An overview of hepatocellular carcinoma with atypical enhancement pattern: spectrum of magnetic resonance imaging findings with pathologic correlation

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Radiol Oncol 2021; 55(2): 130-143. doi: 10.2478/raon-2021-0004

Received 9 October 2020
Accepted 15 December 2020

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Disclosure: No potential conflicts of interest were disclosed.

Background. In the setting of cirrhotic liver, the diagnosis of hepatocellular carcinoma (HCC) is straightforward when typical imaging findings consisting of arterial hypervascularity followed by portal-venous washout are present in nodules larger than 1 cm. However, due to the complexity of hepatocarcinogenesis, not all HCCs present with typical vascular behaviour. Atypical forms such as hypervascular HCC without washout, isovascular or even hypovascular HCC can pose diagnostic dilemmas. In such cases, it is important to consider also the appearance of the nodules on diffusion-weighted imaging and hepatobiliary phase. In this regard, diffusion restriction and hypointensity on hepatobiliary phase are suggestive of malignancy. If both findings are present in hypervascular lesion without washout, or even in iso- or hypovascular lesion in cirrhotic liver, HCC should be considered. Moreover, other ancillary imaging findings such as the presence of the capsule, fat content, signal intensity on T2-weighted image favour the diagnosis of HCC. Another form of atypical HCCs are lesions which show hyperintensity on hepatobiliary phase. Therefore, the aim of the present study was to provide an overview of HCCs with atypical enhancement pattern, and focus on their magnetic resonance imaging (MRI) features.

Conclusions. In order to correctly characterize atypical HCC lesions in cirrhotic liver it is important to consider not only vascular behaviour of the nodule, but also ancillary MRI features, such as diffusion restriction, hepatobiliary phase hypointensity, and T2-weighted hyperintensity. Fat content, corona enhancement, mosaic architecture are other MRI features which favour the diagnosis of HCC even in the absence of typical vascular profile.

Key words: hepatocellular carcinoma; liver cirrhosis; magnetic resonance imaging; diffusion magnetic resonance imaging

Introduction

Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy, and the fifth cause of cancer mortality worldwide.¹² In more than 90% of cases, HCC occurs in a cirrhotic liver.³⁴ The diagnosis of HCC at an early stage is of great clinical importance since curative treatments
Hypervascular lesions without washout. In case nodule larger than 1 cm is detected, the patient should undergo further examination with computed tomography (CT) or magnetic resonance imaging (MRI). The presence of arterial hyperenhancement, followed by washout in the portal-venous or delayed phase, is sufficient for the diagnosis of HCC in the setting of cirrhotic liver without the need for tissue biopsy. In addition to CT and MRI, contrast-enhanced ultrasound (CEUS) is relatively new imaging modality, which allows real-time depiction of the typical vascular profile of HCC. CEUS is used in several indications in cirrhotic liver: to characterize nodules detected on surveillance US allowing prompt evaluation, and thus avoiding unnecessary further imaging in case of benign lesions; to add additional information to CT and MRI in case of suspected arterioportal shunts; and to provide more information for indeterminate nodules on US prior to consideration of liver biopsy. Nevertheless CEUS has some limitations including inability for HCC staging. Thus, once malignancy is detected CT or MRI is necessary for staging disease.

If nodules detected in cirrhotic liver are smaller than 1 cm, an ultrasound follow-up at 3-months intervals is advised, in order to detect lesion growth. Although typical enhancement pattern is highly specific (97–99%), it has low sensitivity, as 30% of HCCs have an atypical enhancement due to immature neovascularization. According to previous publications, the incidence of atypical enhancement pattern was most frequent among small and well-differentiated HCCs. Thus, some HCCs are misdiagnosed, since they do not exhibit these specific imaging criteria, presenting as either iso/hypovascular lesions, rim-enhancing lesions, or hypervascular lesions without washout.

Therefore, we sought herein to provide an overview of atypical manifestations of HCC in terms of vascular behaviour, and focus on their MRI features that might be used for establishing an accurate diagnosis.

**Hepatocarcinogenesis**

Cirrhosis may be caused by chronic viral hepatitis, chronic alcohol abuse, different inherited and acquired metabolic diseases with nonalcoholic fatty liver disease (NAFLD) arising as a new epidemic liver disease in modern world. Among all etiologies, the risk for HCC development is highest in patients with chronic viral hepatitis. Many recent studies have shown that the risk of HCC is reduced among patients with hepatitis C viral infection who achieve sustained virological response (SVR) with interferon-based antiviral therapy. However contradictory data exist on the risk of HCC in patients receiving new direct-acting antivirals (DAA). Namely in contrast to interferon, these drugs can also be used in patients with advanced liver disease in whom cirrhosis has already developed. Additionally, DAA lead to distortion of immune system which not only cause rapid decrease in viral overload but also alters inflammatory profile which can accelerate the growth of already existing preclinical cancer. The role of imaging in these subset of patients is early detection of HCC as the most important complication of longstanding cirrhosis.

It is widely accepted that in cirrhotic liver HCC develops through multistep process of hepatocarcinogenesis starting from low grade dysplastic nodules (DN), followed by high grade DN, early HCC, and finally progressed HCC. Low grade DNs are vaguely or distinctly nodular lesions with mild increase in cell density, no cyto logic atypia, and morphologically indistinguishable from surrounding regenerative nodules. However, this distinction is clinically not so important as low grade DN have only slightly elevated risk of further dedifferentiation. In contrast, high grade DNs are premalignant lesions with cellular and architectural atypia. Rare unpaired arteries are also found in most of high grade DNs. Early HCC is defined as well-differentiated lesion, lacking fibrous pseudcapsule, characterized by five major histological features: (1) increased cell density; (2) various number of portal tracts within the nodule; (3) frequent acinar and/or pseudoglandular pattern; (4) common diffuse fatty change; and (5) varying number of unpaired arteries. Diffuse fatty change is seen in 40% of tumors less than 2 cm in diameter.

Nevertheless, all these features may also be present in high grade DNs, thereby an accurate differentiation among these lesions and early HCC is very difficult, even on pathological examination. To date, the presence of stromal invasion is regarded to be the most important pathological finding for distinction of early HCC from dysplastic nodule. Progressed HCC are distinctly nodular lesions, which in contrast to early HCC, have a propensity for microvascular invasion and
Numerous unpaired arteries. Nodule-in-nodule absent in early HCCs. Therefore, the detection of vascularity, and portal-venous washout is frequently vascular enhancement including arterial hypervascularity. Due to insufficient number of unpaired arteries, typical vascular enhancement including arterial hypervascularity, and portal-venous washout is frequently absent in early HCCs. Therefore, the detection of these nodules on conventional MRI remains very difficult. Previous studies have shown that early HCCs are biologically less aggressive lesions, with much lower incidence of microvascular invasion compared to small hypervascular HCCs. Since early HCC has a great chance for surgical cure and low risk of recurrence, it is of great clinical importance to detect these lesions, and correctly characterize them.

Imaging diagnosis of hepatocellular carcinoma

Current guidelines for HCC diagnosis

According to international guidelines published by AASLD and European Association for the Study of Liver (EASL), non-invasive diagnosis of HCC in cirrhotic patients is based on the detection of arterial hyperenhancement followed by washout in portal-venous phase. Although this vascular behavior is recognized as radiological hallmark for HCC diagnosis, it has low sensitivity, as 30% of HCCs have an atypical enhancement due to immature neovascularization. Atypical enhancement pattern is usually present in small and well-differentiated HCCs. These results indicate that current guidelines for noninvasive diagnosis of HCC may have limited value for early HCC, and may lead to many false negative findings. Therefore, there is an obvious need for new imaging criteria in the diagnosis of early HCC, since liver biopsy recommended for all atypical nodules has many drawbacks, such as bleeding, infection, and inadequate sampling. In this regard recent studies have stressed the utility of ancillary features such as T2-weighted hyperintensity, increased fat content, hypointensity in hepatobiliary phase (HBP), and diffusion weighted imaging (DWI) hyperintensity for the detection of early HCCs. The presence of three or more positive findings among above mentioned ancillary MRI features in nodules with diameter of 1-2 cm without typical vascular profile, has shown to significantly improve sensitivity (77%) without reduction of specificity (95%).

Liver Imaging Reporting and Data System (LI-RADS) was developed by American College of Radiology in order to standardize diagnosis and reporting of lesions and pseudolesions identified in patients who are at risk for hepatocellular carcinoma. Moreover, imaging criteria for various benign and malignant hepatic tumors, including non-HCC malignancies like cholangiocarcinoma are discussed. LI-RADS categorizes hepatic lesions from LR-1 to LR-5 depending on their imaging features, reflecting probability of being HCC. Categories LR-1 and LR-2 include definitely (LR-1) or probably benign lesions (LR-2). LR-3 are lesions with intermediate risk of being HCC, LR-4 include observations that are probably HCC, while LR-5 are considered definitely HCC. LI-RADS algorithm can be applied to both CT and MRI examinations in patients with cirrhosis, chronic hepatitis B infection, and in patients with prior HCC. The categorization of the lesions using LI-RADS is based on major imaging criteria with arterial phase hyperenhancement and washout appearance, being the most important. However, there are a few others major features which favor the diagnosis of HCC. In this regard, enhancing capsule has a strong predictive value for HCC. Histologically, it correlates to either a true capsule or pseudocapsule. It is seen as peripheral rim of smooth hyperenhancement on portal-venous, delayed or transitional phase. In addition, threshold growth defined as increase of ≥50% in diameter over ≤6 months, or ≥100% of diameter increase over >6 months, with minimal increase of at least 5 mm, is a strong indicator of malignancy. Moreover, the use of ancillary features to further define final category is highly recommended. The current European Association for the study of the Liver favours the use of Barcelona-Clinic Liver Cancer (BCLC) staging system for clinical classification of HCC. In this system prognosis
prediction is defined by variables related to tumor status, liver function and health status. The role of imaging in this classification system is to accurately assess the number of tumor nodules, their size, the presence of portal vein invasion and extrahepatic spread of disease. In cases of single HCC nodules less than 2 cm, or 2-3 HCC nodules up to 3 cm, the radical treatment such as resection, ablation and transplantation are possible in cases of preserved liver function. In contrast, for advanced cases chemoembolization or systemic therapy are methods of choice.

One of the preconditions associated with a higher rate of complications in patients with cirrhosis and HCC is sarcopenia, defined as the loss of skeletal muscle mass, quality and function. In this regard, many studies have been published trying to assess the real clinical impact of sarcopenia on the outcome of HCC patients undergoing treatment. However, to date there is no standardization of methodology for sarcopenia evaluation. There are many different CT approaches for assessment of sarcopenia such as measurement of total bilateral psoas muscle area at the middle of the third lumbar vertebra, or measurement of psoas mass thickness at the level of umbilicus, and many others. The lack of standardization and unified cut-off values indicate the need of further studies to clarify the impact of sarcopenia on therapeutic outcome in cirrhotic patients with HCC.

Ancillary MRI features for the diagnosis of HCC

Hepatocarcinogenesis is a complex process that includes not only changes in vascularity, but also changes in architecture, cellular density, hepatocyte function, and Kupffer cell number or function. Therefore, development of hepatoselective contrast agents, such as gadoxetic acid, or gadobenate-dimeglumine, and introduction of DWI into abdominal MRI protocols, allowed evaluation not only of neovascularization, but also of other processes occurring during hepatocarcinogenesis. The hepatocyte-specific contrast agent gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) is a dual contrast agent, which combines the properties of conventional extracellular contrast agents with hepatobiliary phase. It is transported into hepatocytes using organic anion-transporting polypeptide OATP1B1 (synonymous with OATP8) and OATP1B3 receptors. Multiple resistance-associated Protein 2 (MRP2) located in the canalicular membrane of hepatocytes or tumour cells is responsible for excretion of hepatobiliary agents into bile ducts. OATP transporters are typically inhibited, while MRP2 are overexpressed in malignant liver lesions such as HCC, which therefore show hypointensity on hepatobiliary phase. The importance of OATP receptors not only for detection of HCC, but also for prediction of recurrence rate and overall prognosis has been recently shown. In this context, it was demonstrated that progressive loss in OATP immunoreactivity correlates well with the gain of biliary phenotype by neoplastic hepatocytes, which indicates high risk for faster recurrence and overall worse prognosis in patients with HCC.

Many previous studies have shown that reduction of OATP1B/B3 expression occurs early in the course of hepatocarcinogenesis, even before development of neovascularization. On the other hand, regenerative nodules, or low grade dysplastic nodules retain normal expression of uptake OATP1B/B3 transporter and excretery transporter MRP2. Therefore, the first sign of malignancy in cirrhotic nodules could be hypointensity in HBP, which is later followed by development of arterial hypervascularity. The utility of Gd-EOB-DTPA in the detection and characterization of atypically enhancing HCCs has been demonstrated in many recent reports. In this regard, Golfieri et al. tested 111 atypical cirrhotic nodules and shown that HBP hypointensity was the strongest marker of malignancy with 88% of sensitivity, 91% negative predictive value and 93% diagnostic accuracy. The same group of authors have shown that after addition of HBP phase in MRI protocol, sensitivity and specificity for the detection of small HCCs significantly increased, from 88.4% up to 99.4%, and from 88% to 95%, respectively. The high incidence of atypical nodules particularly among small lesions, and their frequent malignancy indicate the need to incorporate Gd-EOB-DTPA in standard MRI protocols for evaluation of cirrhotic liver. Nevertheless, it should be kept in mind that hepatic dysfunction or hyperbilirubinemia can result in diminished uptake of hepatospecific contrast
agent, leading to reduced conspicuity of HCC lesions on HBP.76

The value of DWI in the characterization of cirrhotic nodules could be explained by progressive cellular changes occurring during hepatocarcinogenesis.77 It is well known that DWI signal intensity is influenced by cellular density, architectural changes, as well as vascular changes during malignant transformation of cirrhotic nodules. As one of the major differences between dysplastic nodules and early HCCs is the degree of cellular density, DWI might provide a good insight into histological changes of hepatocellular nodules irrespective of vascularity.78 Notably, since RN and low grade DN are usually histologically identical to the surrounding hepatic tissue, they are isointense on DWI.79,80 On the other hand, HCC and high grade DN, show a progressive increase in cellular density, thickening of cellular plates, leading to progressive restriction of water mobility, which results in increased signal intensity on DWI.81 Since at an earlier stage, the degree of neovascularization may be insufficient for depiction on contrast-enhanced images, small lesions could sometimes be detected only on DWI.81 Opposite to the signal intensity on DWI, the calculation of apparent diffusion coefficient (ADC) values was not shown to be useful for differentiation of benign from malignant cirrhotic nodules.44,82 The subtle cellular changes, and variable presence of fat, necrosis, and vascular changes result in strong overlap of ADC values between malignant and benign nodules. In addition, DWI hyperintensity could be also found in high grade DN, and even in a few low grade DN.83 These results could be explained by heterogeneity of cirrhotic liver which also shows diffusion restriction, thus making it difficult to identify hepatocellular nodules with increased signal intensity on DWI.84 In addition, HCCs are less cellular than metastases, and sometimes difficult to detect on DWI.84 Furthermore, DWI also has other limitations, including limited spatial resolution, susceptibility to motion artifacts, especially for lesions located in the left lateral segment, and close to the diaphragm because of cardiac motion.77 Thus, in general DWI is not used alone in clinical scenarios, but only as a part of MRI protocol.85

The value of signal intensity on T2-weighted images in the identification of HCC lesions was stressed in many previous reports.41 Namely, T2-weighted hyperintensity is considered to be strong predictor of malignancy, and subsequent hypervascularization in hypovascular nodules.40,43 Higher signal intensity on T2-weighted images could partly be explained by peliotic changes in the intratumoral sinusoids of HCC.86 In this regard, Channual et al. have shown that relative signal intensity on T2-weighted images is significantly different between low grade DN on one side, and high grade DN with HCC on the other side.87 Moreover, when T2-weighted hyperintensity was combined with arterial hypervascularity, differentiation could be possible with the sensitivity of 88.6%, and positive predictive value of 99.2%.87 The value of T2-weighted hyperintensity was also shown in the study by Hwang et al., who reported that this feature was present in 76% of hypovascular HCC, and in only 12.9% of dysplastic nodules.88 Although T2-weighted hyperintensity can also occur in dysplastic nodules, probably due to infarction, the signal intensity is usually lower than in HCCs.89

Besides above mentioned imaging characteristics, there are also other ancillary features which could help in characterization of the lesions in cirrhotic liver. One of them is corona enhancement which refers to an ill-defined perilesional enhancement in late arterial phase.48 It develops as a consequence of an early drainage of blood from a tumor into the surrounding hepatic sinusoids and portal venules.90 This occurs due to the obstruction of intranodular hepatic veins by neoplastic cells.90 While capsular appearance is obvious on portal-venous phase, corona enhancement is present in late arterial phase.91 If iron sparing solid mass is seen in the setting of cirrhotic liver with multiple siderotic nodules, this finding should indicate the presence of malignancy.88 It is well known that during hepatocarcinogenesis neoplastic cells loose their capability of iron accumulation.48 Non-enhancing capsule has recently been introduced as another ancillary feature that in particular favors HCC.48 It refers to uniformly thin, sharply demarcated, non-enhancing rim surrounding the lesion.48 Furthermore, mosaic architecture and “nodule-in-nodule” appearance are very well known ancillary features of HCC.30,92 While mosaic architecture is usually seen in large lesions, nodule-in-nodule often represents development of early HCC in high grade dysplastic nodule. The presence of fat inside the cirrhotic nodule is also considered to be ancillary feature of HCC.93 Although the exact underlying mechanism of intralesional fat accumulation is not known, hypoxia which occurs during hepatocarcinogenesis is considered to be the most probable reason.93 Intralesional fat is usually seen in small HCCs (less than 1.5 cm) with decreasing frequency in larger lesions.94 Nevertheless, this finding should not be confused with fat accumula-
Atypically enhanced hepatocellular carcinoma

Iso- or hypovascular HCC

Iso- or hypovascular HCCs are defined as lesions without arterial phase hypervascularity. As the reduction of portal vascularity precedes development of new unpaired arteries, iso- or hypovascularity in arterial phase, with hypointensity in portal-venous phase could be the first sign of early HCC (Figure 1,2).27 The prevalence of hypovascular HCC varies among different studies, ranging from 14% in the study by Leoni et al.,96 to 19.5% by Choi et al.97 If this vascular pattern is identified at dynamic CT, further examination with MRI using hepatospecific contrast agents is necessary. Hypointensity on HBP in nodules hypovascular in arterial phase, indicates that loss of metabolic hepatocyte function occurs before development of neovascularization.65,70 There are many recent studies which pointed out that hypointensity on HBP is one of the imaging findings with highest diagnostic accuracy for detection of early HCC.45,46,71-74 Accordingly, in the study by Sano et al.41 the sensitivity of HBP hypointensity for the detection of early HCC was 97%, while specificity reached 100%. Although several other imaging features, such as nodule-in-nodule appearance, washout in portal-venous phase, and fat content also had specificity of 100%, none of these findings had sufficient sensitivity for HCC detection. Similar results were published by Choi et al. who have shown that 96.6% of hypovascular HCCs were hypointense on HBP, indicating that HBP hypointensity must be considered as imaging biomarker of malignancy.97

FIGURE 1. Hypovascular hepatocellular carcinoma (HCC) in 58-year old woman with cirrhosis. On axial T2-weighted image (A), diffusion-weighted image (B) and on in-phase image (C) tumor is isointense with surrounding liver parenchyma. On opposed-phase image there is a partial drop of signal intensity in the lesion (arrow) corresponding to the fatty component (D). The lesion (arrow) is slightly hypointense on arterial phase (E), while it is clearly hypovascular on portal-venous phase (F). On hepatobiliary phase after administration of gadoxetic acid the lesion (arrow) is hypointense (G). Hematoxylin and eosin (H&E) staining showed well-differentiated HCC with fat deposition; original magnification x 200 (H).
On the basis of these results, it could be concluded that double hypointensity, including hypointensity in the portal-venous phase, and hypointensity in hepatobiliary phase is highly suggestive of hypovascular HCC. On the other hand, Bartolozzi et al. reported that 70% of high grades DNs were also hypointense on HBP, indicating that using only this sign, precise distinction among high grade DN and HCC is not possible. However, differentiation among high grade DNs and early HCC is not crucial from clinical point of view. Namely, in many institutions high grade DN are considered to be early HCCs. Taking into account that high grade DN are premalignant lesions, it is questionable whether exact radiological distinction among these two pathological entities is indeed necessary. If not treated immediately, HBP hypointense nodules should be rigorously monitored as was stressed by many previous studies. The cumulative risk of hypervascularization in these lesions varies from 31-35% in the study by Kim et al., and Hyodo et al., up to 77% in the study by Kumada et al. Similar results were also reported in other studies. Considering that a significant percent of non-hypervascular HBP hypointense cirrhotic nodules are already HCCs, or will develop typical radiological features of HCC in follow-up, they must be characterized as high risk nodules, and if possible should be subject to liver biopsy. However, care should be taken when interpreting HBP phase imaging findings in cirrhotic liver. Namely, in patients with worse Child Pugh class, the uptake of Gd-EOB-DTPA can be very reduced and delayed, affecting relative signal intensity of HCCs. In this regard, the diagnosis of HCC with atypical enhancement pattern may be very challenging in cirrhotic liver, indicating the importance of multiparametric assessment.

Besides hepatospecific contrast agents, further characterization of iso- or hypovascular nodules could be done with DWI. In this context, Hwang et al. reported high diagnostic accuracy of DWI in differentiation between hypovascular HCC and dysplastic nodules, as hyperintensity on DWI was observed in 92% of HCC, in contrast to 16.1% of dysplastic nodules. In the study by Kim et al. DWI restriction was present in 56% of 139 hypovascular, HBP hypointense nodules which subsequently progressed to hypervascular HCC, indicating that DWI hyperintensity is a strong predictor of devel-

**FIGURE 2.** Isovascular hepatocellular carcinoma (HCC) in 55-year old woman with cirrhosis. On T2-weighted image slightly hypointense nodule (arrow) is seen in liver segment VII (A). No lesion is seen on arterial (B) and portal venous phase (C). On hepatobiliary phase after administration of gadoxetic acid the lesion (arrow) is hypointense (D). Diffusion-weighted image shows diffusion restriction of the lesion (arrow) (E). Hematoxylin and eosin (H&E) staining showed well-differentiated HCC; original magnification x 200 (F).
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Moreover, on the basis of these results, it could be concluded that iso- or hypovascular nodules, which show hypointensity on HBP and high signal intensity on DWI, could already be considered as early HCC. Additionally, according to some authors hypovascular nodules, hypointense in the HBP, not hyperintense on DWI, should be further investigated by contrast enhanced ultrasound (CEUS), as this method allows depiction of early arterial phase enhancement, which could be missed on dynamic CT and MRI.

Hypervascular HCC without washout in portal-venous phase

Many small HCCs are depicted only during arterial phase imaging as hypervascular lesions, lacking washout on portal-venous and delayed phase (Figure 3).\(^{103}\) Actually, in HCCs ≤1 cm, arterial enhancement is the most frequent MRI finding (79%) in comparison to other features, such as wash-out in the portal-venous or delayed phase (50%).\(^{104}\) This can raise a diagnostic dilemma, as it is often difficult to differentiate these lesions from non-neoplastic hypervascular pseudolesions, such as small arterioportal shunts, or atypical cirrhosis related nodules.\(^{105,106}\) Moreover, the majority of these small hypervascular nodules detected in cirrhotic liver are benign lesions.\(^{105,106}\)

Differential diagnosis is usually made using T2-weighted images, DWI, and signal intensity on HBP. Concerning the value of T2-weighted signal intensity there are discrepant results in the previous literature.\(^{87,88,107}\) Thus, Hussain et al. concluded that T2-weighted hyperintensity has no additional value in the identification of small HCC, due to very heterogeneous signal intensity of surrounding liver parenchyma.\(^{107}\) In contrast, many other investigators reported that addition of T2-weighted images to dynamic contrast enhanced images significantly improves detection of HCC.\(^{87,88}\) In this regard, HCCs are seen as slightly hyperintense lesions, while arterioportal shunts are isointense with surrounding liver tissue.\(^{43}\) Additionally, the majority of these atypical HCCs are hypointense on HBP phase indicating the lack of functional hepatocytes. Very rarely this atypical vascular profile can occur in large HCCs (Figure 4). In such cases hypointensity on HBP is

**FIGURE 3.** Hypervascular hepatocellular carcinoma (HCC) without washout in 64-year old man with cirrhosis. Axial T2-weighted fat-suppressed image shows hyperintense nodule (arrow) in liver segment VIII (A). On arterial phase the nodule (arrow) is hypervascular (B) without washout on portal-venous phase (C). On hepatobiliary phase the nodule (arrow) is hypointense (D) and on diffusion-weighted image it is hyperintense (E). Hematoxylin and eosin (H&E) staining showed moderately-differentiated HCC; original magnification x 200 (F).
the most useful sequence for distinction from other hypervascular benign lesions, such as focal nodular hyperplasia. Since arterial enhancement and HBP hypointensity are two strongest markers of malignancy in cirrhotic patients, a nodule with arterial hypervascularity, even without wash-out in portal-venous or delayed phase, but hypointense in the HBP, should be highly suspicious of HCC. Another diagnostic problem could be the distinction between these atypically enhancing HCCs, and small hemangiomas in liver cirrhosis. Namely, in cirrhotic parenchyma small hemangiomas can shrink, and become fibrotic and hyalinized, which influences their signal intensity on T2-weighted images. Moreover, similar to HCCs, hemangiomas are hypointense in HBP. In this context Semelka et al. reported that accurate differential diagnosis among small HCCs and hepatic hemangioma less than 15 mm can not be made on the basis of imaging criteria.

HBP hyperintense hepatocellular carcinoma

According to molecular changes during hepatocarcinogenesis, HCCs should typically show hypointensity on HBP. The signal intensity of HCC on HBP is strongly correlated to the expression of uptake transporter OATP8. It is well known that during hepatocarcinogenesis the progressive decrease in OATP8 expression occurs, thus influencing the enhancement ratio of cirrhotic nodules in the HBP. Nevertheless, in 10% of HCCs paradoxical uptake of hepatospecific contrast agent may occur. This can partly be explained by residual functional hepatocytes expressing OATP8 receptors in well-differentiated lesions. In addition, these authors have shown that uptake of Gd-EOB-DTPA was significantly correlated with the maintenance of bile production. Similar results were published by Choi et al. who have shown that among 28 tumors showing iso- or hyperintensity on HBP, only 10 were well-differentiated HCCs (35.7%), while 16 were moderately (57.1%), and two were poorly differentiated lesions (7.1%). A few recent studies have shown that gadoxetic acid uptake in HCCs can be the result of genetic mutations and reversion to their original hepatocyte nature during neoplastic transformation. Namely, in some moderately or even poorly differentiated lesions OATP8 receptor expression can increase due to genetic alterations, followed by decrease in MRP expression. In contrast to normal hepatocytes where excretion of gadoxetic acid occurs via MRP2 transporters localized on canalicular side, in hepatobiliary phase iso- or hy-
perintense HCCs the main pathway of excretion is through MRP3 on sinusoidal side. Therefore, HBP iso- or hyperintensity in HCCs does not indicate well-differentiated lesion, but rather suggest different genetic subtype of HCC. Although differentiation of the tumor cannot be predicted by signal intensity on hepatobiliary phase, Choi et al. have demonstrated that HBP hyperintense HCCs showed significantly higher differentiation grades, less frequent portal vein invasion, and lower recurrence rate. Moreover, patients with hyperintense HCCs showed longer survival than those with hypointense HCCs. All these findings suggest that HBP hyperintense HCCs are probably a particular form of HCC with biologically less aggressive features in comparison to HBP hypointense HCCs. Interestingly, the AFP levels were shown to be significantly higher in hypointense HCCs than in hyperintense HCCs.

However, there are no data in the previous literature about behaviour of HBP hyperintense HCCs in portal venous phase, whether they demonstrate washout or not. Although most reported cases show typical vascular profile, rarely HCCs hyperintense in HBP lack portal-venous or delayed phase washout (Figure 5). The incidence of such nodules is very low, less than 3%. In such cases differential diagnosis towards benign lesions, such as large regenerative nodules (LRNs), and focal nodular hyperplasia is very challenging. LRNs are hyperplastic lesions, 5 mm to 5 cm in diameter, associated with cirrhosis, Budd–Chiari syndrome, certain forms of congenital heart disease, and other conditions. LRNs are typically hypervascular in arterial phase, without washout in portal-venous or delayed phase, iso- or hyperintense in HBP. The distinction between LRNs and atypically enhancing HCCs showing hyperintensity on HBP, requires detailed analysis of other MRI features, such as T2-weighted, T1-weighted, and DWI signal intensity. While HCCs are usually slightly hyperintense on T2-weighted images, hypointense on T1-weighted images with restricted diffusion, LRN and FNH are isointense on both T2- and T1-weighted images, without DWI hyperintensity. If there is any doubt, rigorous follow-up is required, and if nodule grows a biopsy is recommended.

**Conclusions**

The diagnosis of HCC is straightforward when typical imaging features are present. Nonetheless,
due to complexity of hepatocarcinogenesis, HCC can present with atypical vascular profile, especially in small lesions, including iso- or hypovascular nodules without arterial hypervascularity, and hypervascular lesions without washout in portal-venous phase. Additionally, there are HCCs with high signal intensity in HBP. In order to correctly characterize these lesions ancillary features such as T2-weighted hyperintensity, diffusion restriction, and hepatobiliary phase hypointensity together with other MRI characteristics should be carefully examined. Even though these atypical presentations are rare, it is important to recognize them in order to provide the patients optimal and timely treatment.

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