


# Heterogeneity of Hepatocellular Carcinoma on Imaging

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## Abstract

Tumor heterogeneity in hepatocellular carcinomas (HCC) occurs at different levels. On conventional imaging modalities, the spectrum of tumor heterogeneity is evident in the dynamic enhancement pattern, where the characteristic wash-in and wash-out is present in only 60% of small HCCs. In larger HCCs, heterogeneity within the tumor, known as the mosaic pattern, can reflect the presence of different grades of HCC differentiation. The advent of functional imaging techniques has not improved the diagnostic sensitivity of imaging techniques for the diagnosis of HCC. However, the combination of conventional and functional imaging techniques potentially allows the identification of heterogeneity in tumor vascularity, cellularity, and molecular expression.

## Keywords

- ▶ hepatocellular carcinoma
- ▶ liver
- ▶ magnetic resonance imaging
- ▶ contrast media
- ▶ heterogeneity

The noninvasive diagnosis of hepatocellular carcinoma (HCC) represents a major challenge for radiologists. In cirrhotic livers, a new focal lesion has a high pre-test probability of being an HCC.<sup>1–3</sup>

Magnetic resonance imaging (MRI) has a key role in detecting and characterizing HCCs in cirrhotic livers.<sup>4,5</sup> MRI has superior tissue resolution compared with computed tomography (CT). Different meta-analysis and systemic reviews comparing the diagnostic performance of contrast-enhanced CT in comparison to contrast-enhanced MRI found that multiphasic MRI is more sensitive than CT, while both modalities have similar specificity.<sup>6,7</sup> MRI contrast agents improve detection by increasing the contrast between the lesion and the background,<sup>4,6</sup> and different types of contrast agents can improve characterization by showing changes in hepatocyte uptake; biliary excretion; or vascular, extracellular, or intracellular volumes.<sup>6,8</sup> This information can be complemented by information obtained from other sequences such as restriction on DWI, high signal on T2-weighted images, and presence of intralesional fat. Nevertheless, despite considerable recent advances in MRI, the final diagnosis of new focal lesions often relies on histopathology.<sup>4</sup>

Biopsies are required for diagnosis or staging when imaging techniques cannot characterize new liver lesions in cirrhotic patients. Histopathology is still needed for two main reasons: first, HCC is heterogeneous on imaging, with

different lesions within the same patient and even the same tumor having different appearances. Second, HCC is the end-stage of a continuous multistep process,<sup>9</sup> and the MRI findings for pre-malignant lesions and early HCC are not specific and overlap.<sup>10</sup> Hence, the main question is whether a given nodule is a large regenerative nodule, a dysplastic nodule, or an HCC. The aim is to avoid overdiagnosis and consequent overtreatment while avoiding underdiagnosis and consequent undertreatment.

## Heterogeneity Using Conventional Imaging Criteria

Hepatocarcinogenesis is a multistep process during which nodules undergo parallel, simultaneous, and progressive changes, including increased cell density, decreased cell differentiation, enlargement of nodules, and changes in nodule hemodynamics.<sup>9</sup> The MRI characterization of focal lesions in cirrhotic livers is a complex process based on analyzing the lesion's signal intensity on different imaging sequences. In dynamic contrast-enhanced MRI, the signal intensity during the arterial, portal venous, and delayed venous phases reflects differences in the distribution of contrast material between the vascular and extravascular spaces in tumors and liver parenchyma; the noninvasive diagnostic criteria for HCC are based on these characteristics.<sup>4,5,11</sup>

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In the initial phase of hepatocarcinogenesis, normal arterial supply decreases but portal venous supply is still present.<sup>10,12,13</sup> In a more advanced stage, intranodular arterial vascularity increases due to the appearance of unpaired feeding arteries while venous portal blood supply progressively decreases. These phenomena result in the typical and specific enhancement pattern of HCC on MRI using nonspecific gadolinium contrast: arterial hypervascularity and hypointensity or “washout” during the portal venous and/or late dynamic phase. These features represent the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) noninvasive diagnostic criteria for HCC larger than 1 cm. Although this pattern is highly specific, it has limited sensitivity, being found in only ~60% of HCC smaller than 2 cm,<sup>1-3,14,15</sup> because early small HCC in which neoangiogenesis is yet to progress is often hypovascular. The difficulties in differentiating the different stages of HCC progression by imaging, particularly in differentiating low-grade dysplastic nodules from regenerative nodules and high-grade dysplastic nodules from early HCC, probably derive from the fact that the different classifications simply represent parts of a continuum rather than distinct categories (→ Fig. 1).<sup>9</sup>

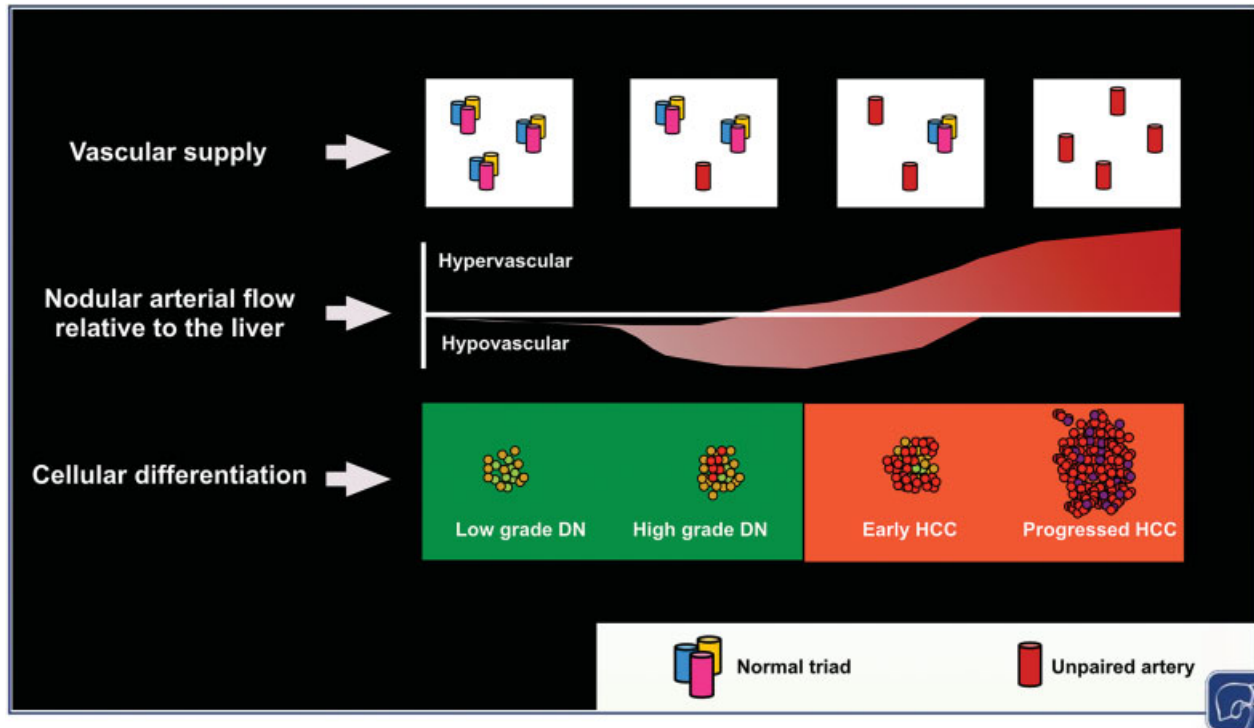
Another source of heterogeneity in the appearance of small HCCs is the presence of fat, also known as fatty metamorphosis. Whereas fat is often present in small, well-differentiated HCCs, small moderately-to-poorly differentiated HCCs rarely contain

fat.<sup>2</sup> Moreover, fatty metamorphosis can also be found in dysplastic nodules and benign entities. Vascular changes sometimes appear in small areas inside a dysplastic nodule or an early HCC, conferring the classical appearance of a nodule within a nodule.

As HCCs grow larger, the heterogeneity of their appearance decreases as the typical vascular pattern develops; this pattern can be identified in more than 70% of HCC between 2 and 3 cm in diameter.<sup>6,7,16</sup> At the same time, heterogeneity within lesions increases as different foci of HCC differentiation coexist, conferring a mosaic pattern resulting from areas with different degrees of vascularization, fatty metamorphosis, and/or hemorrhage.<sup>17</sup>

In 7 to 13% of cases, HCC presents as the diffuse or infiltrative HCC subtype,<sup>18</sup> which is often accompanied by portal vein thrombosis, resulting in vascular phenomena and abnormal patterns of enhancement. Infiltrative HCC is easily missed on T1-weighted images and on arterial phase images, where they usually show no enhancement or slight heterogeneous enhancement within the tumor and the large heterogeneous tumor with ill-defined margins blends into the heterogeneous cirrhotic liver.<sup>19</sup>

Another source of heterogeneity by imaging are the primary liver carcinomas with both hepatocyte and cholangiocyte differentiation, referred to as “combined (or mixed) hepatocellular-cholangiocarcinoma.” Recently, these tumors have increased their attention because of greater frequency and clinical recognition.<sup>20</sup> There are few publications that



**Fig. 1** Phenotypic changes along the continuous process of hepatocarcinogenesis that cause heterogeneity at imaging are marked by the following phases at the histologic level: (1) low- and high-grade dysplastic nodules, which on magnetic resonance imaging (MRI) usually appear iso- or hypovascularized (although a few are hypervascular) compared with liver parenchyma, which histology shows have individual arteries and portal perfusion; (2) early hepatocellular carcinoma (HCC) with residual portal perfusion, which on MRI ranges from iso- or hypo-vascular to hypervascular, which histology shows are well differentiated, vaguely nodular, and contain individual arteries; and (3) progressed HCC, with characteristic imaging features of hypervascularity in the arterial phase and hypovascularity in the venous phase, which histology shows are moderately differentiated, distinctly nodular, with or without vascular invasion, having individual arteries but no portal tracts.

report the radiological appearances of mixed hepatocellular-cholangiocarcinoma. Most series reported imaging features that commonly overlap with those of intrahepatic cholangiocarcinoma and less frequently with those of classic HCC displaying predominantly arterial hyperenhancement and followed by diffuse or patchy washout.<sup>20</sup> Imaging techniques may be useful to guide biopsy on the target HCC-like or cholangiocarcinoma-like areas.

### Heterogeneity on Functional Imaging Techniques

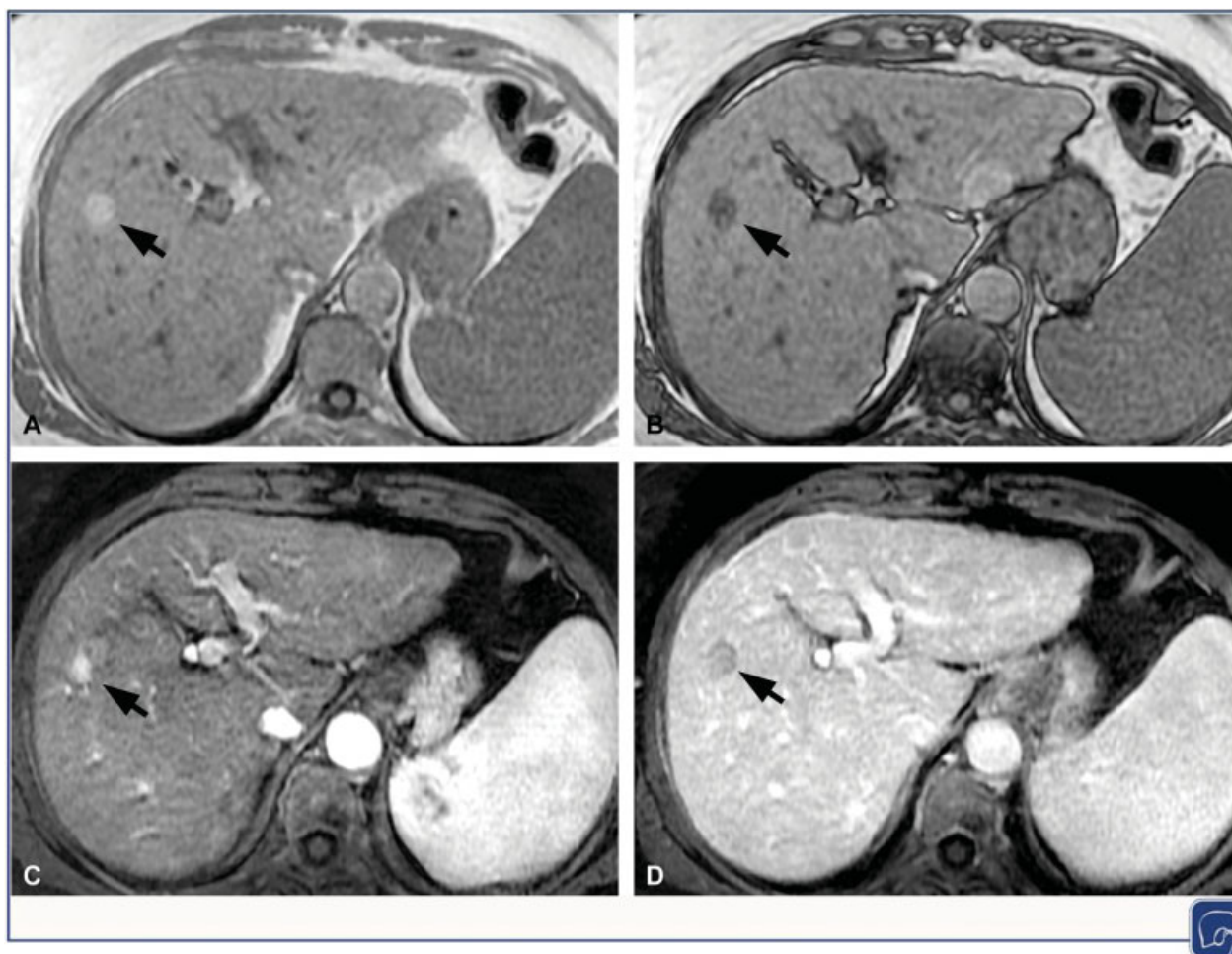
#### Diffusion-Weighted Imaging

Diffusion-weighted imaging (DWI) is a functional MRI sequence that allows the characterization of biological tissues based on the diffusion properties of water molecules. This sequence provides indirect information about cell density and about the integrity of cell membranes in the area of interest. In clinical practice, the concept of “diffusion restriction” refers to a focal liver lesion showing signal intensity higher than the surrounding liver parenchyma on DWI.<sup>21</sup>

Diffusion-weighted imaging now forms part of most routine liver MRI protocols in daily practice because it has a short

acquisition time, does not require intravenous contrast agents, and is more sensitive for detecting focal liver lesions than T2-weighted sequences.<sup>22</sup> Although HCCs typically appear hyperintense at DWI, this finding is not specific for HCC; thus, DWI should be integrated in MRI protocols together with dynamic sequences, rather than used alone (–Fig. 2).<sup>23–25</sup> DWI’s sensitivity for detecting HCC in cirrhotic livers varies widely depending on the size of the tumor and DWI specifications, ranging from 32 to 70% in HCC smaller than 2 cm<sup>22–24,26–28</sup> to more than 90% in larger lesions.<sup>29,30</sup>

The heterogeneity in the visibility and signal intensity of HCC at DWI is the product of complex interactions between various biological factors and MRI characteristics. As the process of hepatocarcinogenesis and tumor differentiation occur in a continuum, the heterogeneity of HCCs also results in overlapping diffusivity characteristics that directly affect DWI’s ability to detect these lesions. Nasu et al<sup>30</sup> reported that the DWI signal intensity of HCC generally increased with increasing histologic grade (i.e., decreasing differentiation), although with large overlaps. Analyzing a series of 98 lesions in 73 patients, Muhi et al<sup>28</sup> found that more than 90% of moderately-to-poorly differentiated HCCs were



**Fig. 2** A 1.2 cm hepatocellular carcinoma located in segment VIII seen on T1 pre-contrast in (A) and opposite phase (B), arterial phase (C), and portal venous phase (D) magnetic resonance imaging. On pre-contrast T1-weighted images, the nodule presented drop in signal on opposite phase relative to liver parenchyma (arrow in A and B) indicating presence of fat. On arterial-phase images, hyperenhancement is seen within the nodule (arrow in C). On portal-venous-phase images, the nodule is hypointense (washout) (arrow in D). This vascular pattern is specific for hepatocellular carcinoma.

hyperintense on DWI, but only 51% of well-differentiated HCCs and none of the dysplastic nodules were hyperintense. Moreover, the microarchitecture of the background cirrhotic parenchyma also influences the visibility of HCCs on DWI, increasing the complexity of interpreting the findings. Diffusivity is also restricted in cirrhotic parenchyma, probably due to fibrosis, so the DWI signal ratio between HCC and cirrhotic parenchyma is reduced.<sup>31</sup> This may explain why the DWI detection rate for HCC decreases with increasing severity of cirrhosis.<sup>30</sup>

Although qualitative visual assessment of DWI is of limited usefulness in characterizing nodules in cirrhotic liver, quantitative approaches such as apparent diffusion coefficients (ADC) and the more recent intravoxel incoherent motion (IVIM) can assess nodules independent of cirrhotic liver background, displaying the findings in parametric maps. IVIM is more reliable; unlike ADC, which ignores the effect of the perfusion fraction in tissue, IVIM treats DWI signal attenuation as a mixture of tissue perfusion and tissue diffusivity effects.<sup>32</sup> In a recent study, Zhu et al<sup>32</sup> found a negative correlation ( $r = -0.62, p < 0.001$ ) between IVIM quantification and the histological grade of HCCs. In a similar study, Wei et al<sup>33</sup> found that the correlation was even better when IVIM was measured in the whole HCC volume ( $r = -0.90, p < 0.001$ ) rather than in a single section ( $r = -0.84, p < 0.001$ ).

#### Heterogeneity on Liver-Specific Contrast Agents

Liver-specific (also called hepatobiliary) contrast agents include gadobenate dimeglumine (Gd-BOPTA) and gadoxetic acid (Gd-EOB-DTPA); the latter is by far the most commonly used liver-specific contrast agent in clinical practice and research. Gadoxetic acid's dual behavior is especially useful in liver imaging. After intravenous injection, it first distributes into the intravascular and extravascular spaces during the arterial, portal, and late venous phases; afterward, during the so-called hepatobiliary phase, it progressively distributes into the hepatocytes and bile ducts.

Gadoxetic acid is eliminated through both renal and hepatic excretion pathways in a proportion of around 50% each in healthy subjects. The uptake of gadoxetic acid by hepatocytes mainly occurs via the active transporter organic anion transporting polypeptides (OATP) 1B1 and OATPB3 located at the sinusoidal pole of the hepatocytes, and the biliary excretion occurs via multidrug resistance protein (MRP) 2 proteins located in the canalicular membrane.<sup>34</sup> The expression of OATP transporters diminishes during hepatocarcinogenesis<sup>35,36</sup>; consequently, most HCCs appear hypointense during the hepatobiliary phase because the expression of OATP is decreased or absent (► **Fig. 3**). The uptake pattern of gadoxetic acid by HCC in the hepatobiliary phase can be explained by the expression of OATP and MRP2. When OATP expression is maintained, the intensity of HCC on hepatobiliary-phase images depends on the expression of MRP2 in the canalicular membrane. In most HCCs, MRP2 is present, and the gadoxetic acid is eliminated to the bile ducts, making these HCCs hypointense on MRI<sup>36</sup> (► **Fig. 4**).

OATP expression decreases prior to complete neoangiogenesis and the presence of unpaired hepatic arteries. Consequently, nodules that are hypointense in the hepatobiliary phase but do not have the features of HCC in earlier postcontrast phases due to a lack of unpaired arteries are common and may represent high-grade dysplastic nodules or early HCCs.<sup>37,38</sup>

On the other hand, around 10% of HCCs are hyperintense in the hepatobiliary phase. This contrast uptake is most commonly associated with well-differentiated HCCs and with either pseudoglandular architecture (classically known as green HCCs) or low expression of MRP2 transporters.<sup>39,40</sup>

Although it has been postulated that hepatobiliary-phase hypointensity generally increases with increasing HCC grade,<sup>41</sup> the reality is more complex, because both tumor and liver characteristics can affect gadoxetic acid uptake and the relative signal intensity of HCC.<sup>42</sup>

Patients with significant liver dysfunction due to the cirrhosis may have decreased parenchymal uptake of gadoxetic acid, reducing the signal contrast between HCC and the surrounding liver; this phenomenon is particularly problematic for the characterization of small tumors. Recently, other biochemical and clinical factors such as prothrombin activity, total bilirubin, and cholesterol levels have been correlated to the quality of liver enhancement in the hepatobiliary phase, suggesting that better enhancement may be obtained in patients with HBV than in those with HCV.<sup>43,44</sup>

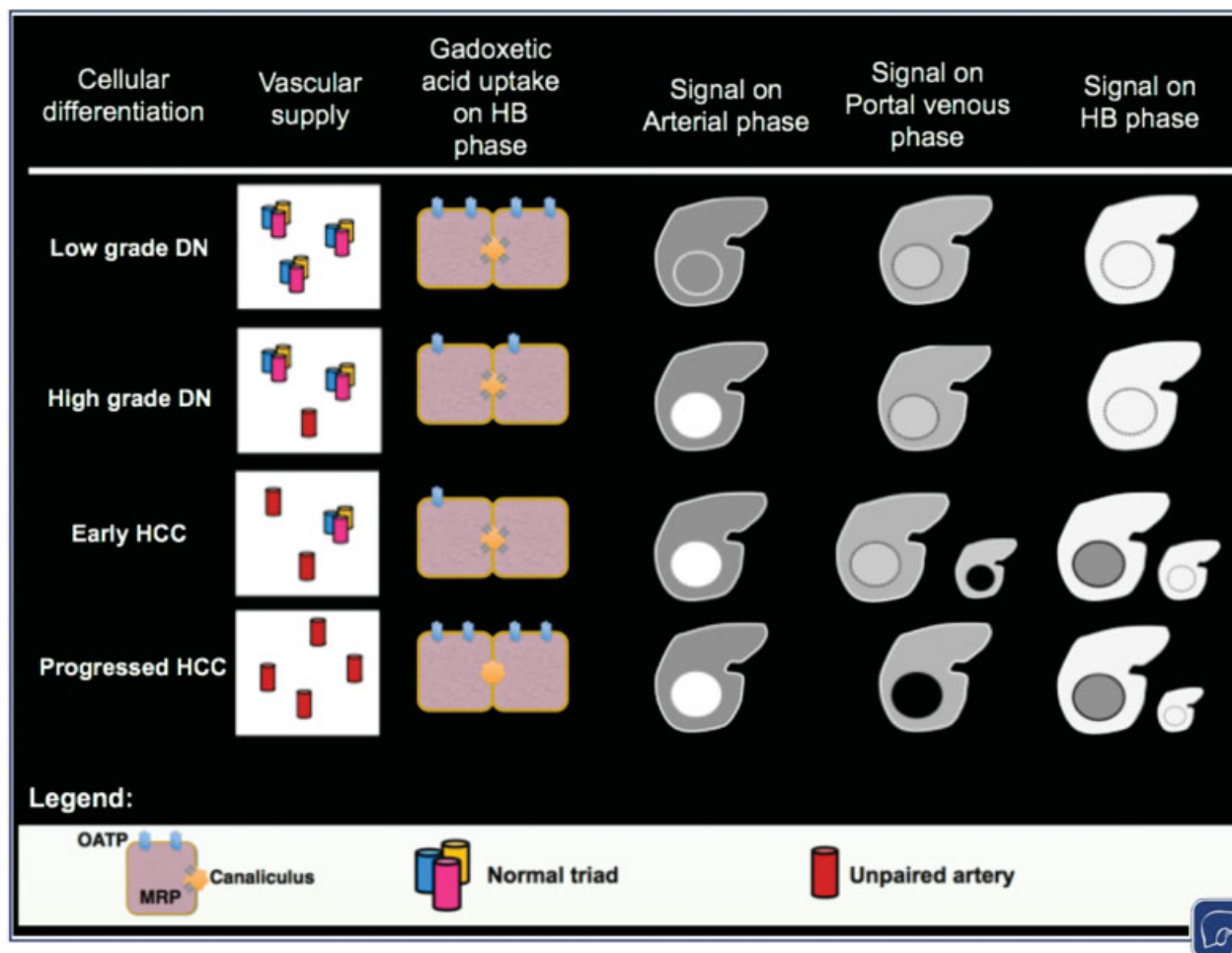
#### Heterogeneity on Liver Perfusion

Perfusion imaging of the liver with dynamic contrast-enhanced MRI characterizes and quantifies functional microenvironmental changes in small vessels that are beyond the resolution of morphological imaging for direct visualization. Dynamic contrast-enhanced perfusion MRI is based on temporal changes in tissue enhancement after intravenous administration of contrast media<sup>45</sup> and reflects pathophysiological changes in the microcirculation. Some groups have reported that dynamic contrast-enhanced MRI can quantify perfusion in HCC and surrounding cirrhotic liver, finding increased arterial perfusion and decreased portal venous flow in HCC compared with cirrhotic liver.<sup>46,47</sup> However, in large HCCs, intratumoral heterogeneity, in particular in histological grade and microvessel density, often hinders characterization by dynamic contrast-enhanced MRI and makes it difficult to correlate the quantitative findings with the histological grade.<sup>48</sup>

#### Heterogeneity in Radiological Response and Tumor Progression

Antiangiogenic drugs are recommended as the first treatment option in cirrhotic patients with advanced HCC. The radiological response to systemic treatment of HCC is usually measured by Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 criteria.<sup>49</sup>

After treatment with antiangiogenic drugs, enhancement decreases either diffusely or in part of the tumor in some HCCs, but remains stable in others. As initially reported in the SHARP trial, the reduction in tumor burden measured by conventional RECIST 1.1 does not parallel the benefit of antiangiogenic drugs. Thus, a panel of experts developed a set of guidelines

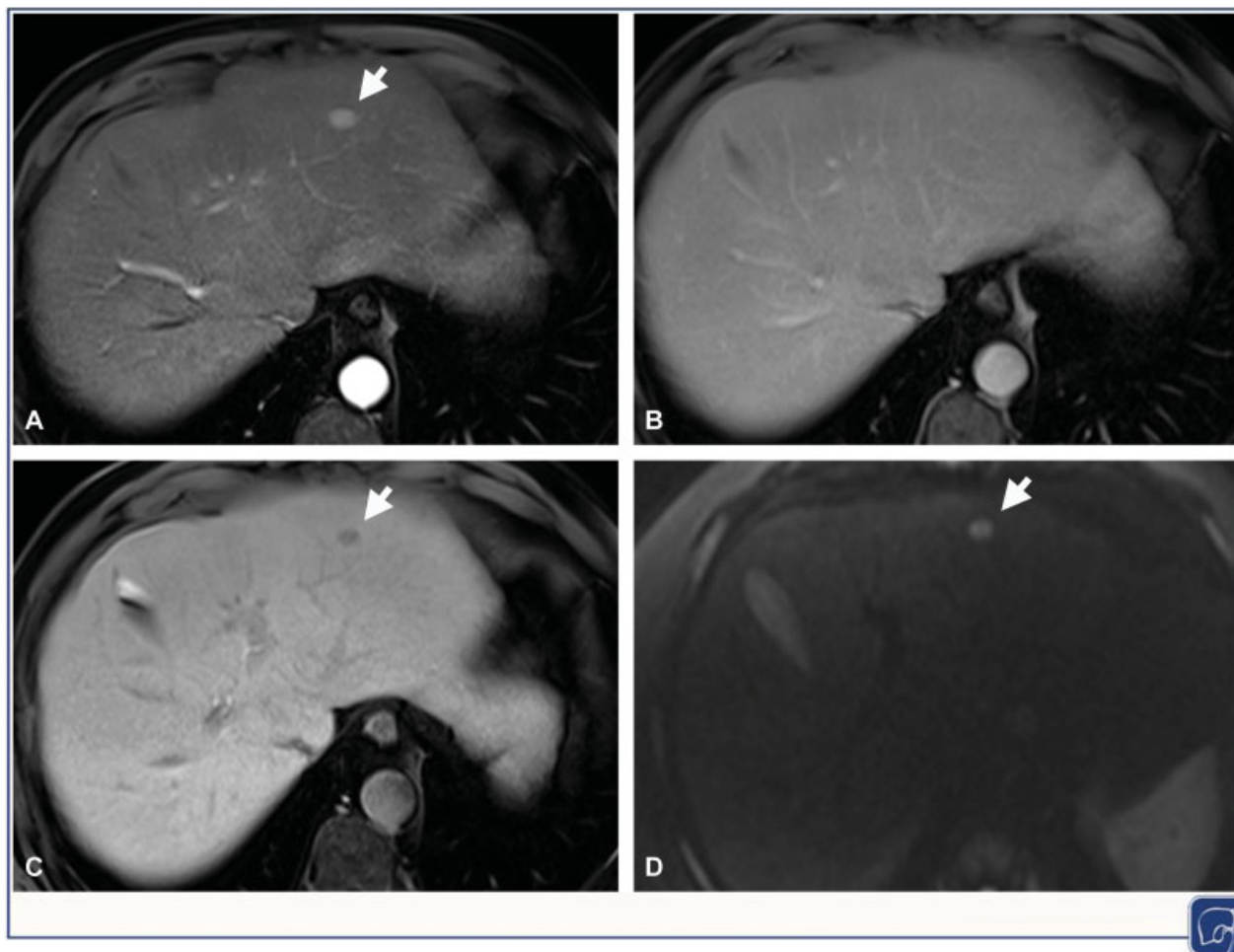


**Fig. 3** Correlation between the continuous process of hepatocarcinogenesis and the level of heterogeneity at imaging obtained by liver-specific contrast agents: (1) low- and high-grade dysplastic nodules still have large number of organic anion transporting polypeptides (OATP) and multidrug resistance protein (MRP) transporters that regulate the uptake and excretion of gadoxetic acid, so these nodules usually appear isointense relative to liver parenchyma on hepatobiliary-phase images, although some high-grade dysplastic nodules may appear hypointense. In early and progressed hepatocellular carcinomas, OATP expression is often decreased or absent, resulting in decreased uptake, and MRP expression is often increased, resulting in increased excretion. Thus, most hepatocellular carcinomas appear hypointense during the hepatobiliary phase. However, around 10% of HCC have increased expression of OATP and decreased expression of MRP, or a pseudogland configuration, both of which result in hepatocellular carcinoma appearing hyperintense on hepatobiliary phase images.

including alternative criteria that take antiangiogenic drugs' mechanism of action into consideration, the modified RECIST for HCC (mRECIST),<sup>50</sup> thus potentially capturing the heterogeneity on HCC in the response to antiangiogenic drugs beyond mere changes in size. In the BRISK trial, a randomized phase III trial comparing brivanib versus placebo in advanced HCC, Lencioni et al<sup>51</sup> analyzed the objective response by mRECIST as a predictor of overall survival in a time-dependent covariate analysis and found a strong association between log hazard ratios for overall survival and log odds ratios for objective response ratio ( $r = -0.80$ ; 95% confidence interval:  $-1-0.23$ ,  $p = 0.091$ ). Note that the 95% confidence interval included 0, indicating that the results are not robust enough to assume that the objective response according to mRECIST predicts overall survival in advanced HCC or to consider it a surrogate end-point.

Other authors have compared the rate of objective response using RECIST 1.1 versus mRECIST. Ronot et al<sup>52</sup> reported that of a total of 64 patients with HCC treated by sorafenib, only 2 (3%)

had an objective response according to RECIST 1.1, whereas 18 (28%) had an objective response according to mRECIST. In a similar study, Gavanier et al<sup>53</sup> found that only 3% had an objective response to sorafenib according to RECIST 1.1, whereas 7% had an objective response to sorafenib according to mRECIST. However, neither study found significant differences in overall survival between patients with an objective response and those with stable disease using either criteria. Interestingly, in both studies the rate of disease progression was very similar using either RECIST 1.1 or mRECIST. The RECIST 1.1 definition of progression takes into account heterogeneity in different situations. Since the response to antiangiogenic treatment is associated with overall survival and helps identify patients who would potentially benefit from second-line therapy, defining the different patterns of response and their implications is important. The BCLC group defined four patterns of radiological progression: intrahepatic increase  $\geq 20\%$  increase in tumor size from the baseline measurement, extrahepatic increase  $\geq 20\%$  increase in tumor



**Fig. 4** Gadoxetic-acid liver magnetic resonance imaging (MRI) in a 67-year-old man with hepatitis C virus-related cirrhosis. Liver MRI in the arterial phase shows a 11 mm hypervascular nodule in segment II of the liver (arrow in A); there was no washout in the portal venous phase (B), and the lesion was hypointense in the hepatobiliary phase (arrow in C). Diffusion-weighted imaging (arrow in D) shows signal restriction. Histopathology after ultrasound-guided biopsy diagnosed well-differentiated hepatocellular carcinoma.

size from the baseline measurement, detection of new intrahepatic lesions, detection of new extrahepatic lesions, and/or vascular invasion. Each pattern is associated with different post-progression survival; intrahepatic growth is the pattern associated with the least aggressive progression, whereas new extrahepatic lesion and/or vascular invasion is associated with the most aggressive progression.<sup>54,55</sup> This heterogeneity might be explained by molecular factors or gene expression and it deserves further investigation.

Immune modulators are among the most important classes of new anticancer therapeutics. Although their role in systemic treatment for HCC is yet to be determined, various ongoing clinical trials are evaluating their efficacy. The novel mechanism of action of immune checkpoint inhibitors through immune and T cell activation can result in unusual patterns of response. Some patients treated with this approach showed morphological changes in lesions that would meet the criteria for disease progression based on traditional RECIST (either increase in size or appearance of new lesions), but later showed profound and durable responses. Dubbed pseudoprogression, the increase in the size of lesions after treatment with immune modulators is the result of an inflammatory-like reaction due

to an increase in the number of immune cells between tumor cells.<sup>56</sup>

Although pseudoprogression is relatively uncommon, it can be challenging to differentiate this transient phenomenon from true progression that would potentially require a change in the therapeutic approach. Thus, it is essential to know how patients are being treated and the mechanisms of action of these treatments to ensure accurate interpretation of morphological changes observed at MRI or CT and optimal decisions about further workup. In patients receiving immune-checkpoint inhibitors, HCC should be reassessed earlier than originally planned (but only between 4 and 8 weeks after the unconfirmed progression) to determine whether the findings represent real progression or an early tumor response.<sup>56,57</sup>

### Future Perspectives

The noninvasive diagnosis of liver nodules by CT and MRI is limited by the high level of heterogeneity in small HCCs, by the overlapping findings between HCCs and dysplastic nodules, and by atypical vascular patterns. Another potential limitation of the noninvasive diagnosis is the inherent

difficulties in detecting small nodules during ultrasound surveillance caused by cirrhotic liver background. A recent controversial point is whether the strategy of HCC surveillance should be done by US or by other contrast-enhanced imaging modalities. Surveillance by CT or MR is generally not recommended because of the radiation risks, the higher cost, and the increase in false positive signals due to nonspecific findings.<sup>4,5</sup>

In the last years, few studies have postulated to use MRI with liver-specific contrast agent for screening of HCC in patients with high risk. Authors found that MRI yielded a detection rate of 84.8%, significantly higher than the 27.3% rate detected by routine US.<sup>58</sup> The same group published another similar study detecting that screening of HCC using MRI is also cost-effective.<sup>59</sup> However, there are some aspects of these studies that are at least controversial and may limit the generalization of reported data including (1) the lower rate of US detection reported by this group (27.3% compared with the 63% of HCC rate detection of HCC at early stage reported by meta-analysis<sup>60</sup>); (2) the high rate of HCC detection at screening MRI (without histological confirmation) suggesting that this strategy may induce HCC over-diagnosis and, in consequence, overtreatment of non-malignant lesions; and (3) concerns on the concept and model for identification of high-risk cirrhotic patients, and the potential bias in the selection of eastern population that can be different than in western countries.

These current limitations of imaging to diagnose HCC limitations have not been overcome with the introduction of functional imaging modalities such as DWI and hepatobiliary phase gadoteric-acid imaging, which are also affected by heterogeneity and are thus potentially an additional source of diagnostic error.

The classic conceptualization of medical images as pictures intended solely for visual interpretation is an obstacle that must be overcome to improve diagnosis.

Radiomics, which is an emerging field of oncological research, assume that radiologic image features could predict the prognosis of oncologic patients, as they are associated with tumor biological characteristics. In the field of HCC, radiomics had been mainly explored to link image texture features with clinical outcome, by building models that positively correlate with aggressive tumor phenotypes (future fast increase in size and vascular invasion) and with increase in recurrence rate and lower survival.

In that regards, some preliminary studies found that the analysis of texture features on dynamic phases (either arterial or hepatobiliary phases) may help to detect those HCC with higher potential aggressive evolution at baseline (i.e., differentiation low- from high-grade HCC,<sup>61</sup> to predict the risk of progression from hypovascular nodules into HCC, or to predict risk of recurrence<sup>62</sup>) or to predict survival assessed with texture analysis of pre-treatment CT scans.<sup>63</sup>

The analysis of these data can be used to develop decision-support tools for diagnosis and to devise predictive or prognostic models for outcomes of interest.<sup>64</sup> Potentially, these models may complement current existing staging systems such as BCLC and would help to plan a more personalized therapeutic

option after the initial diagnosis of solitary HCC in cirrhotic patients. However, a common limitation of radiomics studies is the inclusion of radiologic scans acquired in one or few machines. Therefore, expanding the analysis at large multicentric scales might have affected the radiomics results. Further studies and validations using different scanners, models, and contrast agents are required before their application in clinical research or practice.

## Main Concepts and Learning Points

- The aim of this review is to offer a comprehensive view of the heterogeneity of hepatocellular carcinomas at diagnosis on both morphological and functional imaging techniques.
- The noninvasive diagnosis of hepatocellular carcinoma represents a major challenge for radiologists. Hepatocellular carcinomas can be radiologically and histologically heterogeneous within tumors, between tumors, and between patients.
- The spectrum of heterogeneity depends mainly on hepatocellular carcinoma's degree of differentiation and its size. This heterogeneity reflects and correlates with the histologic continuum spanning the process of hepatocarcinogenesis.
- After systemic treatment, there is also heterogeneity in the pattern of changes seen among different hepatocellular carcinomas and in the type of tumor progression. Further research at the molecular and genetic levels is needed to better understand these changes.

### Conflicts of Interest

Dr. Rimola reports personal fees from Bayer, outside the submitted work.

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