

## A Recent Short Review in Non-Invasive Magnetic Resonance Imaging on Assessment of HCC Stages: MRI Findings and Pathological Diagnosis

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### ABSTRACT

Hepatocellular Carcinoma (HCC) is the third most common cancers, and it considers having resulted in mortality and morbidity in the world. It is also known as the most primary Hepatocarcinogenesis. Magnetic resonance imaging (MRI) is used to detect and diagnosis tumours and staging of cancer, and to predict tumour biology through biomarkers imaging. Moreover, the MRI technique is used to predict the small size of HCC, high ADC value, and fibrous capsule or pseudo-capsule. In this review, the HCC features in MRI

and their implications for prognosis and diagnosis as biomarkers imaging are discussed. Furthermore, the significant findings of HCC staging during the multistep hepatocarcinogenesis are summarized through histopathology and MRI. The review also provides a good Knowledge about early HCC diagnosis, MRI contrast agents, the functional imaging application through MRI include diffusion-weighted sequences, perfusion imaging, radionics analysis, and hepatobiliary contrast agents.

**Key words:** Liver; Hepatocellular carcinoma; Magnetic resonance; Contrast media

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### HIGHLIGHTS

1. In the HCC, the hepatic artery is considered the primary feeder of the cancer cells, while the primary feeder to the liver parenchyma is a portal vein which provides the nutrients and oxygen to these cells.
2. The HCC has significant features through washout of the contrast media at the portal-venous (PVP) and delay phase (DP).
3. The biomarkers used to determine the HCC include alpha-fetoprotein (AFP), Des-Gamma-Carboxy Prothrombin (DCP), and Lens culinaris agglutinin-reactive AFP (AFP-L3), CD34, Forkhead box protein M1(FOXM1), P53, nuclear factor kappa-B (NF-κB), and agrin.
4. DWI is a routine MRI protocol for liver imaging, especially for HCC. Because it provides a better result than other sequences such as T1W and T2W.
5. The contrast of a tumour to the liver in a transitional phase (TP, 3-min delay) would be derived from both true washouts of contrast agent and enhancement of hepatic parenchyma.

## INTRODUCTION

Hepatocellular carcinoma (HCC) is considered the most primary malignant tumour in the liver, and it is estimated the third vital carcinoma in the world, and the most diagnosed after the clinical signs manifests at the advanced stage. The development of HCC is associated with significant risk factors such as cirrhosis, and chronic liver inflammation such as hepatitis B (HBV) and hepatitis C (HCV), cigarette smoking, aflatoxin exposure, alcohol consumption, non-alcoholic fatty liver disease (NAFLD), and autoimmunity cases<sup>[1]</sup>.

Due to the seriousness of this disease, many systems can be followed to detect the HCC staging. The American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) are considered the widest guidelines used to achieve the best diagnostic value of HCC<sup>[1,2]</sup>.

In the HCC, the hepatic artery is considered the primary feeder of the cancer cells, while the primary feeder to the liver parenchyma is a portal vein which provides the nutrients and oxygen to these cells. Thus, the typical features of HCC involved hyper arterial enhancement and delayed washout<sup>[3]</sup>.

The hyperenhancement of contrast media in the hepatic arterial phase (HAP) is considered the first important sign to differentiate the HCC from other pathologies. However, there are another benign and malignant hepatic lesions behaves on this path such as focal nodular hyperplasia, hyper-vascular metastases, haemangiomas, and cirrhotic nodules<sup>[4,5]</sup>.

The HCC has significant features through washout of the contrast media at the portal-venous (PVP) and delay phase (DP), which can define as the hyper-intense lesion become to hypo-intense comparing to the liver parenchyma especially in the DP imaging. The washout in PVP is the HCC, and it has a significant feature through washout of the contrast media at the Porto venous (PVP) and delay phase (DP). It is defined as the hyperintense lesion to hypointense comparing to the liver parenchyma especially in the DP imaging. The washout in PVP is typically at the malignant lesions more than 2 cm. Thus, the diagnostic sensitivity for these lesions size would be high<sup>[6]</sup>.

The HCC shows in different modalities include ultrasound, CT, and MRI. The best modality among the modalities is MRI. Thus, in this review, we provide an overview of recent advances and techniques in MR studies for the diagnosis and the staging of HCC.

### 1. HCC Biomarkers

Biomarkers are considered as an effective and useful method to detect cancer cells because it is used to establish outcome, evaluate recurrence, and to measure the disease progress. Biomarkers are used as measurable indicators of the presence and severity of cancer cells. The biomarkers provide many technological approaches such as solid tissue samples, body fluid, imaging, and physiological measurements<sup>[11]</sup>.

The biomarkers evaluation in the hepatocytes and vascular tissue have an essential role in the diagnosis of the degenerative nodules (DN) and HCC. The biomarkers used to determine the HCC include alpha-fetoprotein (AFP), Des-Gamma-Carboxy Prothrombin (DCP), and Lens culinaris agglutinin-reactive AFP (AFP-L3), CD34, Forkhead box protein M1(FOXM1), P53, nuclear factor kappa-B (NF- $\kappa$ B), and agrin<sup>[12]</sup>.

### 2. Supplementary Imaging Techniques

#### 2.1. Diffusion Weighted Imaging (DWI)

DWI is a functional MRI sequence; it gives the impression of the change in the diffusion properties of water molecules in the biological tissues, and it provides additional information for tissue cellularity<sup>[13]</sup>. However, the high cellular tissue of the diffusion water proton "apparent" would be decreased with the high density of hydrophobic cellular membranes. The decreased was due to water diffusion hindrance by constitutive tissue elements whereby the diffusion time would be increased<sup>[14]</sup>. The same thing happens when the tissue has many small cells within the lesion, and HCC is known to have many small cells compared with normal hepatocytes. Therefore, the cells number in HCC is higher than the normal liver cells<sup>[15]</sup>. Thus, the diffusion of water is restricted, and this could be indicated by the low value of Apparent diffusion coefficient (ADC)<sup>[16]</sup> which is considered as post-processing of DWI sequences<sup>[15]</sup>. Therefore, the diffusion restriction indicates the signal intensity of a tumour which is higher compared with the surrounding parenchyma, and the b-value (expressed in seconds per millimeter square) DW MR images would be high<sup>[17]</sup>. Also, the restriction of diffusion in malignant tumours is higher than the benign lesions<sup>[18]</sup>.

DWI is a routine MRI protocol for liver imaging, especially for HCC. Because it provides a better result than other sequences such as T1W and T2W<sup>[17]</sup>. In addition, the DWI has a short acquisition time and do not need to use the contrast agents. DWI sequences are applied to evaluate the liver lesions by single shot spin-echo (SE) echo-planar technique combined with fat suppression. It can also be applied by using free breathing (FB) and respiratory triggered (RT). The studies show the HCC detection efficiency using FB-DWI is higher than the RT-DWI<sup>[19]</sup>. However, DWI could not be as a stand-alone sequence; it should combine with Gd-EOB- DTPA to assess the three major processes in the multistep hepatocarcinogenesis including the vascular changes, tissue diffusivity, and hepatocyte change. The recent meta-analysis study showed that the diagnostic accuracy and specificity for HCCs would be improved with the combination of gadoxetic acid-enhanced MRI and DWI<sup>[20]</sup>.

Moreover, the combination of DWI and DCE would improve the efficiency of small HCC (sHCC) detection<sup>[21]</sup>. The hypovascular lesions of more than 10 mm in diameter, which appears as a hyper-intense in DWI are closely linked with the hypervascular HCC. The apparent diffusion coefficient (ADC) measurement helps to provide additional information about morphological characteristics, analysing the structure, quantitative index of diffusion characteristics, and tissue components<sup>[18,19]</sup>. And can be calculated by using two different values of b-value (one value is low, and the other is intermediate or high)<sup>[15]</sup>. The sensitivity and specificity of ADC are reached 92% to differentiate between the HCC and dysplastic nodules (DN), LGDNs. Thus, the qualitative and quantitative of the DWI can be used to differentiate between HCC grades<sup>[24]</sup>.

Also, the DWI can be used to predict microvascular invasion (MVI) in HCC. MVI plays an essential role as a prognostic factor for HCC recurrence, mostly after the liver resection or liver transplantation<sup>[25]</sup>. For detecting the MVI, the T2W and DWI images are used by applying the concept of diffusion- and T2-weighted imaging mismatch. Furthermore, the DWI/T2 mismatch concept provides more specificity as a predictor of MVI reaches 95%.

Another application of DWI is to differentiate the necrosis tissues inside a tumour after given the therapies, and that is because the necrosis tissue has a higher ADC value than the tumour tissue itself<sup>[26]</sup>. Therefore, the ADC values indicate treatment response even when there is no changing in the tumour size, the ADC values increased in the patients who were treated with transarterial radio-embolization (TARE), because of the raised in the necrosis tissue

inside a tumour<sup>[22,23]</sup>. Despite this application of DWI, it also has many disadvantages such as technical aspects which need to be considered. They include the different of scanner equipment's, low comparability and reproducibility of ADC measurements, low ADC maps susceptibility due to noise and artifacts, and lack of standardized DWI protocol due to the challenging in a moving liver<sup>[25,26]</sup>.

## 2.2 Perfusion magnetic resonance imaging

The concept of dynamic contrast-enhanced (DCE)- perfusion MR imaging is taking multiple images within a few seconds after contrast agents injected. The perfusion is considered as a hemodynamic analysing method for tissue; it permits for quantitative assessment by using different parameters such as blood volume, tumour blood flow, permeability-surface area product, and mean transit time<sup>[30]</sup>.

The contrast enhancement of the tissue related to the timing of the contrast agent within the tissue and this differentiate the relation to the microcirculatory pathophysiological changes. The main aim of MRI perfusion is demonstrating the vascular changing of HCC (angiogenesis development)<sup>[31]</sup>.

In general, the perfusion imaging depends on the permeability of cell membranes to passes the fluids and nutrients inside the cell. In the normal cells, the Space of Disse which separates the sinusoids was considered large compared with HCCs. Thus, the exchange of low molecular weight materials such as contrast media would be restricted in HCCs, and that is because of the loss of sinusoidal space inside the capillaries during the tumour proliferation (Figure 1)<sup>[30]</sup>.

Furthermore, the liver has a dual blood supply which occurs within HCC development; the perfusion parameters alteration would occur with the development of HCC. In HCC, the blood flow and volume, hepatic and arterial perfusion is higher than the liver parenchyma<sup>[31]</sup>. Also, the DCE-MRI can quantify the perfusion rate in the HCC by increasing the arterial flow and decreasing of the portal venous flow. However, the difference of HCC in the perfusion imaging in most cases is not significant except the arterial fraction (ART) cases. In the ART parameter, the perfusion time can be estimated by equations which gained from the addition of two input inflow (arterial and portal) into one input<sup>[32]</sup>. The figure below demonstrates the HCC lesion in perfusion images.

## 2.3. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI)

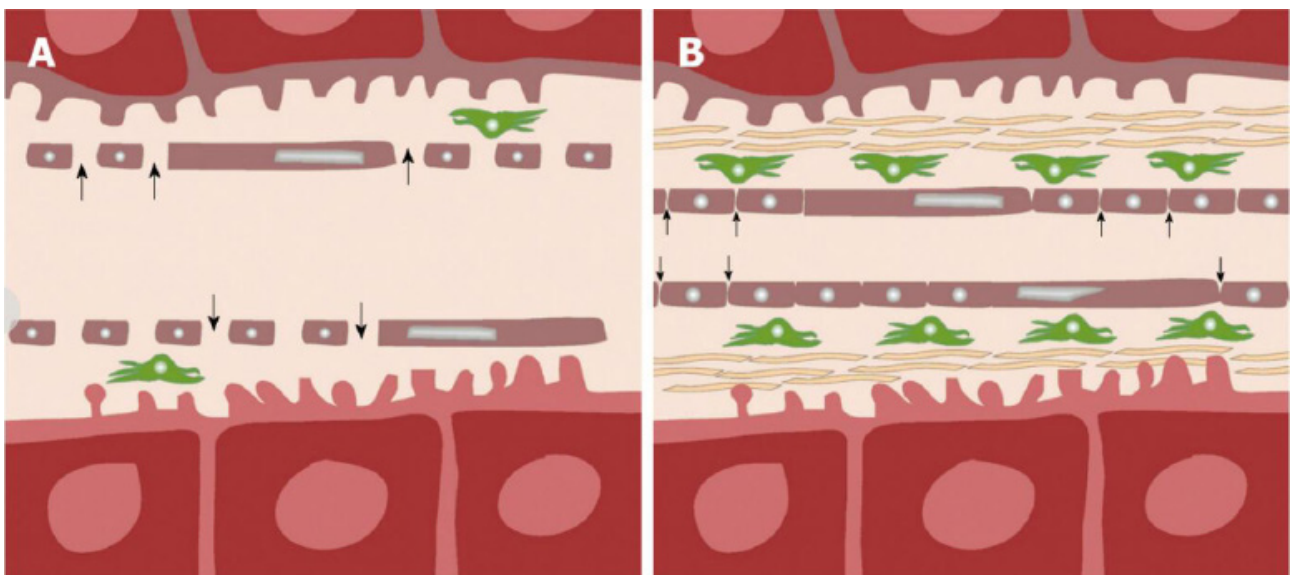


Figure 1 Schematic diagram showing pathophysiological differences between normal (A) and HCC (B) liver [31].

The DCE-MRI consists mainly of T1W images before, during, and after the contrast agent injection. The transition of contrast agent between the intravascular to the extravascular in the extracellular space (EES) will change the T1W signals. This transition depends on the blood flow (perfusion) and vessel leakiness (permeability). Thus, the DCE-MRI could be used to detect the alteration in EES, perfusion, and permeability<sup>[33]</sup>.

DCE-MRI signals used one of following techniques; semi-quantitative (model-free) or quantitative (model based) analysis and both of these analytic methods have many parameters associated with tumour angiogenesis such as volume transfer constant (Ktrans), Kep, and the volume fraction of EES (Ve)<sup>[28,29]</sup>. The Ktrans, Kep is correlated with vascular endothelial growth factor (VEGF) expression, and tumour microvessel density<sup>[34]</sup>, and it is found in the high grades HCC (HGHCC). It is lower than low grades HCC (LGHCC), while the parameter EES (Ve) have not significantly changed between high grade and low-grade HCC<sup>[35]</sup>. Hence, DCE-MRI imaging may use to predict the tumour permeability stimulated by anti-angiogenic agents, and it used to predict biomarker imaging<sup>[33,34]</sup>.

Moreover, the DCE-MRI is used to measure the biomarkers changing in tumour blood flow, intravascular volumes, interstitial, and vascular permeability. Also, DCE-MRI is used to predict the effects of anti-angiogenic drugs and predict the patient's survival outcome<sup>[35,36]</sup>.

## THE MULTISTEP HEPATOCARCINOGENESIS OF HCC

The cancer cell development coincides with the evolution of the mutation in the cell. Thus, the cell replication at a high rate and the apoptosis will occur. The hepatocarcinogenesis is a primary mechanism known as 'multistep hepatocarcinogenesis,' and this step leads to cancer development from cirrhotic liver to the HCC. The multistep hepatocarcinogenesis changing involves the cell density increases, nodules enlarge, hemodynamic change, and Kupffer cells decrease. In the first stage, the portal perfusion still presents and decreases normal arterial supplies, and later on, the intramodular arterial vascularity increases and the portal supplies would be decreased<sup>[35]</sup>. In the same time, this would be happened in the chronic infection (HBV and HCV) through enforcing the body's immune system to attack the normal hepatocytes frequently. Therefore, the

damaging of the cell cycle would be happened and leads to develop the carcinogenesis<sup>[4]</sup>.

### 1. Regenerative Nodules (RN)

RN or cirrhotic nodule are considered as a benign hepatocellular nodule, this nodular region surrounding by fibrotic/scar tissue; this region arose from the regenerative process after hepatic tissue injury. This nodular can be monoacinar, or multiacinar (have more terminal tracks). RNs can be classified into micromodels (less than 3mm), or macro-nodules (above 3mm), and this classified depends on the size of nodule<sup>[40]</sup>.

### 2. Degenerative Nodules (DN)

DN is considered any small dysplastic nodular which is focal nodular regions ( $\geq 1$  mm) without definite evidence of malignancy that is deemed to be pre-cancerous. There are a different between these nodules and the liver parenchyma through different texture, cellular changing, and colour. The DNs subdivided into low grade (LGDNs; the features closer to RNs) and high grade (HGDNs; in the image seems more intimate to HCC). Thus, the LGDNs can transform into HGDNs. However, the difference between these nodules is very tight due to the arterial and portal supplies are consistent and variable. LGDNs have a clonal cell population features without changing in architectural or cellular atypia, the density of cell mildly increases with the monotonous pattern. In this, the DNs cannot see the nodule-in-nodule pattern, and it is considered as a slow and low malignant potential and uncommonly developed to HCC. However, the follow up is not urgent action. The HGDNs are considered as a precancerous in the liver. Despite the small size, the risk of malignant transformation is high, and the biopsies procedure is necessary at these nodules<sup>[41]</sup>.

### 3. Nodule In Nodule HCCs

These nodules can be defined as a small nodular HCC with diameter reaches to 2 cm with or without clear margins inside the large nodule, where the tumour tissues with less differentiated replaced with well-differentiated tumour tissues, and this replacement is closely to tumour proliferation. In histology, the inner nodule is composed of non-differentiated cancer tissue, while the large nodule is a well-differentiated cancer tissue due to the content of fewer components of iron or fat<sup>[11]</sup>. Moreover, this sign indicates the morphological marker for the tumour dedifferentiation.

What the replacement happens in the nodule pattern is detected, in the small nodular HCCs with clear margins, more than half have a thin fibrous capsule and mildly differentiated with low percentage tumour invasion. Thus, even the size is considered small, but these nodules have a high risk to developed into advanced cancers.

### 4. Early HCCs

Early HCCs (in-situ carcinoma) can be defined as well-differentiated cell proliferation and its referred to sHCC with vaguely nodular type. In the sHCC, the hemodynamic changing and the angiogenesis were incomplete, and these lesions are supplied with blood through the portal vessels<sup>[35]</sup>. Thus, it manifests as an atypical enhancement pattern on dynamic images<sup>[42]</sup>. In the histological features, the differentiation between early HCC and HGDNs are difficult, and the most sign used for differentiation between them is the presence of tumour cells invasion at the portal tracts of fibrous septa. The cell density at early HCC stage is higher than normal liver parenchyma. Also, the nuclear, cytoplasm ratio and irregular size are increased. In addition to that, the thin trabecular pattern and varying numbers

in the portal tracts may occur.

Most of early HCC in MRI have been shown as a hypointense on T1W and hyperintense on T2W, and this will be helpful through significant enhancement during the hepatic arterial phase (HAP) of a dynamic gadolinium contrast study. Because there are hemorrhage and existence of lipid, glycogen, and copper, the intensity of T1W images would be not harmonic. Because the HCC does not uptake the superparamagnetic iron oxide agents (SPIO), the Gadoxetic acid-enhanced MR imaging is considered usefully for early HCC detection<sup>[28]</sup>.

### 5. Progressed HCCs

Progressed HCCs or well-differentiated HCC are considered the malignant hepatocellular definitely and can be classified into two categories: sHCC with a diameter less than 2 cm and it includes two distinct types (indistinct margins and distinct margins), and large HCC (LHCC) with diameter above 2 cm and both of them have a distinctly nodular macroscopic feature. However, the size of the HCC lesions differs between organizations, such as the American Association for the Study of Liver Diseases (AASLD) which recommends that the sHCC is less than 1cm and the LHCC above 1 cm. Though, the European Association for the Study of the Liver-European Organisation for Research and Treatment of Cancer (EASL-EORTC) divides the HCC size into three groups; less than 1 cm, 1-2 cm, and more than 2 cm<sup>[3]</sup>.

However, some of LHCC have variable macroscopic features. In this stage, the tumour capsule (inner layer contains pure fibrous tissue that finds at advanced HCC, while outer layer containing portal venules or sinusoids)<sup>[11]</sup> or a pseudo-capsule can be seen at LHCC more than 5cm. Thus, the HCC and RNs would be differentiated from each other<sup>[43]</sup>. In addition to that, the MVI is distinctive features for HCC and can be predicted it by using the contrast agent with specific features such as irregular tumour margins with large size, the presence of peritumor enhancement, and peritumor hypointensity in both hepatobiliary phase (HBP) and DWI. The Gd-EOB-DTPA dynamic enhanced MRI predicts the MVI presence with high specificity and low sensitivity<sup>[25]</sup>.

## MRI CONTRAST AGENTS

The contrast media that used in MRI is classified into three types based on bio-distribution: extracellular fluid agents (ECFAs) including extracellular Gadolinium-based contrast agents (GBCAs) or extracellular contrast media-enhancement (ECCM), blood pool agents (BPCAs), and organ-specific contrast agents, such as SPIO and Gadolinium-based hepatobiliary contrast agents (GBHCAs) including Gd-BOPTA and Gd-EOB-DTPA. The extracellular GBCAs consists of gadolinium chelated to an organic compound such as DTPA and makes shortening of T1 time. It also gives a vascular tissue differentiation characterization, and hence the signal intensity would be increased<sup>[44]</sup>, while SPIO and GBHCAs are specific contrast media used for early HCC detection.

SPIO particles travel into the reticuloendothelial system by Kupffer cells, and it travels through the hepatobiliary system by excretion the bile duct in hepatocytes. The GBHCAs specific to the hepatocytes was due to used Gadobenate dimeglumine (gadoxetic acid) which is specific to liver cells. Despite that, the SPIO and mangafodipir trisodium agents are suitable contrast enhancements for early HCC in MRI, some of HCCs containing Kupffer cells similar in normal hepatocytes. Thus, the difference between the HCC and the normal tissues would be difficult to identify by using



this contrast media. Some of RNs appears hypointensity in T1W, T2W, and DWI images due to the increase of iron deposition (siderotic regenerative nodules), and that related to the increase of the magnetic field inhomogeneities. Also, these nodules do not consider as premalignant nodules.

The gadoxetic acid has a unique feature in hepatic cells and can be given as a bolus and dynamic imaging. After intravenous bolus injection, just 50% of the injection dose is absorbed by hepatocytes and excretion by bile ducts through the multidrug resistance protein 2 (MRP2)<sup>[36]</sup>, while the second 50% excreted by the kidneys<sup>[45]</sup>. Thus, the contrast of a tumour to the liver in a transitional phase (TP, 3-min delay) would be derived from both true washouts of contrast agent and enhancement of hepatic parenchyma<sup>[46]</sup>.

The sensitivity of gadoxetic acid higher than ECCM enhanced CT or MRI for detecting the sHCC due to gadoxetic acid provides information on both vascular phase as well as HBP. However, the gadoxetic acid shows as a hypointensity in both HBP and TP, this would make miss-diagnosis with cirrhotic nodules on their enhancement pattern<sup>[46]</sup>. Also, the GBCAs have an essential limitation represents that it cannot differentiate between the benign and malignant lesions in the small size (mainly less than 2 cm)<sup>[3]</sup>.

The Gadolinium ethoxybenzyl magnetic resonance imaging (Gd-EOB-DTPA) is a new liver-specific MRI contrast media. It is a water-soluble contrast agent which combines with a nitrobenzyl group, and latter attached to gadolinium diethylenetriamine pentaacetic acid. It is used to detect a hepatic tumour and focal liver lesions by distributing this material in the vascular and extracellular spaces and provides a distinctive parenchymal enhancement through the late-phase images, and also it gives information on hepatocyte function<sup>[25]</sup>. This contrast agent is helpful to detect the early HCC due to the precancerous lesions fill with EOB. Thus, the signal will be dropping. The differentiate between a malignant tumour and lesions depends on the uptake and excretion of the contrast media through a combination between HBP and dynamic MRI<sup>[47]</sup>. Nowadays, the Gd-EOB-DTPA is considered as the first and the accurate choice for hepatic lesions detection especially the early HCC, and has been widely used in the evaluation of preoperative settings, and this is because the sensitivity of this material is higher than the sensitivity of other contrast agents<sup>[48]</sup>.

The suitable dose of Gd-EOB-DTPA is 0.025 mmol/kg, and this amount is considered the lower effective amount of dose to detect the liver lesions. After injecting an adequate amount of Gd-EOB-DTPA, it follows by 20 mL of normal saline 'saline flush' and the injection rate between 1 to 2 mL/s. The Gd-EOB-DTPA enhancement rate reaches the highest point after 20 min from the injection and stays at the liver for several hours. Thus, the image can take after 20 min<sup>[49]</sup>.

The dose standard for GBCAs contrast agent in the MRI is 0.1 mmol/kg which injects by intravenous at the rate 2 mL/sec and then followed with normal flush saline of 30-40 mL<sup>[50]</sup>. After injection, the GBCAs are rapidly spread into the extracellular space by the capillaries. The renal excretions considered as the primary pathway to eliminate this contrast agent.

Another contrast agent used in MRI is gadobenate dimeglumine (Gd-BOPTA/Dimeg, MultiHance®, Bracco, Milan, Italy), it is considered as paramagnetic gadolinium ions combined with two meglumine molecules. The standard hepatic imaging dose of Gd-BOPTA is 0.05 mmol/kg (0.1 mL/kg of a 0.5 mol/L solution), this contrast agent should inject with undiluted solution then followed by normal saline of 30-40 mL, and also the suitable time to take the image after 45 min from injection time<sup>[51]</sup>. However, the Gd-

BOPTA enhancement rate reaches the highest point after 1-3 hours after injection, and just 5% of this drug transport to hepatocytes and excretion by the biliary system<sup>[18]</sup>.

In summary, the HCAs has many advantages which help to improve the diagnostic value of HCC such as high sensitivity of detection for small lesions less than 2 cm, enhancement improved for the arterial lesions, and detection the lesions which have less enhancement of contrast agent especially in the HBP<sup>[52]</sup>.

## MRI ILLUSTRATIONS AND FINDINGS EARLY

### 1. Current Diagnostic Standards of HCC According to Existing Guidelines and Ancillary Features

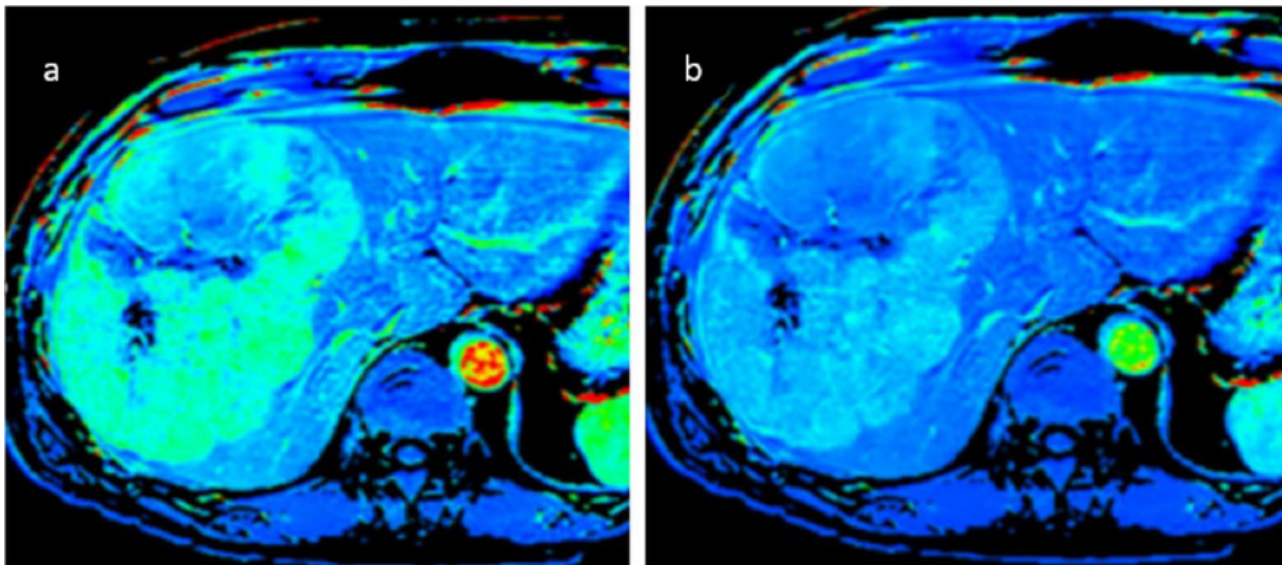
The MRI used many sequences for detection the liver lesions such as standard morphological sequences and functional imaging tools like DWI, perfusion imaging, T2-weighted sequences, multiphasic contrast agent (HAP, PVP, TP, and DP), MR-elastography, and radionics analysis<sup>[32,48]</sup>. Moreover, the delay time uses in the four phases is fixed to standardize liver imaging. Thus, the different enhancement patterns in the lesions would be determined the different diseases<sup>[5]</sup>.

The typical dynamic enhancement pattern of HCC or the significant features are hypervascularity at the HAP and washout on a PVP and DP, and capsule appearance<sup>[46]</sup>. Though, the ancillary features represent liver detection of the imaging stages (except the LR-4 to LR-5). It undergoes to the Liver Imaging Reporting and Data System (LI-RADS) by using the contrast agents such as gadoxetic acid. These features include many patterns such as the hyperenhancement at the arterial phase and hypointensity in the HBP, smooth hypointense rim surrounds the lesion as a capsule appearance in the HBP imaging, Mild to moderate T2 hyperintensity, and washout ratio in the PVP and TP imaging<sup>[54]</sup>.

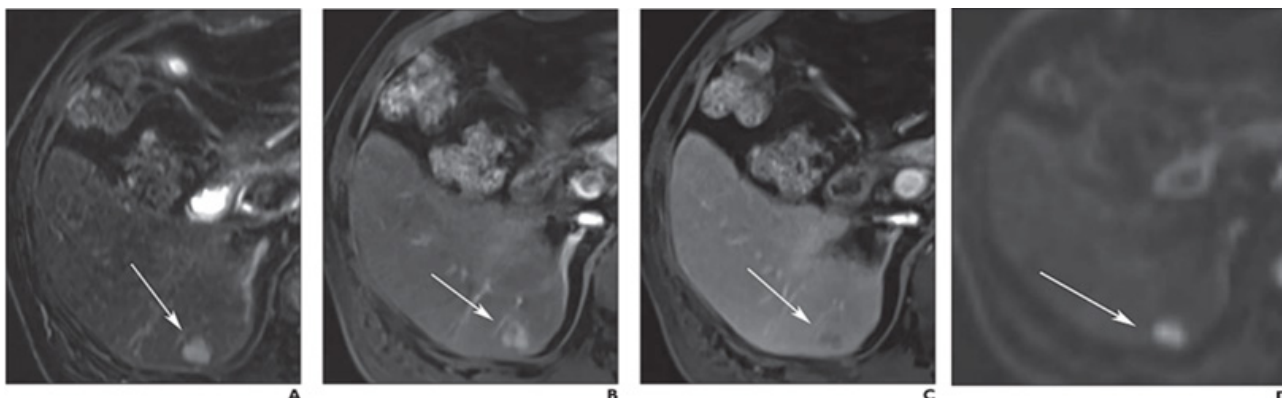
In the arterial phase, the reason for hyper-enhancement increased in this phase was due to the increase in the arterial supplies for the intranodular. While the washout appearance in the PVP and DP depends on different factors such as the new drainage in the veins, the liver background enhancement, the amount of blood supply in the portal vein, the hyper-cellularity rate of a tumour, and the fundamental components of the cancer tissue. Indeed, the hemodynamic changing in the intranodular through the development of carcinogenesis starts with decreasing the arterial supplies with a presence portal perfusion, after that the decreases on both arterial supplies and portal blood supplies would occur. And, subsequently the increase of arterial vascularity is developed, and the hypervascular pattern would appear<sup>[35]</sup>. Figure 3 shows the typical features for HCC.

Also, in the arterial phase, the most HCC exhibits global or diffuse hyperenhancement, and it would be homogeneous or heterogeneous enhance. However, in this phase, some of HCCs exhibits as at different enhancement pattern such as irregular margin enhancement with central hypoenhancing areas, and this pattern is not a typical imaging feature of HCC<sup>[55]</sup>.

In the early stage of HCC which depends on many factors like hemorrhage; the level of necrosis; the degree of fibrosis; fatty changes; and histologic pattern. Hence, the early HCC would be a different appearance on MRI. The HCC T1W images may vary in appearance; they include hypointense, isointense, or hyperintense comparing with normal liver parenchyma, while the T2W images usually appear as hyperintense. The contrast enhancement provides a more accurate result for differentiated diseases, especially in the early HCC.



**Figure 2** HCC on the perfusion images derived from semi-quantitative analysis; (relative arterial enhancement and maximum enhancement) the HCC is characterized by high vascularity intensity signals, shown as hot-spots signals.



**Figure 3** Typical enhancement patterns of HCC; A: hyperintensity On T2-weighted image, B: arterial enhancement (arrow) On arterial phase image, C: tumour shows washout On portal venous phase image, D: diffusion restriction On DW image[3].

Moreover, the differentiated diagnosis between early HCC and both of cirrhotic nodules, and low-grade HCC are easy in MRI through the intensities of T1W and T2W images. At the early HCC, the T2W images appear bright (hyperintensity), and the siderotic regenerative nodule (siderotic dysplastic nodule) would be dark (hypointense) at T1W and T2W images, while the LGHCC would be shown as hyperintensity at T1W and hypointense or isointense in T2W images<sup>[56]</sup> various cirrhosis-related nodules are frequently detected in patients with chronic liver disease, while diverse hypervascular hepatic lesions are incidentally detected but undiagnosed on dynamic computed tomography and magnetic resonance imaging (MRI). However, some HCC may manifest as a hyperintensity in T1W due to the present of some components inside tumours such as copper, fat, proteins, haemorrhages, and glycogen<sup>[32]</sup>.

On the other hand, after contrast agent was injected, the nodules in early HCC appear without arterial enhancement and washout the PVP/ DP. It also appear as a hypointensity in the hepatobiliary phase (HBP) and restriction (hyperintensity) on DWI<sup>[57]</sup>. In the other hand, the HGDN will appear without arterial enhancement, without washout in the PVP/DP, without hyperintensity on DWI but hypointense in the HB phase<sup>[57]</sup>. In addition to that, the fibrous capsule found in the progressed HCC shows in the T1W image as a hypointensity thin rim, and it shows as a hypointense or hyperintense rim on T2-weighted images. Also, it appears as rim

enhancement in both PVP or DP and that because of the retention of the extracellular contrast agent inside the fibrous tissue or peritumoral sinusoids. Figure 4 shows this features of the fibrous capsule in HCC. Moreover, in the HBP, the hyperintensities of liver parenchyma may becloud the enhancement of fibrous capsular through DP or TP. However, some of HCC with pseudocapsule may show as a hypointense rim in both T1W and T2W imaging.

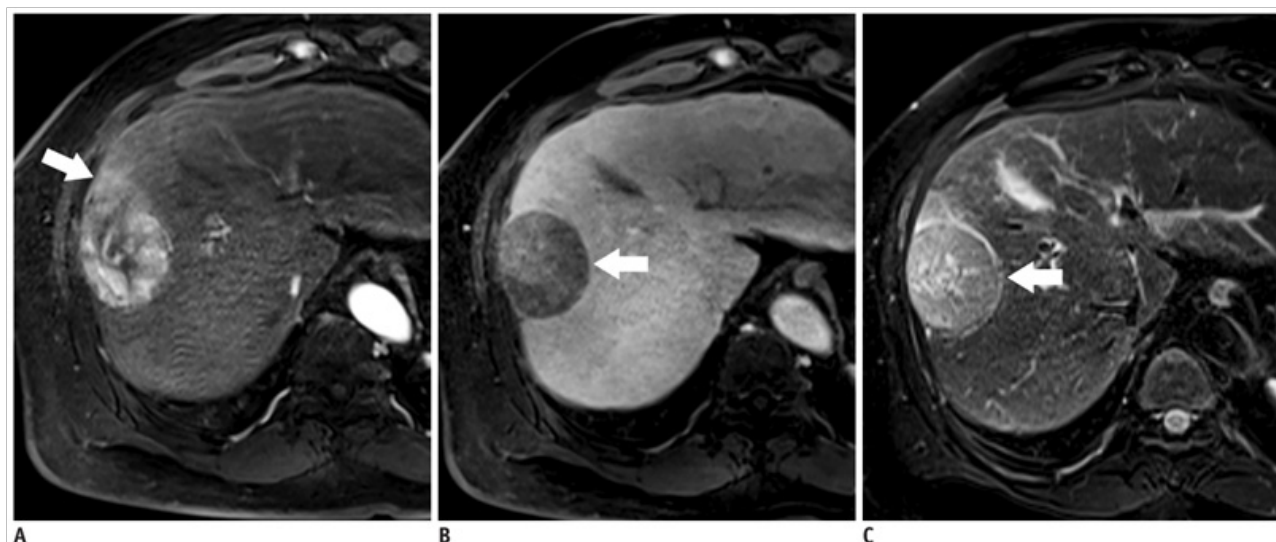
According to the perfusion imaging which offers qualitative information on the vascular profile (tissue Vascularization) while the diffusion imaging is providing qualitative information on the cellular profile (Cellularity). Figure 5 shows the schematic comparison between DWI and perfusion maps.

In summary, the following Table provides the overview of the HCC patterns at the different MRI sequences.

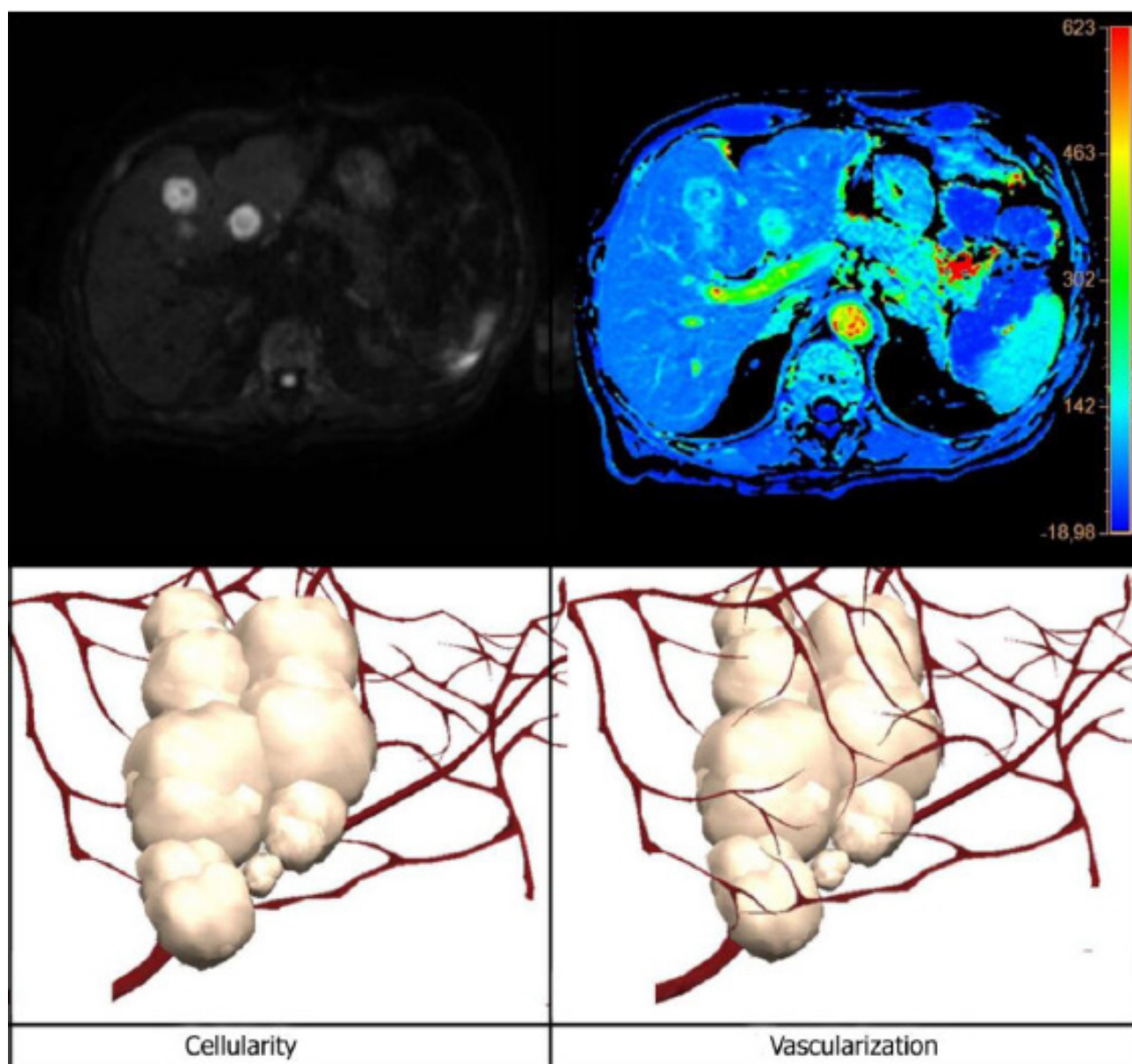
## 2. MR Spectroscopy

Mass Spectrometry or Nuclear Magnetic Resonance spectroscopy (MRS) is a non-invasive technique; it used to detect the metabolomics concentration in tissues which are widely used to give additional information for carcinogenesis mechanisms<sup>[58,59]</sup>; it uses the magnetic properties of definite atomic nuclei including proton (<sup>1</sup>H), carbon-13 (<sup>13</sup>C) for image perfusion and metabolism<sup>[13]</sup>, and phosphorus-31 (<sup>31</sup>P). In the <sup>1</sup>H-NMR spectroscopy, the HCC tissues is exhibited by a high level of lactate (Lac) with signals at





**Figure 4** Patient with fibrous encapsulated progressed HCC; A:T1W shows hyperintensity mass with hyperemia of surrounding liver parenchyma; B: Mass is hypointense on transitional phase with thin capsule appearance; C: T2-weighted image shows slight hyperintensity and hypointense capsule [11].



**Figure 5** Schematic comparison between diffusion weighted images (on the left) and perfusion maps (on the right).

Lesion	Sequences						
	Unenhanced T1	Arterial	Portal venous	Delayed	Hepatobiliary	DWI	T2
GBCAs	HCC classic						
	HCC green						
	HCC hypovascular						
GBHCAs	HCC classic						
	HCC green						
	HCC hypovascular						

Isointense lesion   
 Hyperintense lesion   
 Hypointense lesion   
 Slightly hyperintense lesion

**Table 1** Schematic representation showing dynamic contrast enhanced sequences, diffusion weighted images, and T2-weighted features in typical, green, and hypovascular hepatocellular carcinoma, comparing information from extracellular contrast agent and hepatobiliary contrast agent.

(1.30-1.35 ppm), phosphoethanolamine (PE), glutamine (Gln) with signal at (2.11-2.17 ppm; 2.45 ppm) with signals at (2.45 ppm), phosphocholine (PC), and low level of glucose (Glc) with signals at (4.61-4.67; 5.20-5.28 ppm) and monounsaturated fatty acids (MUFA). The glycolytic shift in the cancer tissues can be confirmed by increases the Lac level and decreases the Glc level through following the Warburg effect which has a high lactate production even in the presence of oxygen or at the low level of aerobic oxidation during the tricarboxylic acid (TCA) cycle<sup>[58]</sup>.

For the HCC patients who associated with cirrhosis liver disease increases the contribution (high levels) of aromatic amino acids [histidine (His) with signal at (7.07-7.09 ppm; 7.91 ppm), tyrosine (Tyr)with signal (at 3.94-3.95 ppm; 6.88-6.91 ppm; 7.17-7.18 ppm), and phenylalanine (Phe) with signal at (7.34-7.37 ppm; 7.40-7.44 ppm)], and  $\beta$ -hydroxybutyrate ( $\beta$ -HB) with signal at (1.18 ppm)].

In the HCC patients associated with Non-Alcoholic Fatty Liver Disease (NAFLD) involve the strong contribution of glutamine/ glutamate (Gln/Glu) due to immunohistochemically expression of Glutamine Synthetase (GS). When the HCC exhibits with high GS staining the Gln level is high (2.45 ppm), while lysine – which is found in beta-oxidation of fatty acids- with signal at (2.96 ppm) and Total Glutathione (GSX) with signal at (2.55 ppm) were found in HCC with a weak GS staining<sup>[59]</sup>.

In the liver cells, Gln is produced from Glu by glutamine synthetase (GS), and it is associated with ammonium detoxification. Also, it plays an essential role in biosynthesis and energy metabolism and nucleotides production through cell proliferation. The Oxidation of Gln is the main source of energy of the cell proliferation. The GS associated with Glypican 3 which is considered as one of the HCC biomarkers. Moreover, the overexpression of GS is associated with a mutation in  $\beta$ -catenin<sup>[59]</sup>.

Despite the advantages of MRI such as the high sensitivity and specificity to detect the pathologies of the HCC, cirrhotic nodules, and other. It has many disadvantages such as higher susceptibility

to artifacts, difficulty breath-holding, and less consistent image quality<sup>[53]</sup>.

In the GBHCAs, the nodules without organic anionic transporting polypeptide [OATP] ( proteins in hepatocytes found in sinusoidal membrane helps to absorb the contrast agent)<sup>[18]</sup>. This represents the HCC usually on the early stage; it will not take the contrast agents and would be appearing as hypo/is intensity at the HBP due to less level of prognostic serum tumour markers<sup>[37]</sup>. This is because the tumour cells lose organic anion transporting polypeptides (OATP1B1/B3) in cell membranes facing sinusoidal blood<sup>[60]</sup>. However, some of HCCs appear as a hyperintensity on HBP because of the uptake for hepatobiliary contrast media, and this would happen due to genomic alteration through hepatocarcinogenesis<sup>[61]</sup>, it is also independent on the histologic differentiation of a tumour.

In addition, the purpose of MRI I to detect the HCC and diagnostic aims. MRI can be used to evaluate the treatment outcome of some therapy procedures such as radiofrequency ablation (RFA)<sup>[7]</sup>, electroporation treatment<sup>[8]</sup>, and TACE<sup>[9,10]</sup>.

## CONCLUSION

Hepatic imaging MRI plays an essential role in the detection and assessment for the early HCC. The major advantages of MRI are providing the high contrast resolution for the tissue, the absence of ionizing radiation, and can apply for the functional imaging techniques. In this review article, the radiological and pathological findings associated with the HCC and had been described. And these findings provide the radiologist to understand more clearly how the histopathological findings and radiological features can identify the HCC. The early HCC detection provides a high chance of cure treatments for liver resection, liver transplant, and radiofrequency ablation. The combination of MRI and histopathological findings diagnosis the early HCCs. Also, the article provides information



to understand the difference in hepatocellular nodules through the multistep hepatocarcinogenesis. This could be used to distinguish between benign and malignant tumours. Given this scenario, this paper may help the radiologist suggest the diagnosis and detection for early HCC.

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