Introduction:

The incidence of hepatocellular carcinoma is gradually increasing in the incidence in the recent past. If detected early and treated adequately the prognosis of the patients suffering from this malignancy is very good. Computed tomography (CT) and Magnetic Resonance (MR) imaging play important roles in the early diagnosis and staging of the disease. In this article, the basic concepts of these two imaging techniques are discussed in detail.

Key concepts:

- Basis of hepatocarcinogenesis
- Current management guidelines recommend multi phasic CT or MR imaging with extracellular contrast agent for diagnosis and staging of hepatocellular carcinoma (HCC)

ABSTRACT

Hepatocellular carcinoma (HCC) is a malignancy that predominantly occurs in the setting of cirrhosis. Its incidence is rising worldwide. Computed tomography (CT) and magnetic resonance (MR) imaging play critical roles in the diagnosis and staging of HCC, basic concepts of which are discussed, the diagnostic performance of CT and MR imaging with extracellular contrast agents and MR imaging with hepatobiliary contrast agents reviewed and major and ancillary imaging features used in the diagnosis and characterization of HCC are examined in depth.

Keywords: Hepatocellular Carcinoma; CT Scan; MRI Scan.
Another imaging feature characteristic of progressed HCC is capsule appearance; the combination of arterial phase hyper enhancement and capsule appearance strongly suggest the diagnosis of HCC, even in the absence of washout appearance.

Cirrhosis-associated nodules which are hypo intense in the hepatobiliary phase are likely to be malignant or premalignant, even in the absence of arterial phase hyper enhancement or venous phase "washout."

MR imaging with hepatobiliary agents is the most sensitive method for detecting small HCCs and premalignant lesions likely to progress to HCC.

HEPATOCA R CIN OGENESIS

When a hepatic nodule becomes a dysplastic nodule, the normal hepatic arterial flow is decreased while portal venous flow is maintained. The evolution toward HCC is characterized by increased arterialisation and an increase in the arterial blood supply and sinusoidal capillarisation.

The presence of new unpaired arteries not accompanied by bile duct has been shown to be able to differentiate neoplastic nodules from regenerative nodules. The number of unpaired arteries gradually increases as the cirrhotic nodules get converted to HCC. The degree of arterialisation also correlates well with HCC differentiation, particularly in lesions with a diameter less than 3 cm. In fact, well-differentiated HCCs often receive preferential portal venous blood, whereas moderately and poorly differentiated tumours are supplied with arterial blood. In addition the lesions measuring more than the 3 cm also get preferential blood supply from the hepatic artery.

Sinusoidal capillarisation is another common neoangiogenetic process. It involves transformation of fenestrated hepatic sinusoids into continuous capillaries, coupled with collagenisation of the extra vascular spaces of Disse and deposition of laminin and basement membranes near the endothelial cells and hepatocytes. The sinusoidal capillarisation appears to be directly related to tumour differentiation.

Together with these vascular changes, other modifications can be observed and exploited with current imaging techniques, such as a progressive decrease in the number of Kupffer cells and number of biliary canaliculi.

CT scan or MRI?

Both modalities provide:

- excellent sensitivity for nodular HCCs larger than 2 cm
- modest sensitivity for 1-2-cm HCCs
- poor sensitivity for HCCs smaller than 1 cm

Advantages of CT are that it is widely available, rapid, robust, and compared with MR imaging needs less expertise to perform and to interpret images.

Disadvantages include radiation exposure and relatively low soft tissue contrast.
By comparison, MR imaging provides higher soft-tissue contrast and permits assessment of a greater number of tissue properties, which in principle may help in lesion detection and characterization. Disadvantages are that, MR imaging is more time consuming, less robust, and more prone to artefacts. It requires greater expertise to perform and interpret images and its availability is limited. Thus, while MR imaging may be preferred over CT at many academic centres, there is insufficient data to recommend MR imaging over CT in community or less-specialized centres. MR imaging with hepatobiliary contrast agents is emerging worldwide as a leading method for diagnosis and staging of HCC. It is the most sensitive method for detection of small HCCs and also of premalignant lesions.

DIAGNOSIS AND STAGING
Multi phasic CT and MR imaging with extracellular agents permit diagnosis and staging of HCC based mainly on assessment of vascularity (Fig.1).

![Fig.1.CECT ABDOMEN: Typical cirrhotic changes are evident by enlarged left lobe, irregular nodular outer surface and widened fissures. There is malignant infiltration of the left hepatic lobe in segment IV, that enhances in the arterial phase and displays wash out on portovenous phase. Furthermore, there is malignant thrombus in the left branch of portal vein that follows the same enhancing criteria. GB stones, splenomegaly and left renal stone are other findings.](image)

Staging systems are the key to predict the prognosis of patients with cancer. It also helps in stratifying the patients according to prognostic variables in the setting of clinical trials and in guiding the treatment plan. As an example, Barcelona Clinic Liver Cancer (BCLC) staging system links the stage of the disease to a specific treatment strategy.

MAJOR IMAGING FEATURES OF HCC ASSESSED IN THE VASCULAR PHASES OF CT AND MR IMAGING

*Arterial phase hyper enhancement:* It is Characteristic of but not specific for progressed HCC.

*Differential diagnosis* includes benign perfusion alterations, small haemangiomata, small focal nodular hyperplasia-like lesions, atypical cases of focal or confluent fibrosis, atypical cirrhotic nodule, atypical dysplastic nodule, and non-HCC malignant conditions such as small Indian childhood cirrhosis (ICC) or small hyper vascular metastases such as neuro endocrine tumours.

*Washout appearance:* It is Characteristic of but not specific for progressed HCC.

*Differential diagnosis* includes cirrhotic nodules and dysplastic nodules.
The Pitfall is focal areas of parenchymal distortion and enhancing fibrosis may create false perception of "washout."

**Limitation:** Although washout appearance may be assessed in either the portal venous phase or delayed phase with extracellular agents, for definitive diagnosis of HCC washout appearance probably should be evaluated only in the portal venous phase after administration of gadoxetate disodium, because hypo intensity relative to liver in the transitional phase may reflect hyper enhancement of liver rather than de-enhancement of a mass.

**Capsule appearance:**
It is Characteristic of and relatively specific for progressed HCC.

**Pitfall:** peripheral enhancement of intra hepatic cholangiocarcinoma and fibrous tissue surrounding cirrhotic nodules and dysplastic nodules may be mistaken for capsule appearance.

**Arterial phase hyper enhancement plus washout or capsule appearance:**
It is diagnostic of HCC
In patients at risk for developing HCC, the combination of arterial phase hyper enhancement plus washout or capsule appearance has near 100% specificity for HCC.

Limitations: While this combination has high specificity, it has low sensitivity, as most early HCCs, many small progressed HCCs, and many infiltrative HCCs do not exhibit this combination of imaging features (Fig.2).

Fig.2. MR ABDOMEN (plain & contrast): Selected MR images demonstrate heterogeneous enhancing lesion in segment VIII of right lobe of liver. Note that the peripheral components on the right side of the mass demonstrate more characteristic early arterial enhancement with washout, becoming hypointense comparedto the remainder of the liver. The central non-enhancing component remained non enhancing even in further delayed post contrast phases.

Rim enhancement, which is more obvious in delayed images.
The main limitation of CT and MR imaging with extracellular contrast agents is low per-lesion sensitivity. Only HCCs that have developed sufficient neoangiogenesis to show arterial phase hyper enhancement and that also exhibit washout or capsule appearance can be unequivocally diagnosed. In general, these are progressed, moderately differentiated HCCs. Approximately 40% of HCCs lack arterial phase hyper enhancement and cannot be diagnosed as definite HCC. These include most early HCCs; poorly differentiated, infiltrative HCCs, which may have weak, patchy arterial phase hyper enhancement; some nodular HCCs with tiny hyper vascular foci too small to be perceived. Additionally, Approximately 40%-60% of small HCCs, even if hyper enhanced in the arterial phase, do not exhibit a washout or capsule appearance in the venous phases.

**DIAGNOSIS AND STAGING OF HCC WITH HEPATOBILIARY AGENTS**

Hepatobiliary contrast agents can be divided broadly into the following five classes:
- Extracellular agents
- Reticulo endothelial agents
- Hepatobiliary agents
- Bloodpool agents
- Combined agents

Currently available hepatobiliary contrast agents include gadoxetate disodium and gadoxetate dimeglumine, both of which are gadolinium-based agents. On intra venous administration, these agents rapidly distribute in the vascular-interstitial compartment, enhance the extracellular space, and permit acquisition of dynamic images that allow for HCC diagnosis based on perfusion characteristics (2). After distribution in the extracellular space, these agents enter hepatocytes via OATP8 receptors. The agents subsequently are excreted into the biliary canaliculi as well as back into the sinusoidal space by transporter molecules, expressed only in "functioning" hepatocytes.

Hepatobiliary agents permit assessment of tumour vascularity and hepatocellular function based mainly on signal intensity relative to liver in the hepatobiliary phase, which in turn depends on a complex interplay between numerous incompletely understood factors, the dominant determinant is OATP8 expression (3). Nodules with low or no OATP expression do not uptake hepatobiliary agents and appear hypo intense in the hepatobiliary phase, while nodules with preserved or elevated OATP expression uptake the agents and tend to be iso intense or hyper intense. Since OATP expression declines during hepatocarcinogenesis, the assessment of signal intensity helps in the detection and characterization of hepatocellular nodules in the cirrhotic liver.

These concepts can be exploited for diagnostic benefit. In patients with cirrhosis or chronic hepatitis, the addition of hepatobiliary phase images increases conspicuousness, delineation and improves the per-lesion sensitivity for the diagnosis of HCC.

Another benefit is in the interpretation of small
nodular lesions characterized by arterial phase hyper enhancement and venous phase iso enhancement. Such lesions are indeterminate if evaluated only in the vascular phases but, after exclusion of haemangioma; these are highly suspicious for malignancy if they demonstrate hypo intensity in the hepatobiliary phase.

A related benefit is in the differentiation of hyper vascular HCCs from hyper vascular pseudo lesions such as focal arterio -portal shunts. For most vascular pseudo lesions, the underlying OATP expression is preserved and the hepatobiliary phase signal intensity is the same as that of background liver, in contradistinction to HCCs, which characteristically appear hypo intense.

Hepatobiliary phase complicates the differentiation of HCC from other benign entities such as confluent fibrosis, which also appears hypo intense in this phase and could be misinterpreted as HCC.

HEPATOBLIARY PHASE IMAGING FEATURES OF HCC

T1 hypo intensity
It is characteristic of HCC (including both early and advance lesions), but not specific for HCC. However differential diagnosis includes high-grade dysplastic nodule, low-grade dysplastic nodule, large cirrhotic nodule, siderotic nodule, nodular or confluent area of fibrosis, intra hepatic cholangiocarcinoma, and haemangioma.

Limitations of this study: HCCs may be difficult to recognize in the hepatobiliary phase in patients with severe liver dysfunction, cholestasis, iron overload, or marked fibrosis. Even in the absence of these conditions, infiltrative HCCs may be difficult to identify in the hepatobiliary phase.

T1 hyper intensity
Observed in 5%-12% of moderately differentiated HCCs
The differential diagnosis includes non malignant nodule like, focal nodular hyperplasia.
Features that favour HCC include focal defects in contrast agent uptake, presence of hypo intense rim, and absence of architectural features of focal nodular hyperplasia (central scar and radiating fibrous septa)

ANCILLARY IMAGING FEATURES OF HCC
The presence of Intra lesional fat is characteristic of but not specific for early HCC.

The differential diagnosis includes low-grade and high-grade dysplastic nodules, steatohepatitic variant of HCC.

Limitation: incremental value of intra lesional fat for diagnosis of HCC is limited since this feature often coincides with other more discriminatory imaging features.

The Corona enhancement is Characteristic of progressed, hyper vascular HCC. It helps to differentiate progressed, hyper vascular HCC from vascular pseudo lesions such as arterio-portal shunts and thought to represent a frequent site of peri lesional satellite metastases.

Limitations: May be difficult to recognize at CT scan or MR imaging; hence, incremental value
of this feature for diagnosis of progressed HCC may be modest. It is not characteristic of the lesion and therefore does not help in diagnosis of early HCC.

Pitfall: May overlap and blend with tumour enhancement, causing tumour to appear larger than it really is.

**Nodule-in-nodule architecture:** Corresponds to nodule-in-nodule growth pattern observed at histology and suggests emergence of progressed HCC within dysplastic nodule or early HCC.

Limitation: nodule-in-nodule architecture is uncommonly depicted in HCCs at CT scan or MR imaging; hence, incremental value of this feature for diagnosis of HCC may be modest.

**Mosaic architecture** Characteristic of and frequently observed in large HCCs. Helps in the differentiation of HCC from ICC.

Limitation: mosaic architecture is uncommon in small HCCs; hence, incremental value of this feature for diagnosis of small HCC may be modest.

**Favours diagnosis of malignancy but not specific for HCC:**
Mild-moderate T2 hyper intensity
Mild-moderate T2 hyper intensity
Lesional iron sparing

**CONCLUSION**
Multiphase CT scan and MR imaging with extracellular agents provide valuable information regarding vascularity and have excellent accuracy for diagnosis of large nodular HCCs, but they have limited sensitivity for early HCCs as well as for small and progressed HCCs. MR imaging with hepatobiliary agents may be the most sensitive technique for detection of such HCCs. Ancillary imaging features provide incremental information that helps to characterize nodules and may improve the sensitivity for HCC (4).

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