conventional imaging and would either need newer imaging modalities like Gd-EOB-DTPA MRI and/or biopsy for confirmation of diagnosis.⁷

Hypovascular Nodules

Hypovascular liver lesions are frequently identified and most likely metastases. About 10% of HCC are hypovascular. Delayed enhancement is found in malignant tumors like cholangiocarcinoma.

Diffuse Hepatocellular Carcinoma

Poorly demarcated, heterogeneously diffuse, infiltrating lesions representing HCCs are not uncommon. On MRI such lesions have a variable but homogenous T1-T2W appearances (T1 hypointensity and T2 hyperintensity).⁸ Diffuse infiltrating HCCs demonstrate hypoenhancement or nodular patchy enhancement on arterial and heterogeneous reticular enhancement on delayed contrast phases.

Portal vein thrombosis is common in such diffuse infiltrating HCC (5–44%).

Hepatocellular Carcinoma in Non-cirrhotic Liver

The overall reported prevalence is upto 54% of all HCC especially in oriental countries. Fibrolamellar HCCs are major differentials. HCCs in non-cirrhotic livers are larger, well-demarcated, solitary lesions with large areas of necrosis and are usually diagnosed at a later stage. Such HCCs uncommonly may show calcification, fibrosis and central scar.¹

RADIOLOGICAL DIFFERENTIALS

Transient Hepatic Intensity Differentiation (THID)/Transient Hepatic Attenuation Differentiation (THAD)

THAD/THIDs are peripherally located, wedge shaped, segmental liver parenchymal areas formed due to portal flow redistribution in proximity to focal lesion, mostly

Tumor thrombus	Non-tumor thrombus
Tumor in continuity with the vessel thrombosis	This may not be present
Expansile	Non-expansile
Tumor thrombus enhances post contrast, especially in arterial phase	No thrombus enhancement
Tends to have neovascularity	No neovascularity
Thrombosed vessel appears larger	Appears shrunken/normal size

due to direct tumor infiltration or a gross extrinsic mass effect to the portal vein and it radicles with a resultant arterio-portal shunting.¹ Anomalous blood supply gives rise to such lesions, and are seen in non malignant condition as well. These THADs/THIDs have a waxing and waning course and a follow-up imaging eventually suggests or confirm these pseudo-lesions. On MRI, the THIDS have T1-T2 mismatch and demonstrate a post contrast accentuation without washout. There may be pooling of hepatocyte specific contrast on delayed phases as the normal vessels course through them. Although benign, these lesions merit a closer and careful evaluation if in a cirrhotic background, to avoid missing an HCC.

Arterio-portal Shunt

Pseudotumours like arterio-portal (A-P) shunts should be ruled out with the help of angiography or CTHA. During such events, use of Gd-EOB-MRI or Kupffer phase of Sonazoid-enhanced US would be useful as they would determine the presence reduced number of Kupffer cells in hepatobiliary phase.

Differentiation Between Hepatocellular Carcinoma and Regenerative Nodules

Regenerating nodules less than 3 mm or less in size are termed as micronodules whereas, those more than 3 mm are called macronodules. These nodules may diffusely involve the liver parenchyma making it difficult for detection and identification. The vascular profile of the regenerative nodule is similar to the normal liver parenchyma. These lesions enhance with gadolinium in the portal phase and appear similar to the rest of liver parenchyma. They retain the hepatocyte specific contrast medium due to the preserved hepatic function making it difficult for detection on CT or MR imaging.¹

It is believed that the presence of iron is responsible for the low signal intensity within the regenerative nodules on the standard spin echo T1W and T2W images. There are certain limitations when siderotic nodules are imaged with GRE (Gradient echo) sequences, but a longer TE (Time to Echo) allows better sensitivity for their detection.¹

Differentiation Between Hepatocellular Carcinoma and Dysplastic Nodules

Dysplastic nodules are considered premalignant.¹ On CT, the dysplastic nodules are iso to hyperdense and on MRI hyperintense on T1W and hypointense on T2W. They have a variable vascular profile, and hence can be confused with regenerative nodule as well as HCC. Dysplastic nodules usually have portovenous blood supply and hence it is difficult to distinguish low-grade dysplastic nodules from regenerative lesions. The high-grade dysplastic nodules have a predominant hepatic arterial supply, and therefore appear similar to HCC.²

Dysplastic nodules lack a capsule, whereas the HCC may have it. Invasion into vascular channels if present indicates presence of HCC rather than dysplastic nodule.

RECENT ADVANCES IN IMAGING

With the present day spectrum of imaging modalities, the following enlisted modalities are considered most sensitive to determine the initial pathogenesis of HCC although they are not widely available.

- (1) Contrast enhanced ultrasound,
- (2) EOB-MRI,
- (3) CTAP,
- (4) CTHA, and
- (5) MDCT/dynamic MRI, SPIO (Superparamagnetic iron oxide)-MRI.

Contrast Enhanced Ultrasound

On conventional ultrasound, HCC may present as a solitary mass or there may be surrounding satellite nodules or multifocal. Diffuse tumor infiltration is also sometimes seen. There are several limitations of US in evaluation or detection of HCC, but it is screening test of choice due to its easy availability, safety and cost effectiveness.

US has been reported to have a sensitivity of between 65% and 80% and a specificity of greater than 90% when used as a screening test for HCC.

A new technique (defect reperfusion imaging) has been described, formulated to facilitate accurate diagnosis of liver cancer, which shows arterial enhancement and venous washout.

Phase	Time after injection
Arterial phase	2-3 min
Kupffer phase	6-10 min

Contrast enhanced US is a recent advancement and has two phases: the vascular and Kupffer phases. Sonazoid is intravenously injected.

Vascular Phase

Detection of intranodular blood flow within the HCC is fairly high with contrast enhanced US using sonazoid. Gold standard investigation still remains a four-phase MDCT imaging, which is comparable or superior to other investigations, mainly in cases where detection of arterial flow pattern with the nodule. But when it comes to identification of neoplastic activity in a hypovascular nodule, contrast enhanced ultrasound-Sonazoid gives the maximum information. Per-se, contrast enhanced US may be considered superior to identification of intranodular arterial blood flow.

Kupffer Phase

This phase is very stable and hence entire liver scanning is performed in this phase. The principle on which this pharmacokinetics based is that the intravenously injected Sonazoid reaches to the sites of Kupffer defect and defect reperfusion is identified, allowing the cancer detection easy and more definitive. Futuristically, contrast enhanced ultrasound has been projected as investigation for screening and staging of liver tumors.²

A Kupffer defect is evaluated in Kupffer phase 6–10 min post arterial enhancement of the lesion. Entire liver needs to be scanned to determine the defect site. A re-injection of contrast is being performed if a Kupffer defect is identified using Sonazoid, without considering the presence or absence of arterial blood flow.

The sensitivity to diagnose an HCC approaches 100% after determination of the arterial vascularity within the defect area.² Concerned nodules cannot be identified on B-mode US, but can be readily diagnosed using defects in Kupffer phase contrast enhanced US, though.⁸ Additional injection of Sonazoid facilitates determination of neovascularization within the Kupffer defect which may eventually help in RFA (radiofrequency thermal ablation).² This new innovation is now considered as a vital breakthrough in liver cancer imaging. No special device or analysis is required. The induction of such technique allows identification of nodules that show hypervascularity on CT but remain indeterminate on B-mode US with a sensitivity of about 100%. If the nodules are without arterial enhancement, these may differ from nodules detected on CT. This technique of defect reperfusion imaging has a potential to aid in the treatment planning. It can also be applied in as a screening tool in patients with cirrhosis, local tumor status and post treatment follow-up.

GADOLINIUM ETHOXYBENZYL MAGNETIC RESONANCE IMAGING

There is a recent breakthrough in liver cancer imaging with the advent of Gd-EOB-DTPA-enhanced MRI. EOB-MRI may facilitate the most sensitive and earliest assessment of the early features of HCC. The precancerous lesions show EOB pooling. The signal drop in the hepatobiliary phase within these lesions helps to determine the presence of an early HCC.

The molecular and functional status of HCC is becoming a reality of near future. Hepatocyte specific gadolinium chelating agents are relatively new. Gadoteric acid (Gd-EOB-DTPA, Primovist, Bayer) and gadopentate dimeglumine (Gd-BOPTA, Multihance, Bracco) are meant to improve diagnosis of HCC and have proven to be similar or better than double contrast MRI or SPIO imaging. The hepatocyte specific contrast agent for MRI, Gd-EOB-DTPA (gadoterate sodium). This contrast agent pooled

in with the hepatocytes and excreted via kidney and from the liver through the bile duct. With 6–20 min post injection (hepatobiliary phase), the liver appears diffusely hyperintense. The HCC nodules are devoid of hepatocytes and normal parenchymal cells, hence show hypointensity. As this is a direct feature, the interpretation is easier, in comparison to SPIO agents which depict the liver as a black due to drop in signal deteriorating the spatial resolution.⁹

The multistep hepatocarcinogenesis evaluation is facilitated by the functional pharmacokinetics of the Gd-EOB-DTPA MRI.

Gd-BOPTA	Gd-EOB-DTPA
Dose—0.1 mmol/kg	0.025 mmol/kg
3–5% taken by hepatocytes & excreted	50% taken up & excreted
Max. del. Enhance-60 min.	20 min
Sensitivity of hepato. phase lower	Much higher

CONFLICTS OF INTEREST

All authors have none to declare.

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