RadioGraphics

MR Imaging of Hypervascular Lesions in the Cirrhotic Liver: A Diagnostic Dilemma[1]

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LEARNING OBJECTIVES

After completing this journal-based CME activity, participants will be able to:

- Describe the pathophysiologic mechanisms that occur in the multistep process of carcinogenesis in cirrhotic nodules.
- Discuss the MR imaging appearances of the spectrum of hypervascular lesions in the cirrhotic liver.
- Explain the treatment of hypervascular lesions on the basis of the Barcelona Clinic Liver Cancer system.

TEACHING POINTS

See last page

Cirrhosis is characterized by a spectrum of hepatocellular nodules that mark the progression from regenerative nodules to low- and high-grade dysplastic nodules, followed by small and large hepatocellular carcinomas (HCCs). Characterization of small nodules on the basis of imaging and histopathologic findings is complicated by an overlap in findings associated with each type of nodule, a reflection of their multistep transitions. Vascularity patterns change gradually as the nodules evolve, with an increasing shift from predominantly venous to predominantly arterial perfusion. Regenerative and low-grade dysplastic nodules demonstrate predominantly portal perfusion and contrast enhancement similar to that of surrounding parenchyma. Differentiation of high-grade dysplastic nodules and well-differentiated HCCs on the basis of dynamic imaging and histologic findings is challenging, with a high rate of false-negative results. Some small nodules that lack hypervascularity may be early HCCs. Progressed small and large HCCs usually present no diagnostic difficulty because of their characteristic findings. Although characterization of hypervascular lesions in the cirrhotic liver is difficult, it is a key step in disease management and is the radiologist's responsibility.

Abbreviations: ADC = apparent diffusion coefficient, DWI = diffusion-weighted imaging, HCC = hepatocellular carcinoma, SPIO = superparamagnetic iron oxide, 3D = three-dimensional

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Introduction

The incidence of hepatocellular carcinoma (HCC) and its death rates have increased during the past 10 years and are not expected to reach a plateau until 2020. Worldwide, HCC is the third most common cause of death from cancer (1,2). Prospective studies have shown that HCC now constitutes the main cause of death among patients with cirrhosis; the annual incidence of HCC among such patients is 2.0%–6.6% (3). When it is detected after the onset of symptoms, patients with HCC have a dismal prognosis (5-year survival rate, 0%–10%); however, patients with small HCCs may be cured (5-year survival rate, >50%). Ideally, tumors would be detected when they are solitary and smaller than 2 cm, a major diagnostic challenge (4,5). The widespread practice of surveillance, which is recommended for patients with cirrhosis, has increased the number of patients who are diagnosed with early-stage HCC, when curative options may be pursued (5–7).

Cirrhotic livers are characterized by irreversible remodeling of the hepatic architecture, including bridging fibrosis and a spectrum of hepatocellular nodules (5,8–10). Various types of hypervascular lesions are common among patients with cirrhosis. The ability to differentiate between malignant and benign nodules is limited; nodules are primarily characterized on the basis of differences in vascularity. Regenerative and low-grade dysplastic nodules have predominantly portal venous blood supplies and demonstrate as much enhancement as the liver parenchyma. High-grade dysplastic nodules and HCCs demonstrate a loss of portal vascularization and have more nontriadal arteries. High-grade dysplastic nodules and early HCCs usually are hypovascular, but they may enhance in the arterial phase, whereas those that are larger and more advanced usually appear as hypervascular nodules. The transition from regenerative and dysplastic nodules to HCC is not characterized by discrete steps; rather, it is marked by a continuum of vascular pattern changes. Many of the intermediate stages are atypical, making their characterization difficult. Typical HCCs may be diagnosed at imaging. The algorithm for evaluating small nodules found during screening of patients at risk for HCC was recently changed: Now, a nodule larger than 1 cm that demonstrates arterial enhancement followed by washout at computed tomography (CT) or magnetic resonance (MR) imaging may be diagnosed as HCC (7,11,12).

Teaching Point

In several studies, including a meta-analysis, the specificities of MR imaging and CT were found to be comparable for depicting HCC in the cirrhotic liver, although other studies have reported that MR imaging has higher sensitivity than CT (81% versus 68%, 70% versus 50%, 77% versus 54%, and 85% versus 68% for MR imaging and CT, respectively) (13–17). The sensitivity of MR imaging for depicting HCC depends on the clinical setting and the size of the nodules. Krinsky et al (18) reported that MR imaging ws sensitive in only 33% of patients with known HCC before transplantation. When the nodules were stratified by size, the sensitivity of MR imaging was 100% for lesions larger than 2 cm, 52% for 1–2-cm lesions, and only 4% for lesions smaller than 1 cm, findings that illustrate the difficulty in detecting small lesions.

Although MR imaging usually has higher sensitivity than CT, depicting and characterizing hypervascular lesions in patients with cirrhosis is challenging at any modality, especially when lesions are small. Differentiating HCC from other hypervascular lesions is a key step in treating patients and is the responsibility of the radiologist (8). In this article, we review the spectrum of hypervascular lesions that occur in the cirrhotic liver, discuss their appearances at MR imaging and the difficulty in characterizing small lesions, and present several case scenarios.

MR Imaging Protocols

MR imaging may be performed with a 1.5- or 3.0-T system with an abdominal phased-array coil. The protocol for imaging patients with cirrhosis includes the following images: *(a)* breath-hold, T1-weighted, dual-echo, in- and out-of-phase, gradient-echo, with out-of-phase images obtained before in-phase images because of the shorter echo time of out-of-phase images; *(b)* coronal and axial T2-weighted, single-shot, turbo spin-echo images; *(c)* axial T2-weighted, fat-suppressed, single-shot, turbo spin-echo images; and *(d)* axial unenhanced and contrast material–enhanced T1-weighted, fat-suppressed, three-dimensional, gradient-echo images with volumetric interpolated breath-hold examination and dynamic evaluation (arterial-dominant, portal, and equilibrium phases). This sequence is followed by coronal T1-weighted, fat-suppressed, three-dimensional imaging. We also perform diffusion-weighted imaging with apparent diffusion coefficient (ADC) mapping.

Each sequence should be performed during end expiration to achieve a consistent breath-

holding pattern and facilitate comparison of the different types of images. If motion correction techniques are employed, inspiration images may be obtained, a method that may be helpful for patients who have difficulty holding their breath. Subtraction imaging should always be used to help analyze the contrast enhancement of nodules that demonstrate high signal intensity on T1-weighted images. Because the arterial-dominant phase is important for image interpretation, a technique that captures this phase in a timely manner should be used. The presence of gadolinium contrast material in hepatic arteries and portal veins and an absence of the material in hepatic veins are reliable landmarks of optimal timing of the arterial-dominant phase.

Diffusion-weighted Imaging

DWI operates on the basis of incoherent intravoxel motion and allows noninvasive quantification of water diffusion and microcapillary blood perfusion (19). Tissue cellularity and intact cell membranes are the main factors that determine the impedance of water diffusion. Tissues that are associated with restricted diffusion include those found in tumors, cytotoxic edema, and abscesses. Tissues with low cellularity or disrupted cell membranes, such as cysts, hemangiomas, and treated or necrotic tumors, allow a greater degree of water diffusion (20,21).

DWI may depict and help characterize focal hepatic lesions. A small amount of diffusion weighting with a low *b* value (<200 sec/mm^2) nulls the intrahepatic vascular signal intensity, creating so-called black-blood images and improving depiction of focal liver lesions. Studies have demonstrated the superiority of DWI over T2-weighted MR imaging for depiction of lesions (22,23). Images with higher *b* values provide diffusion information that aids in lesion characterization (22,24,25). Malignant lesions have lower mean ADC values than do benign lesions, with varying degrees of overlap (22–24,26). However, it may be difficult to differentiate HCC from dysplastic nodules or an adjacent cirrhotic liver because they have similar ADC values (24,27,28).

DWI is also used to evaluate response to treatment (eg, chemotherapy, radiation therapy, and local ablation) in patients with HCC. An increased ADC value 1–2 weeks after transcatheter arterial chemoembolization indicates early tumor response to therapy, which may be a sign of tumor necrosis before a change in tumor size occurs. Nonviable portions of tumor have high ADC values, and viable tumor portions have low ADC values (20,21,29–32). Some studies have reported that DWI findings may be used to predict response to transcatheter arterial chemoembolization in patients with HCC; high pretreatment ADC values are indicative of poor response to treatment and likely reflect the partially necrotic state of a tumor before intervention (33).

DWI is available at most facilities and may be incorporated into conventional protocols. Information from DWI should always be interpreted in conjunction with conventional MR imaging findings. The major limitation of DWI is its lack of standardization, which presents a challenge to its widespread adoption in body imaging.

Contrast Agents

Gadolinium-based extracellular contrast agents are the most widely available MR imaging contrast agents worldwide. They are distributed within the extracellular interstitial space and shorten the T1 relaxation times of adjacent water protons, causing enhanced signal intensity on T1-weighted images (34). Other MR imaging contrast agents, such as hepatobiliary-specific and superparamagnetic iron oxide (SPIO) agents, are also available at some facilities. Hepatobiliary-specific contrast agents are taken up by functioning hepatocytes and excreted in the bile. They cause T1 shortening and increase the signal intensity of the liver, bile ducts, and some hepatocyte-containing lesions on delayed T1-weighted images (34,35). SPIO is a reticuloendothelial-system-specific contrast agent that causes signal loss on T2- and T2*-weighted images. The iron oxide particles of the contrast agent are phagocytized by the macrophages, and they mainly accumulate in the liver (80%), as well as in the spleen and bone marrow (34,36,37).

Cirrhosis-associated Nodules

Cirrhosis is characterized by progressive fibrosis of the liver parenchyma and a spectrum of hepatocellular nodules, most of which are regenerative (38–40). Regenerative nodules play a role in the stepwise carcinogenesis of HCC, most frequently through dedifferentiation, which occurs in the following order: regenerative nodule, low-grade dysplastic nodule, high-grade dysplastic nodule, small HCC, and, finally, large HCC (38–40). The major changes that characterize the progression from regenerative nodules through the steps of HCC development are progressive loss of portal vascularity and increased arterial blood flow. Although characterization of nodules may be made challenging

MR Imaging Appearances of Cirrhotic Liver Nodules

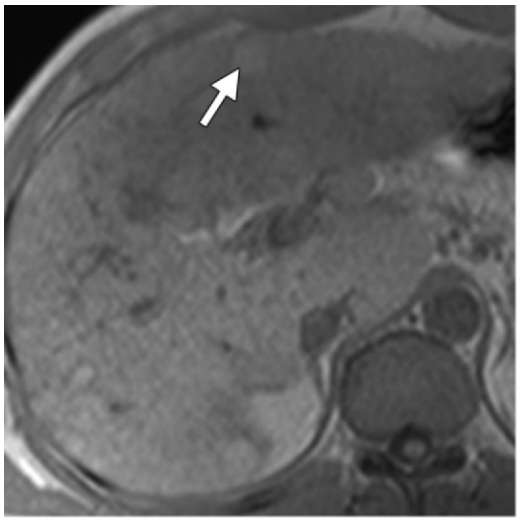
Type of Nodule	Appearance				
	T1-weighted Images	T2-weighted Images	Dynamic Images	Hepatobiliary Contrast Material	SPIO Contrast Material
Regenerative	Varies	Iso- or hypointense	Enhances as much as liver parenchyma	Enhances as much as liver parenchyma	Enhances as much as liver parenchyma
Low-grade dysplastic	Varies, often hyperintense	Iso- or hypointense	Enhances as much as liver parenchyma	Enhances as much as liver parenchyma	Enhances as much as liver parenchyma
High-grade dysplastic	Varies, often hyperintense	Iso- or hypointense	Usually hypovascular, but may enhance in arterial phase	Enhances as much as liver parenchyma	Enhances as much as liver parenchyma
Early HCC	Varies, often hyperintense	Iso- or hypointense	Usually hypovascular, but may enhance in arterial phase	May or may not enhance (depending on degree of differentiation)	May or may not enhance (depending on degree of differentiation)
Progressed HCC	Varies, often iso- or hypointense	Moderately hyperintense	Enhancement in arterial phase and washout in portal or equilibrium phase	May or may not enhance (depends on degree of differentiation)	May or may not enhance (depends on degree of differentiation)
Large HCC	Heterogeneous, predominantly hypointense	Heterogeneous, predominantly hyperintense	80%–90% enhance in arterial phase, washout in portal or equilibrium phase	No enhancement	No enhancement

by the presence of overlapping features (even at the histopathologic level) of some cirrhotic nodules, familiarity with their multistep progression and manifestations at MR imaging is important (Table). Visualization of nodules in the cirrhotic liver also may be complicated by fibrosis-related heterogeneity, and heterogeneous enhancement caused by changes in blood flow may be mistaken for tumor. Moreover, small nodules infrequently demonstrate typical findings of HCC (40).

Regenerative Nodules

Regenerative nodules, also known as cirrhotic nodules, result from continuous injury to the liver parenchyma and appear as innumerable benign nodules surrounded by fibrous septa at histologic analysis (38,39). Most regenerative nodules do not progress in the dedifferentiation process. They may or may not be visible at MR imaging and are usually iso- to hypointense on T2-weighted images, with variable signal intensity on T1-weighted images. Those that contain substantial amounts of lipids, protein, and copper are hyperintense on T1-weighted images. After administration of gadolinium-based contrast material, regenerative nodules enhance as much as or slightly less than surrounding parenchyma (Fig 1) (8,41). They have normal hepatocellular and phagocytic functions and enhance to the same degree as adjacent liver on delayed T1-weighted images after administration of hepatobiliary-specific or SPIO contrast material (8,35). Rarely, regenerative nodules may infarct and exhibit hyperintense signal intensity on T2-weighted images, a finding that may be mistaken for HCC (41).

Other types of regenerative nodules are steatotic and siderotic. Steatotic regenerative nodules result from fat deposition and are usually multifocal. They appear as hyperintense lesions on in-phase gradient images and exhibit signal loss on out-of-phase images (Fig 2) (8). Siderotic nodules are caused by iron deposition and are



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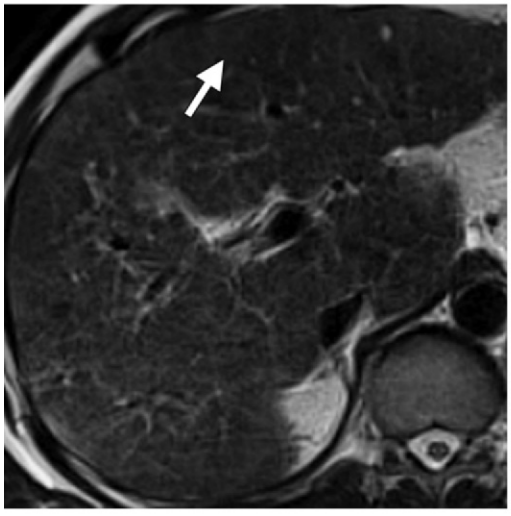

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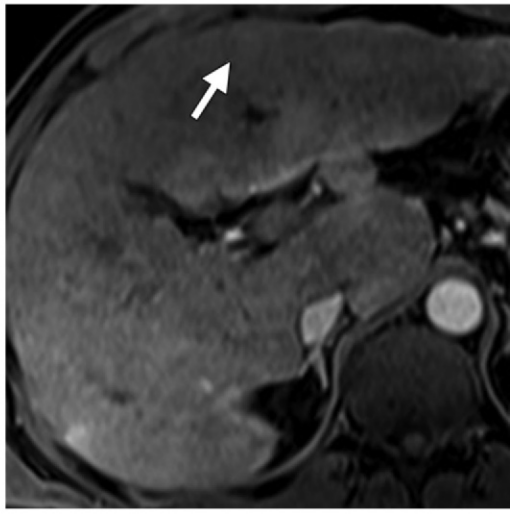
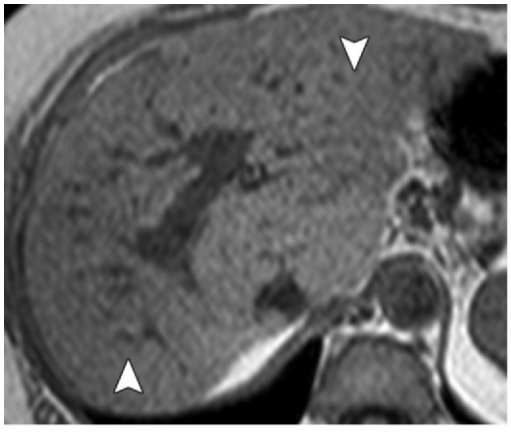


c.

Figure 1. Regenerative or low-grade dysplastic nodule in a 54-year-old man with cirrhosis resulting from hepatitis C infection. **(a)** Axial T1-weighted gradient-echo in-phase MR image shows a small hyperintense nodule (arrow) in the left lobe of the cirrhotic liver. **(b)** Axial T2-weighted MR image shows that the nodule (arrow) is isointense and poorly defined. **(c)** Axial T1-weighted spoiled gradient-echo MR image obtained during the arterial phase shows that the nodule (arrow) enhances as much as surrounding parenchyma. It demonstrates no diffusion restriction and is not visible on diffusion-weighted images. These findings are indicative of a regenerative or low-grade dysplastic nodule, which may not be differentiated at MR imaging.



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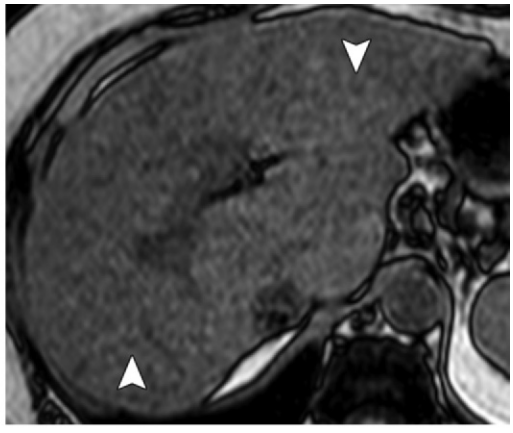
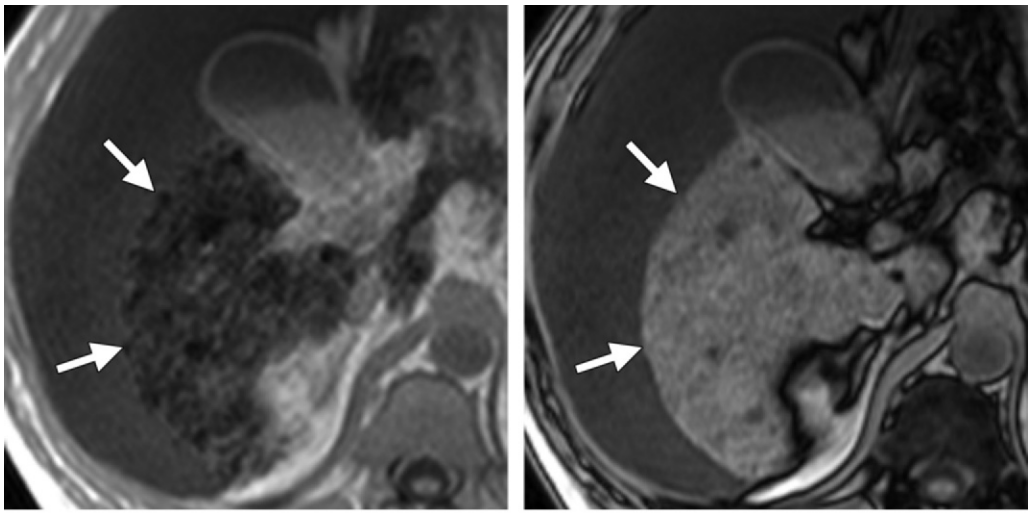


b.

Figure 2. Steatotic regenerative nodules in a 49-year-old woman with cirrhosis secondary to fatty liver disease. Axial unenhanced T1-weighted two-dimensional spoiled gradient-echo in-phase **(a)** and out-of-phase **(b)** MR images show multiple steatotic nodules (arrowheads) throughout the hepatic parenchyma. Signal intensity of the nodules is lower on out-of-phase images than in-phase images, a finding indicative of fat. The nodules also demonstrated enhancement similar to that of background liver (not shown).



a. b.

Figure 3. Siderotic nodules in a 55-year-old man with cirrhosis resulting from hepatitis C infection. Axial unenhanced T1-weighted two-dimensional spoiled gradient-echo in-phase **(a)** and out-of-phase **(b)** MR images show marked loss of signal intensity (arrows) throughout the hepatic parenchyma secondary to diffuse siderotic nodules. Ascites is also seen surrounding the organs. If, as in this case, in-phase T1-weighted images have a higher echo time than out-of-phase images, in-phase images are more sensitive to magnetic susceptibility artifacts caused by iron deposits.

hypointense on T1- and T2-weighted images, a result of their magnetic susceptibility (Fig 3). Siderotic nodules may be regenerative or dysplastic; however, it is not possible to determine the type at MR imaging. Siderotic regenerative nodules are not considered premalignant (42,43).

Dysplastic Nodules

Dysplastic nodules are regenerative nodules that contain atypical cells. They lack definite signs of malignancy at histologic analysis and have varied appearances at MR imaging (38–40,44). Dysplastic nodules have been found in 15%–28% of cirrhotic liver explants (8).

Low-Grade Dysplastic Nodules

At histologic analysis, low-grade dysplastic nodules are characterized by preserved hepatic architecture, low-grade cytologic atypias, varying numbers of portal tracts, and an inconstant increase in the number of unpaired arterioles. They have low malignant potential (38–40). Similar to regenerative nodules, low-grade dysplastic nodules have variable signal intensity on T1-weighted MR images, depending on their content; are usually iso- or hypointense on T2-weighted MR images; and demonstrate enhancement similar to that of surrounding parenchyma after administration of gadolinium-based contrast material (Fig 1). Although it is not possible to differentiate low-grade dysplastic nodules from regenerative nodules because of their similar imaging features, there are no significant practical consequences (8,39–41).

High-Grade Dysplastic Nodules

At histologic analysis, high-grade dysplastic nodules are characterized by moderate cytologic and architectural atypia to a degree insufficient to render a diagnosis of HCC. High-grade dysplastic modules have reduced numbers of portal tracts, progressive sinusoidal capillarization, and increased numbers of unpaired arteries. They are premalignant and may be difficult to distinguish from well-differentiated HCC (38–40,44).

At MR imaging, high-grade dysplastic nodules demonstrate variable signal intensity on T1-weighted images, depending on their content, and are usually iso- or hypointense on

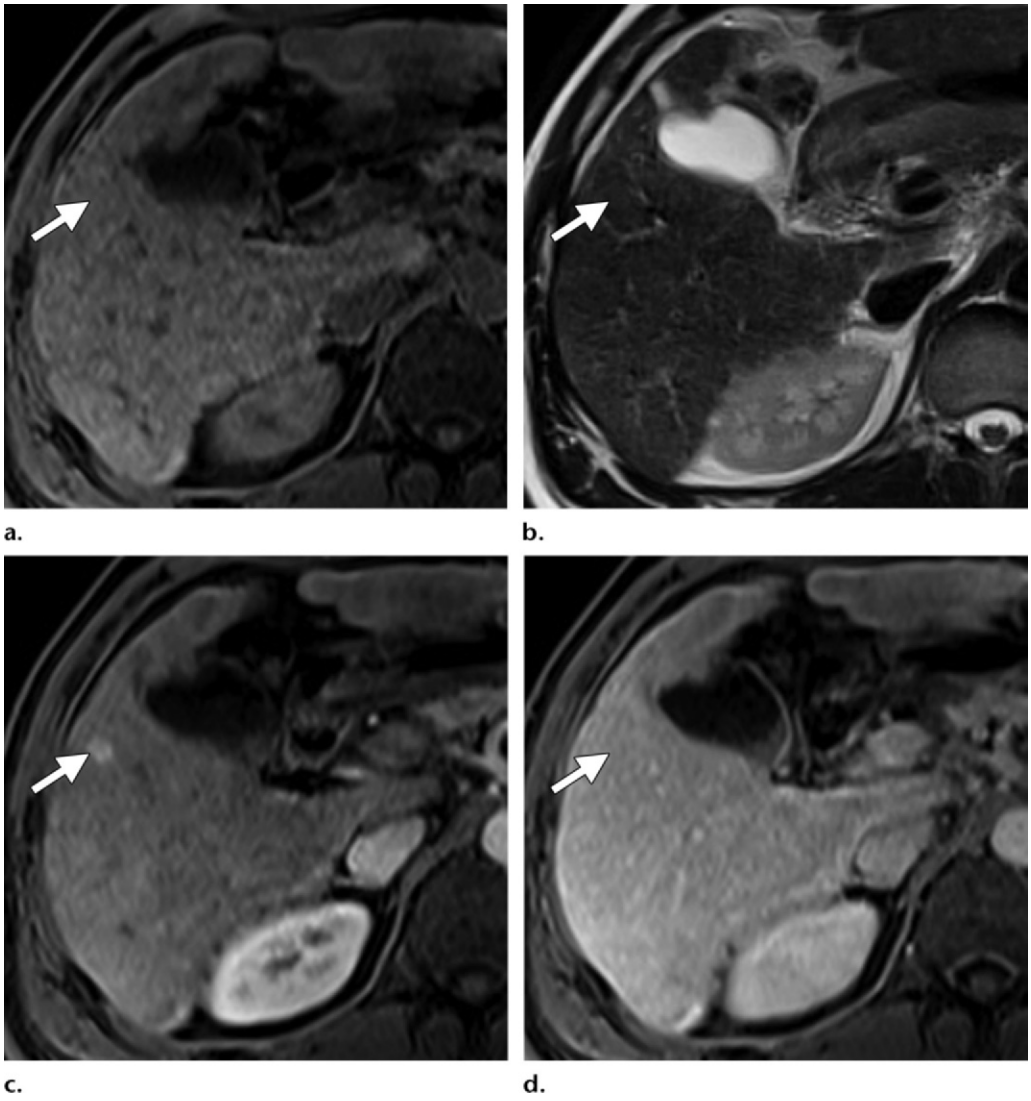


Figure 4. High-grade dysplastic nodule or small HCC in a 52-year-old man with cirrhosis resulting from hepatitis C infection. **(a, b)** Axial unenhanced T1-weighted three-dimensional (3D) spoiled gradient-echo **(a)** and contrast-enhanced T2-weighted **(b)** MR images show a small isointense nodule (arrow) in segment V of the liver. **(c)** Axial contrast-enhanced MR image obtained in the hepatic arterial phase shows intense enhancement of the nodule (arrow), a finding indicative of hypervascularity. **(d)** Axial contrast-enhanced MR image obtained in the equilibrium phase shows that the nodule (arrow) demonstrates no washout. Follow-up images showed a larger nodule that was diagnosed as HCC.

T2-weighted images. Most are hypovascular, although they may exhibit arterial enhancement similar to that seen in HCC (7,39,40). Establishing a differential diagnosis for high-grade dysplastic nodules and early HCC on the basis of imaging and pathologic characteristics may be difficult, but some pathologic markers are distinctive (Figs 4, 5) (7,8,39–41,44). Hepatobiliary and SPIO contrast agents are not useful for characterizing low- and high-grade dysplastic nodules and well-differentiated HCCs because both of these lesions enhance after administration of contrast material (34,35).

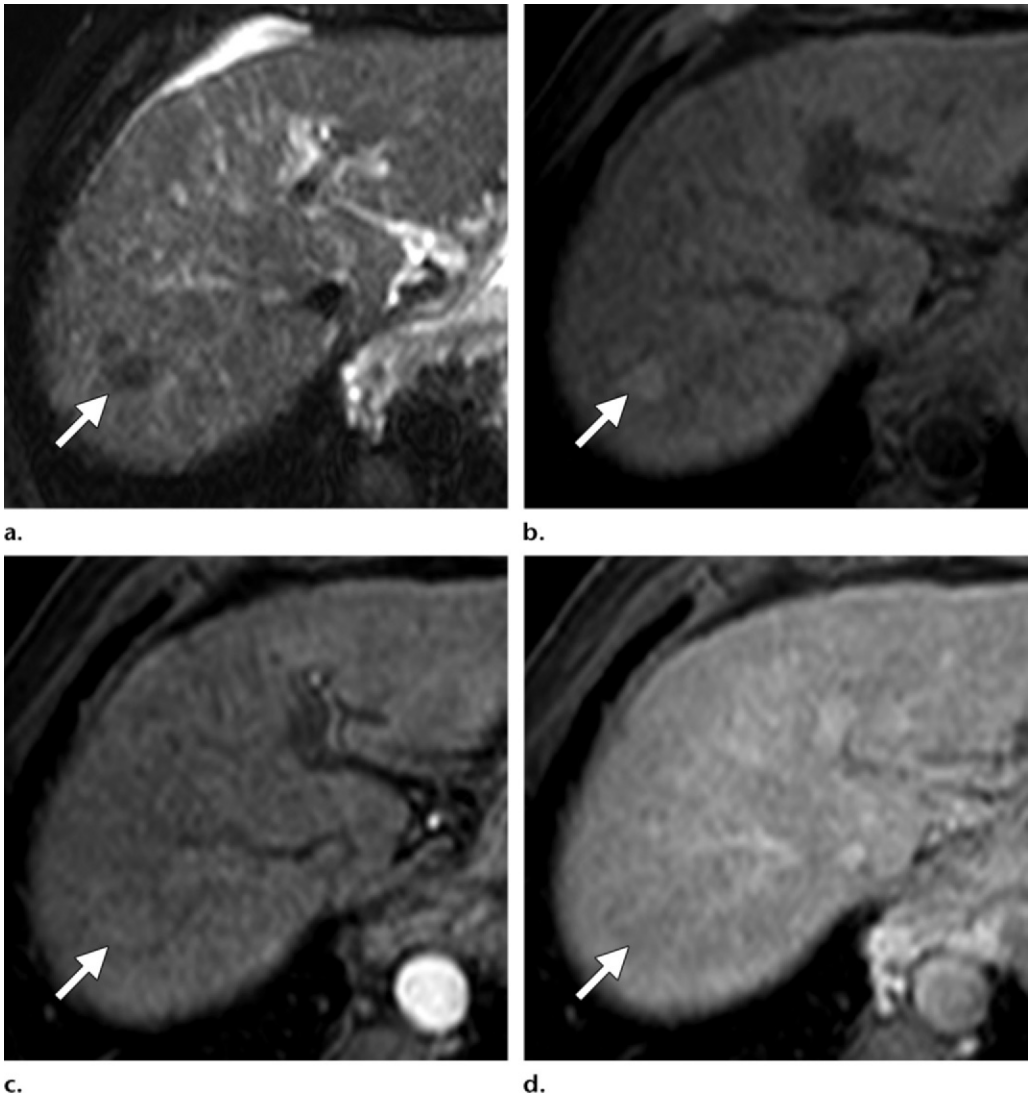


Figure 5. High-grade dysplastic nodule or early HCC in a 46-year-old man with cirrhosis resulting from hepatitis C infection. **(a)** Axial T2-weighted fat-saturated MR image shows a small hypointense nodule (arrow) in the right lobe of the cirrhotic liver. **(b)** Axial unenhanced T1-weighted spoiled gradient-echo MR image shows the nodule (arrow), which is hyperintense. **(c)** Axial T1-weighted spoiled gradient-echo MR image obtained in the arterial phase shows the nodule (arrow), which enhances as much as surrounding parenchyma. **(d)** Axial T1-weighted spoiled gradient-echo MR image obtained in the equilibrium phase shows that the nodule (arrow) demonstrates no washout.

Nodule-in-Nodule Appearance

A dysplastic nodule may harbor a focus of HCC (38,39). At T2-weighted MR imaging, such nodules appear hypointense, with the same degree of enhancement as surrounding parenchyma and a high-signal-intensity focus with arterial enhancement, a finding known as the nodule-in-nodule appearance (Fig 6) (39–41,44). The nodule-in-nodule appearance is uncommon, occurring in approximately 6% of patients with dysplastic nodules (39).

Hepatocellular Carcinoma

At histologic analysis, HCC is characterized by an abnormally high number of muscularized, unpaired arterioles and capillarized vessels (38–40). Its MR imaging appearance varies depending on its size, grade, and biologic features (8,10,34,39,40,45–47).

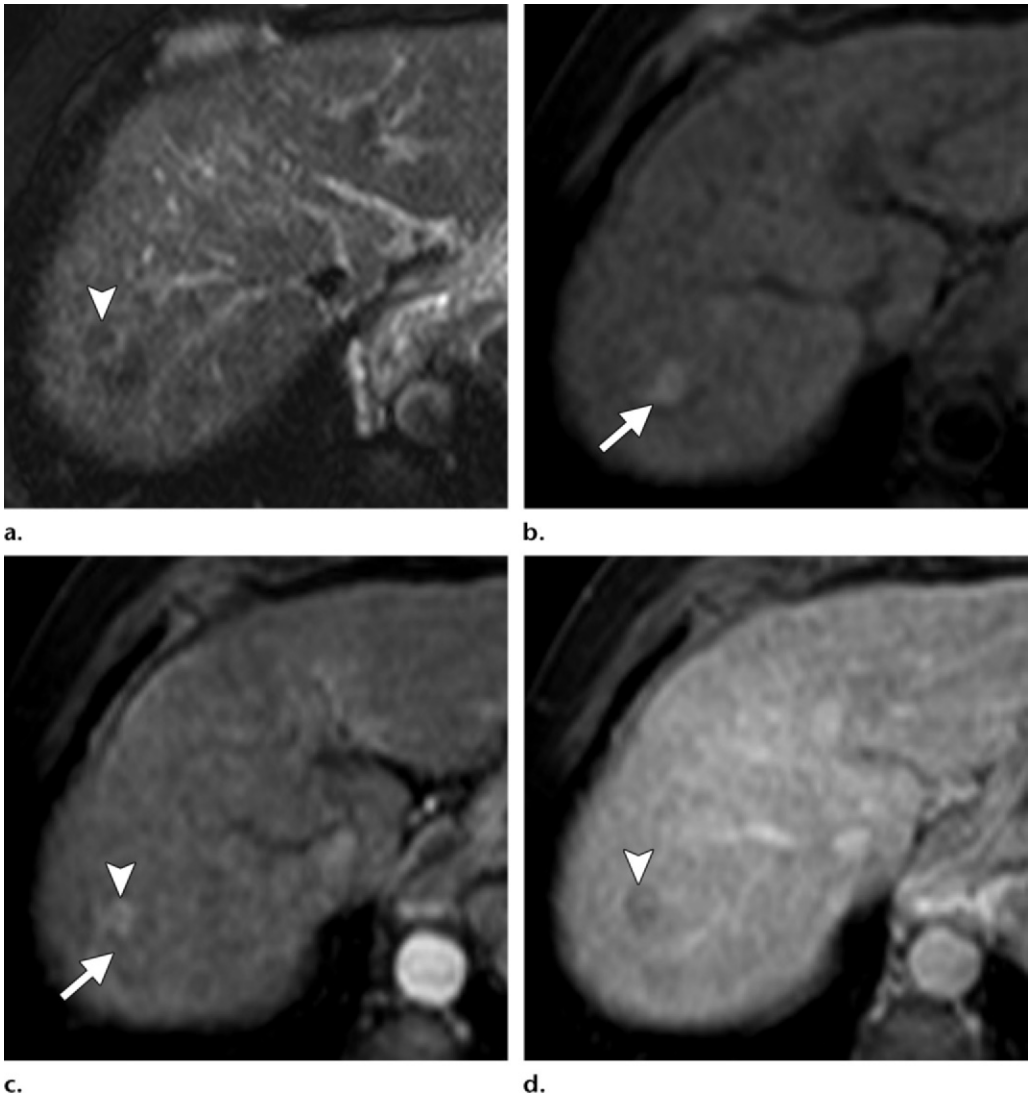


Figure 6. Nodule-in-nodule appearance at 4-month follow-up examination (same patient as in Fig 5). **(a)** Axial T2-weighted fat-saturated MR image shows a high-grade dysplastic nodule (arrowhead), the anterior portion of which is slightly hyperintense compared with previous images (cf Fig 5). **(b)** Axial unenhanced T1-weighted spoiled gradient-echo MR image shows the hyperintense nodule (arrow). **(c)** Axial T1-weighted spoiled gradient-echo MR image obtained in the arterial phase shows the nodule, the anterior portion of which is hypervascular (arrowhead). The rest of the nodule enhances similarly to the adjacent liver (arrow). **(d)** Axial T1-weighted spoiled gradient-echo MR image obtained in the equilibrium phase shows washout of the hypervascular portion of the nodule (arrowhead). These changes confirm that the nodule identified at the first examination was a high-grade dysplastic nodule that developed a focus of HCC, referred to as a nodule-in-nodule.

Small HCCs

Small HCCs are smaller than 2 cm and divided into two types: early, which are indistinctly (vaguely) nodular, and progressed, which are distinctly nodular (40,44,48). At histologic analysis, early HCCs are well-differentiated, with neoplastic cells replacing normal cells; portal tracts may be present. It is difficult to differentiate small HCCs from surrounding parenchyma. Invasion of portal tracts is frequently visible, a finding that helps distinguish early HCCs from high-grade dysplastic nodules. Early HCCs receive blood supply from a reduced number of trapped portal tracts and insufficiently developed nontriadal arteries. Cellular crowding and low blood supply cause relative hypoxia, which may cause

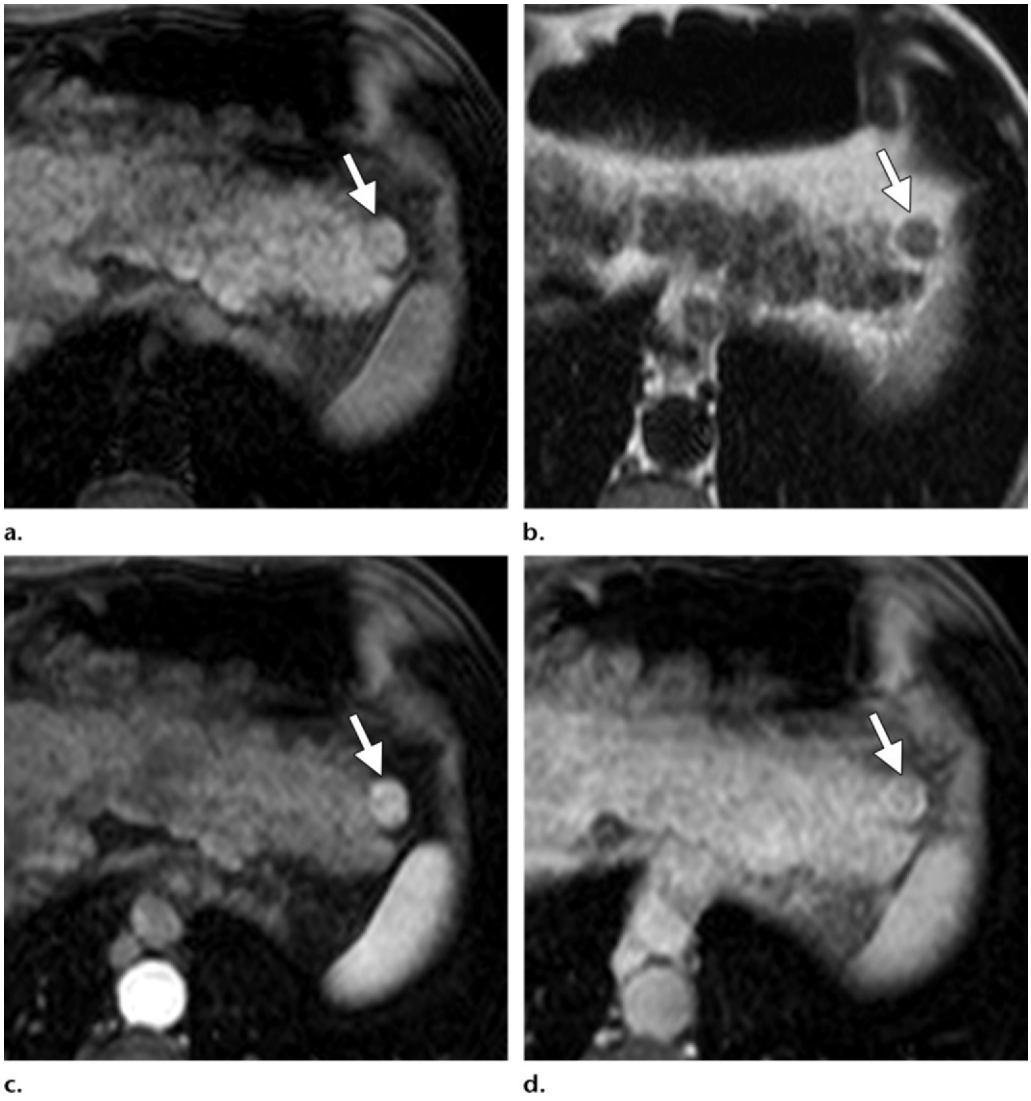


Figure 7. Small progressed HCC in a 54-year-old woman with cirrhosis resulting from hepatitis C infection. **(a)** Axial T2-weighted MR image shows a slightly hyperintense nodule (arrow) in segment II of the liver. **(b)** Axial unenhanced T1-weighted 3D spoiled gradient-echo MR image obtained in the arterial phase shows the nodule (arrow), which is small and isointense. **(c)** Axial T1-weighted spoiled gradient-echo MR image obtained in the arterial phase shows that the nodule (arrow) demonstrates intense enhancement, a finding indicative of hypervascularity. **(d)** Axial T1-weighted spoiled gradient-echo MR image obtained in the equilibrium phase shows venous washout with capsule enhancement (arrow). Despite its small size, this nodule may be diagnosed as HCC on the basis of imaging findings alone, with no biopsy or second examination.

the steatotic changes that occur in about 40% of cases of early HCC. Early HCCs are rarely associated with microscopic vessel invasion, produce no metastases, and have a 5-year survival rate of 89% (40,44,48,49). The frequency and natural history of early HCCs are poorly understood (48). They have been found to recur within 3 years of resection in only 8% of cases (49).

Imaging Findings.—Currently, a diagnosis of early HCC on the basis of imaging is unreliable. Such lesions tend to demonstrate high signal intensity on T1-weighted MR images and be hypo- or isointense on T2-weighted MR images (40). Early HCCs demonstrate relative arterial hypovascularity (most are hypo- or isointense in the arterial phase) and decreased portal supply, which is indicated by hypointensity in the portal phase. Hypovascularity is likely caused by a loss of portal vascularization and insufficient development of unpaired arteries. Such lesions are expected to demonstrate progressively increased arterialization and a continued decrease in portal blood until they become typical HCCs (Fig 5) (7). Use of hepatobiliary contrast agents has recently been shown to improve diagnosis of HCCs of all sizes (<1 cm, 1–2 cm, and >2 cm). On hepatobiliary-phase MR images, liver parenchyma that contains functioning hepatocytes demonstrates enhancement, and HCCs that contain malfunctioning hepatocytes demonstrate no enhancement and appear as hypointense lesions (50,51). However, well-differentiated small HCCs may demonstrate enhancement on hepatobiliary-phase images, a result of residual hepatocyte activity and the reason for false-negative findings in some cases. Ahn et al (50) reported that in two patients, early HCCs could only be identified on hepatobiliary-phase images. Close follow-up is recommended for patients with lesions that are smaller than 1 cm and visible only on hepatobiliary-phase images (50). Early HCCs enhance as much as surrounding parenchyma after administration of SPIO contrast agents (40). Fatty changes are visible in 40% of cases.

In contrast, progressed small HCCs have morphologic and histologic characteristics similar to those of large HCCs and are easily differentiated from the background cirrhotic liver. At histologic analysis, no portal tracts are seen, but numerous nontriadal arteries and well-developed sinusoidal capillarization are present. Microscopic vessel invasion is present in nearly 27% of cases (49). Tumor-cell invasion of portal vein branches and intrahepatic metastases may be present and are associated with a 5-year survival rate of 48% (40,44,48).

Progressed HCCs usually pose no diagnostic difficulty at MR imaging. These lesions tend to be well-defined, homogeneous, and round or oval, with variable signal intensity on T1-weighted images and, usually, moderately hyperintense signal intensity on T2-weighted images. Most nodular HCCs demonstrate typical findings after administration of gadolinium-based contrast material, with enhancement during the arterial phase and washout in the portal or delayed phase that becomes less intense than surrounding liver (Fig 7) (40,48).

Teaching Point

Early HCCs are the earliest recognizable form of HCC, although they are difficult to differentiate from high-grade dysplastic nodules. Establishing a definitive diagnosis usually requires a biopsy; however, most hypovascular HCCs and those with equivocal imaging findings are early HCCs. Progressed HCCs are small nodular lesions with characteristics similar to those of classic HCCs and usually do not pose a diagnostic problem (40,48).

Although they are critical for making treatment decisions, imaging findings are not always conclusive for small HCCs. In 2011, the American Association for the Study of Liver Disease (AASLD) updated its guidelines with the following recommendations: Small HCCs that are larger than 1 cm may be diagnosed on the basis of imaging findings (contrast-enhanced CT or MR imaging) alone when findings are typical (hypervascularity followed by washout) of HCC. Lesions that are smaller than 1 cm should be re-examined every 3 months with the technique that was used to depict the nodule; most such lesions are cirrhotic and, therefore, stable at follow-up. If the nodule is stable, patients should resume routine screening for HCC. If the nodule changes, four-phase (unenhanced, arterial, portal, and equilibrium) multidetector CT or MR imaging should be performed. Similarly, lesions larger than 1 cm should be evaluated with four-phase CT or dynamic contrast-enhanced MR imaging. Typical findings lead to a diagnosis of HCC. If an atypical appearance is present, a second examination with CT or MR imaging (whichever was not

used the first time) may be performed. Typical findings of HCC confirm the diagnosis; biopsy is recommended for patients with atypical findings (Fig 8) (7). Patients with liver nodules that have a nonspecific vascular profile and negative biopsy results should undergo enhanced follow-up imaging. If biopsy results are negative, imaging should be repeated at 3–6-month intervals until the nodule disappears, enlarges, or has findings characteristic of HCC. If the lesion enlarges but remains atypical for HCC, another biopsy is recommended. Smaller lesions are less likely to be associated with microscopic vascular invasion and are more responsive to curative treatments. Thus, HCCs should be diagnosed when they are smaller than 2 cm (7).

Clinical decisions concerning the management of nodules in patients with negative biopsy results should take into account the lack of knowledge of the natural history of early-stage HCC and the limitations and pitfalls of guided biopsy. These limitations may lead to false-negative results in as many as 10% of cases, with small foci of HCC that may be missed at histologic analysis present in at least one-third of dysplastic nodules. Different grades of dysplastic changes also may affect different parts of the nodule. Little is known of the accuracy of differential diagnoses for low- and high-grade dysplastic nodules and HCCs created on the basis of a small biopsy specimen obtained from one part of a nodule (46).

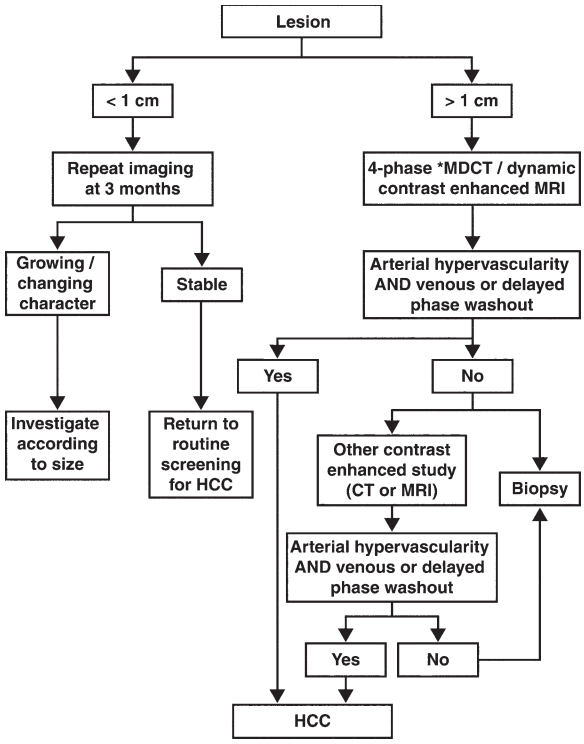


Figure 8. Chart shows the algorithm for evaluating small nodules found at screening in patients at risk for HCC. *MDCT* = multidetector CT. (Adapted and reprinted, with permission, from reference 7.)

Classification.—The Liver Imaging Reporting and Data System (LI-RADS) was recently created in an attempt to facilitate classification of liver lesions as either definitely benign (LR1) or definitely HCC (LR5). The designations of probably HCC (LR4) and probably benign (LR2) may be used to classify lesions with some, but not all, features of HCC or benignity. The designation LR3 is used for indeterminate lesions with equivocal imaging features that may not be categorized as probably benign or probably malignant (52).

Teaching Point

When evaluating nodular lesions in patients with cirrhosis, radiologists should recognize that hepatocarcinogenesis is a continuous process that has been arbitrarily divided for practical and didactic purposes. The continuous histologic changes that nodules undergo result in significant overlap of enhancement patterns and findings on T1- and T2-weighted MR images, complicating their imaging and histopathologic differential diagnosis. Differences in the histologic criteria that are used to characterize hepatocellular nodules and changes in nomenclature over time have also contributed to the overlap in histologic findings. As nodules dedifferentiate, portal vascularization progressively decreases, and blood supply from nontriadal arteries increases. At imaging, this process is seen as a progressive change from enhancement similar to that of the adjacent liver to a loss of portal vascularization that appears as an area of hypoenhancement in the portal phase, followed by an increase in the number of hypervascular nontriadal arteries in the arterial phase. Lesions that exhibit enhancement similar to that of the adjacent liver are probably regenerative and low-grade dysplastic nodules. A diagnosis of HCC may be made when hypervascularity is followed by washout at imaging. However, nodules with a loss of portal supply and development of an insufficient number of nontriadal arteries to produce hypervascularity are difficult to diagnose. These equivocal findings of high-grade dysplastic nodule and early HCC are responsible for the high rate of false-negative imaging and histologic results.

Teaching Point

There are some features that help classify cirrhotic nodules. For instance, size is an important parameter. Although nodules that are smaller than 1 cm are probably benign and nodules larger than 2 cm are probably malignant, nodules that are between 1 and 2 cm are difficult to classify. Nodules that demonstrate interval growth are suspicious for HCC. Regenerative nodules, low- and high-grade dysplastic nodules, and early HCCs have variable signal intensity on T1-weighted images; however, well-differentiated HCCs tend to be hyperintense. Hyperintensity on T2-weighted images is highly specific to HCCs and is rarely present in small lesions. Regenerative and low-grade dysplastic nodules demonstrate enhancement similar to that of adjacent liver, whereas high-grade dysplastic nodules and early HCCs tend to be hypovascular; high-grade dysplastic nodules and early HCCs also may demonstrate arterial enhancement. Capsular enhancement and internal mosaic architecture are also highly specific to HCCs and are rarely seen in small nodules. The presence of fatty changes in a dominant nodule is also suspicious for HCC.

Case Scenarios.—The following five case scenarios are presented for practical purposes.

1. A cirrhotic liver that demonstrates homogeneous enhancement on contrast-enhanced images but lacks a dominant nodule on T1- and T2-weighted MR images probably contains only regenerative and low-grade dysplastic nodules.

2. A dominant nodule that is hyperintense on T1-weighted MR images and iso- or hypointense on T2-weighted images with enhancement similar to that of the surrounding liver probably represents a regenerative or low-grade dysplastic nodule or, less likely, a high-grade dysplastic nodule. If it becomes hypovascular, it has probably progressed to a high-grade dysplastic nodule or early HCC, and if it demonstrates high signal intensity on T2-weighted images, a progressed HCC should be suspected. When it demonstrates hypervascularity with washout, a diagnosis of HCC may be made on the basis of imaging findings alone.

3. A nodule that is hyperintense on T1-weighted MR images and iso- or hypointense on T2-weighted images with arterial enhancement and no washout is probably a high-grade dysplastic nodule or early HCC. In contrast, the absence of a nodule on T1- and T2-weighted images and the presence of arterial enhancement with no washout may indicate transient arterial enhancement.

4. A rarer lesion is the nodule-in-nodule (ie, a dysplastic nodule with an HCC focus), which classically manifests as a low-signal-intensity nodule on T2-weighted MR images with a hyperintense focus that enhances in the arterial phase.

5. A nodule that is hyperintense on T2-weighted MR images with arterial enhancement and venous washout may be diagnosed as HCC.

Teaching Point

The likelihood of a nodule being HCC increases with its size; nodules smaller than 1 cm have low likelihood. Thus, recently updated guidelines recommend that patients with indeterminate nodules smaller than 1 cm should be monitored. Nodules larger than 2 cm are likely malignant, whereas those between 1 and 2 cm should be closely monitored with imaging and repeated biopsy (Fig 8) (5,7).

Large HCCs

Large HCCs have a characteristic MR imaging appearance and are usually diagnosed with no difficulty. They typically are hypointense on T1-weighted images and moderately hyperintense on

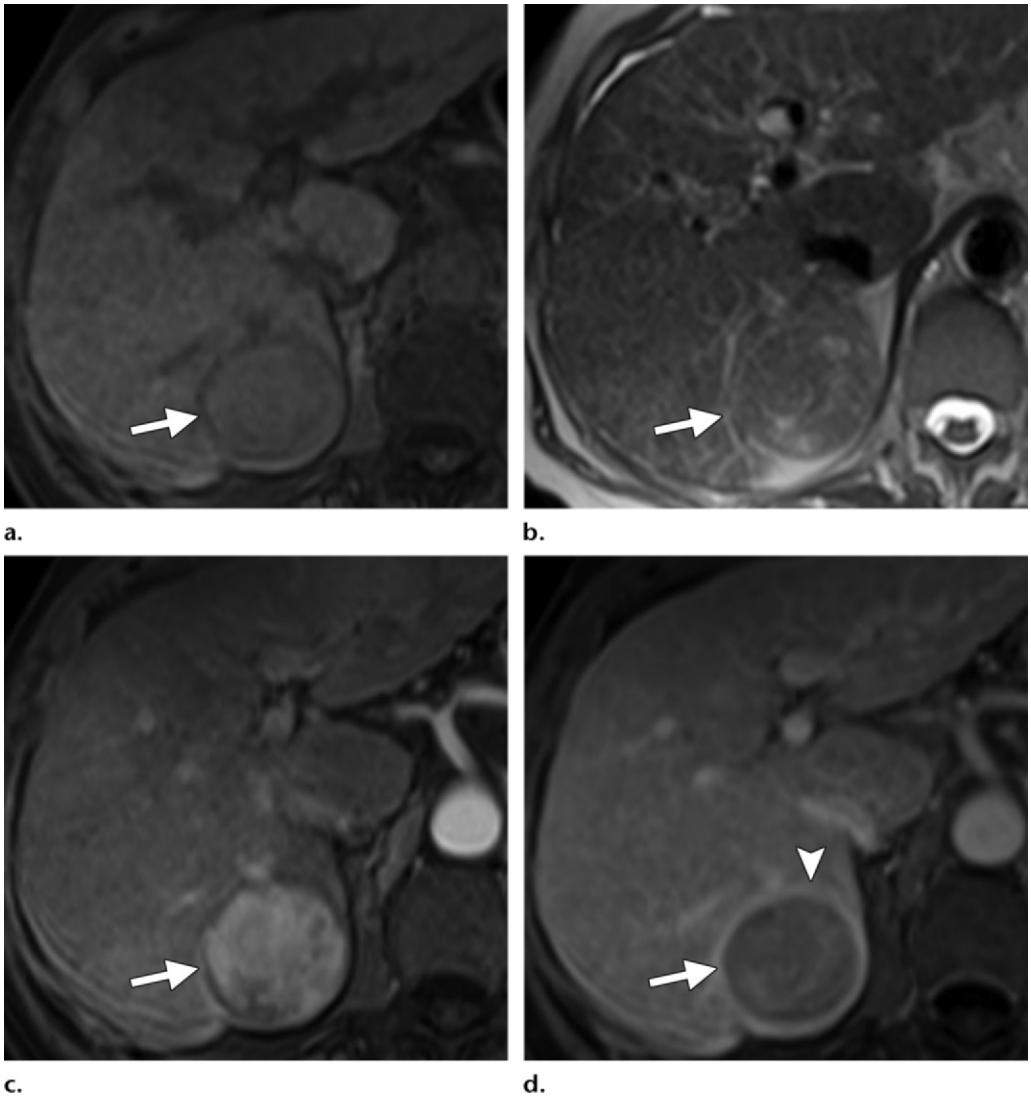
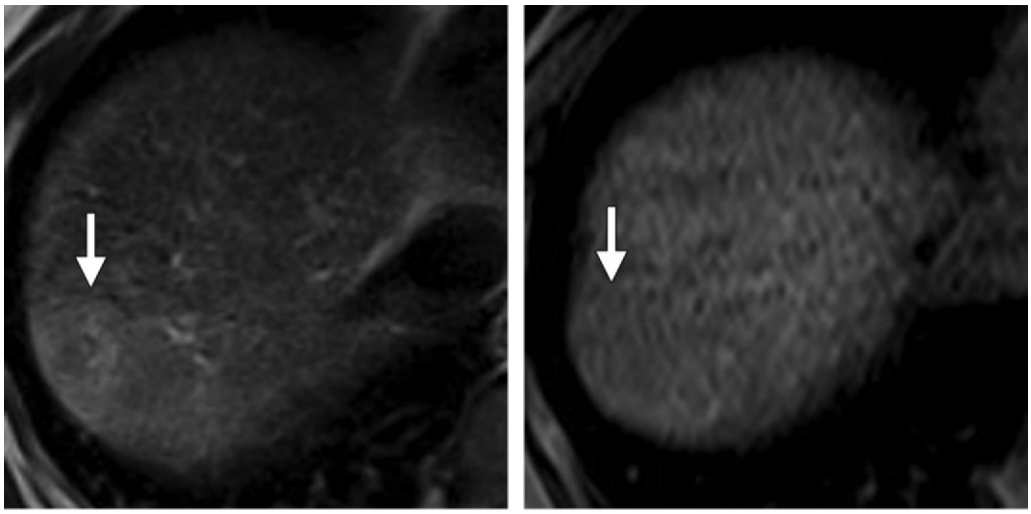


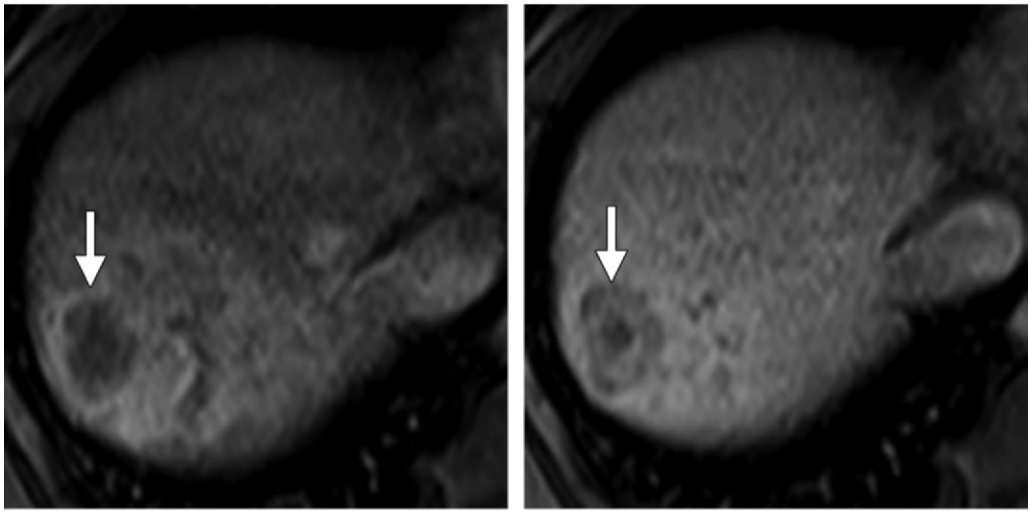
Figure 9. Large HCC in a 55-year-old man with cirrhosis resulting from hepatitis C infection. **(a)** Axial T2-weighted MR image shows a heterogeneous mass (arrow) with slightly high signal intensity in segment VII, abutting the liver capsule. **(b)** Axial T1-weighted spoiled gradient-echo MR image shows that the mass is isointense (arrow). **(c)** Axial T1-weighted spoiled gradient-echo MR image obtained in the arterial phase shows heterogeneous hypervascular enhancement of the mass (arrow). **(d)** Axial T1-weighted spoiled gradient-echo MR image obtained in the equilibrium phase shows washout (arrow). A thin circumferential hypointense rim (arrowhead) is seen around the periphery of the tumor, a finding indicative of a capsule, with typical late enhancement after administration of gadolinium-based contrast material.

T2-weighted images, with arterial enhancement and washout in the portal or delayed phase. They may be heterogeneous, have a mosaic pattern with patchy internal areas of hyperintensity on T2-weighted images, have variable signal intensity on T1-weighted images, or demonstrate inhomogeneous enhancement after administration of gadolinium-based contrast material (Fig 9) (8,39,41). Atypical manifestations are uncommon. Rarely, an HCC that is larger than 2 cm may be hypovascular; such cases require biopsy in order to make a diagnosis (Fig 10) (7).

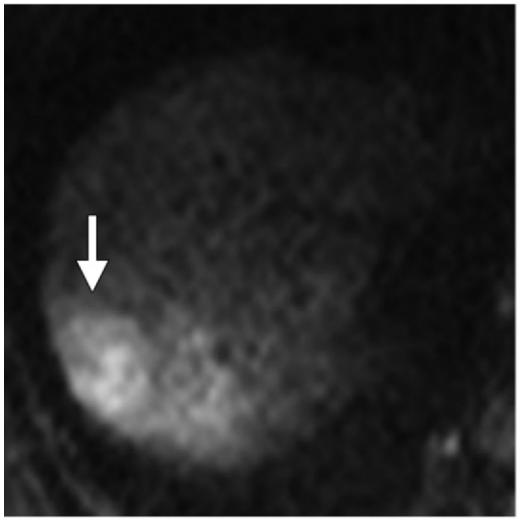
Large HCCs usually appear as heterogeneous lesions at MR imaging, with variable signal intensity depending on their content. Intralesional fat, hemorrhage, or necrosis may be present. Intralesional fat is characterized by signal loss on



a. b.



c. d.



e.

Figure 10. Biopsy-proved hypovascular HCC in a 58-year-old woman with cirrhosis resulting from hepatitis C infection. **(a)** Axial T2-weighted MR image shows a slightly high-signal-intensity nodule (arrow) in the dome of the liver. **(b)** Axial unenhanced T1-weighted fat-saturated 3D spoiled gradient-echo MR image shows that the nodule (arrow) is isointense. **(c, d)** Axial unenhanced T1-weighted fat-saturated 3D spoiled gradient-echo MR images obtained in the arterial **(c)** and equilibrium **(d)** phases show that the nodule (arrow) is mainly hypovascular. **(e)** Axial respiration-triggered fat-suppressed single-shot spin-echo echo-planar diffusion-weighted MR image (b = 800 s/mm^2) shows restricted diffusion within the nodule (arrow).

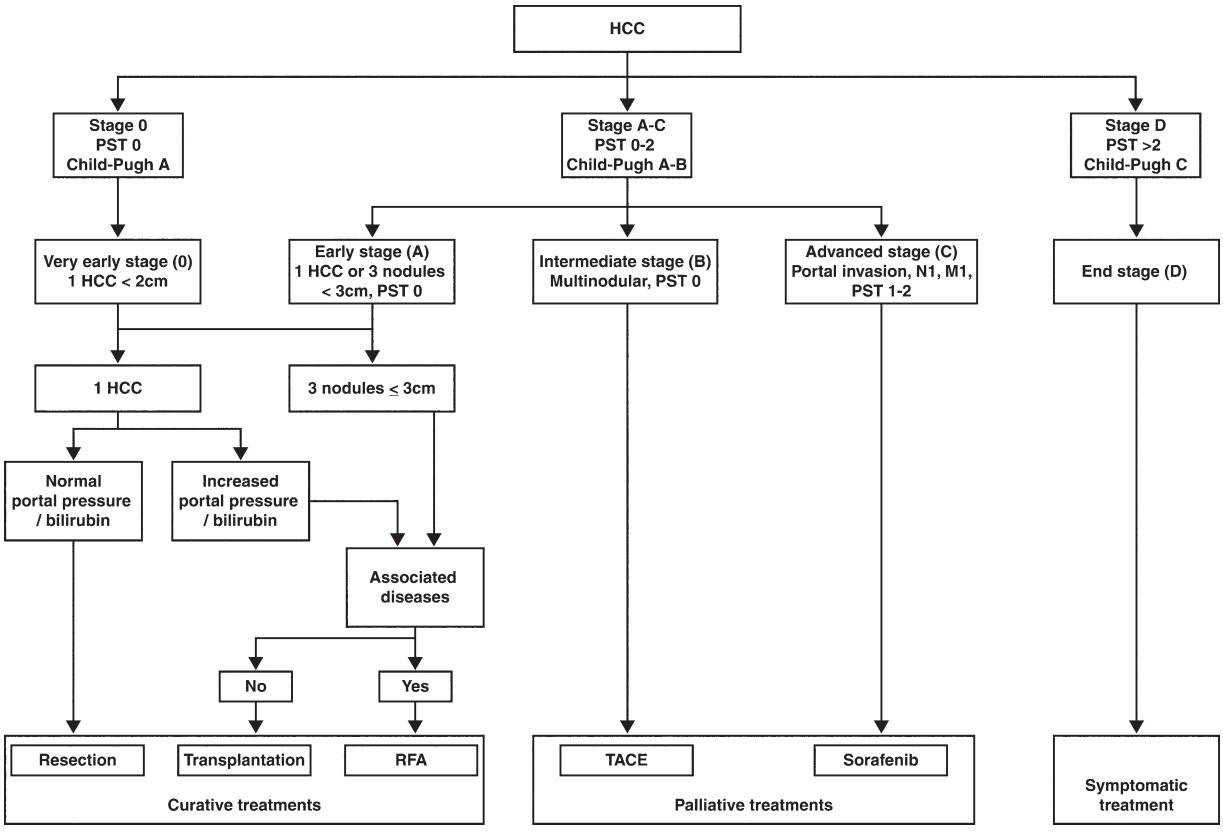


Figure 11. Chart shows the Barcelona Clinic Liver Cancer staging and treatment allocation system. *PST* = performance status test, *RFA* = radiofrequency ablation, *TACE* = transcatheter arterial chemoembolization. (Adapted and reprinted, with permission, from reference 7.).

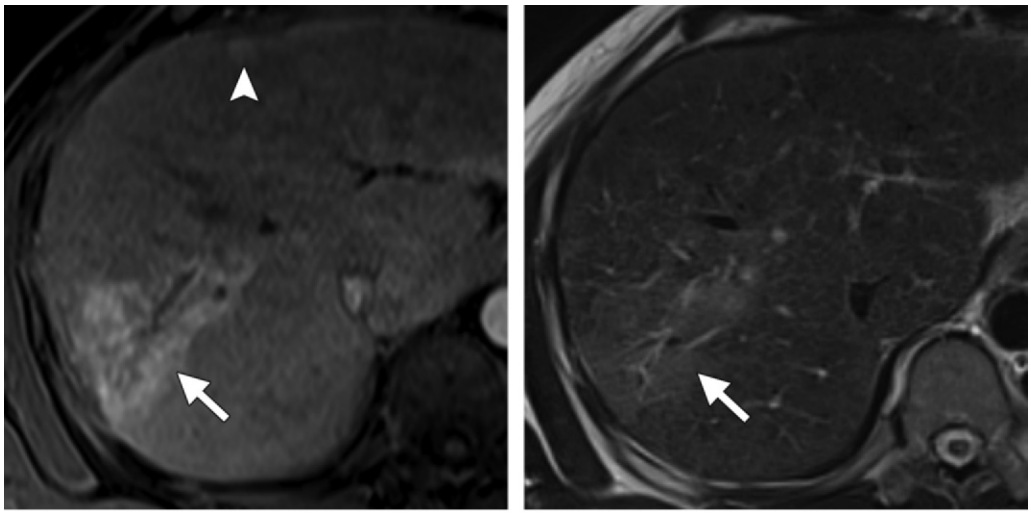
out-of-phase images (compared with in-phase images) and low signal intensity on fat-saturated images. Because the fat component usually enhances differently than the rest of the lesion, it usually does not demonstrate hypervascularity after gadolinium-based contrast material is administered, but some enhancement may be seen (53). The hemorrhage component of HCCs is hyperintense on T1-weighted images and hypointense on T2-weighted images. Intralesional necrosis is hypointense on T1-weighted images and hyperintense on T2-weighted images with no enhancement (8,10,34,45,54,55).

Most large HCCs (65%–82%) have a capsule composed of fibrous tissue and compressed vessels that appears as a thin circumferential rim around the periphery of the tumor and is usually hypointense on T1- and T2-weighted images, with typical late enhancement after administration of gadolinium-based contrast material (Figs 7, 9). Capsules that are thicker than 4 mm may be hyperintense on T2-weighted images (8,10,34,45,54).

Uptake of hepatobiliary and SPIO contrast agents varies according to the degree of differentiation. Poorly differentiated HCCs do not enhance (compared with surrounding liver) after administration of hepatobiliary agents or accumulate SPIO agents; thus, they are more apparent on contrast-enhanced images. Well-differentiated HCCs demonstrate enhancement similar to that of adjacent liver parenchyma after administration of hepatobiliary and SPIO contrast agents and may not be depicted on contrast-enhanced images (34,35).

Treatment of Cirrhotic Nodules

Radiologists play a central role in making treatment decisions for patients with cirrhosis. Algorithms for the follow-up of patients with cirrhotic nodules and guidelines for treatment in those with HCC are developed on the basis of imaging findings. An erroneous diagnosis of HCC has important implications for patient care. According to the Barcelona Clinic Liver Cancer ((BCLC) system, patients with stage 0 HCC (<2 cm) and no vascular invasion or spread and those with stage A HCC (a solitary tumor <5 cm or as many as three nodules that are <3 cm) should undergo curative treatment such as ablation, resection, or transplantation; 5-year survival rates for patients with



a. b.

Figure 12. Transient arterial enhancement in a 45-year-old man with hepatitis C infection–related cirrhosis secondary to portal vein thrombosis. **(a)** Axial MR image obtained in the arterial phase shows a small area of homogeneous enhancement (arrowhead) in segment IV of the liver. A wedge-shaped area of enhancement (arrow), with the wide base toward the periphery, is also seen. **(b)** T2-weighted MR image shows a corresponding slightly hyperintense area indicative of a perfusion defect (arrow), a finding that is not as rare as commonly thought.

stage 0 or A HCC are 50%–75% (56). Patients with stage B HCC (large or multinodular tumor with no vascular invasion, extrahepatic spread, or cancer-related symptoms), particularly those with compensated cirrhosis, should undergo chemoembolization; among these patients, expected 3-year survival rates are 50%. Patients with stage C HCC (advanced tumor with vascular involvement, extrahepatic spread, or physical impairment) should enroll in research trials to assess new antitumoral agents; these patients have 3-year survival rates of less than 10%. Finally, patients with stage D HCC (impaired physical status or excessive tumor burden and severe liver impairment) should undergo symptomatic treatment only; among patients with stage D HCC, 1-year survival rates are less than 10% (Fig 11) (56).

Other Conditions That May Mimic Hepatic Lesions

Transient Arterial Enhancing Lesions

Nonspecific, transient, arterially enhancing lesions must be differentiated from small HCCs. The most common conditions that cause transient hepatic arterial enhancement are spontaneous or postbiopsy arterioportal shunting and pseudoaneurysm, HCC neovascularity, portal vein compression, and tumoral or nontumoral portal vein thrombosis. Arterioportal shunting and pseudoaneurysm may occur spontaneously in the cirrhotic liver or form secondary to biopsy or ablation and are usually peripheral with a wedge-shaped area of enhancement, and they are isointense relative to surrounding parenchyma on T1- and T2-weighted MR images and in the equilibrium phase. Less often, they may be nodular or have an irregular outline. Moreover, such lesions may be mildly hyperintense on T2-weighted images and associated with mild, prolonged parenchymal enhancement. In HCC, neovascularization may appear as an area of arterial hypervascularity surrounding the malignancy. This area of enhancement may be ill-defined and lead to overestimation of tumor size in the arterial phase. Blood flow in portal veins may be reduced, a result of thrombosis or compression by a focal lesion. Portal vein thrombosis may result from tumor or direct invasion of the HCC or have a nontumoral cause, such as blood flow changes secondary to cirrhosis. In these cases, transient arterial enhancement is caused by occlusion or compression of the portal vein with reduced portal vascularity and a compensatory increase in arterial supply. Transient arterial enhancement is seen as a wedge-shaped area that conforms to the segment or lobe with reduced portal supply (Fig 12) (41,57–62).

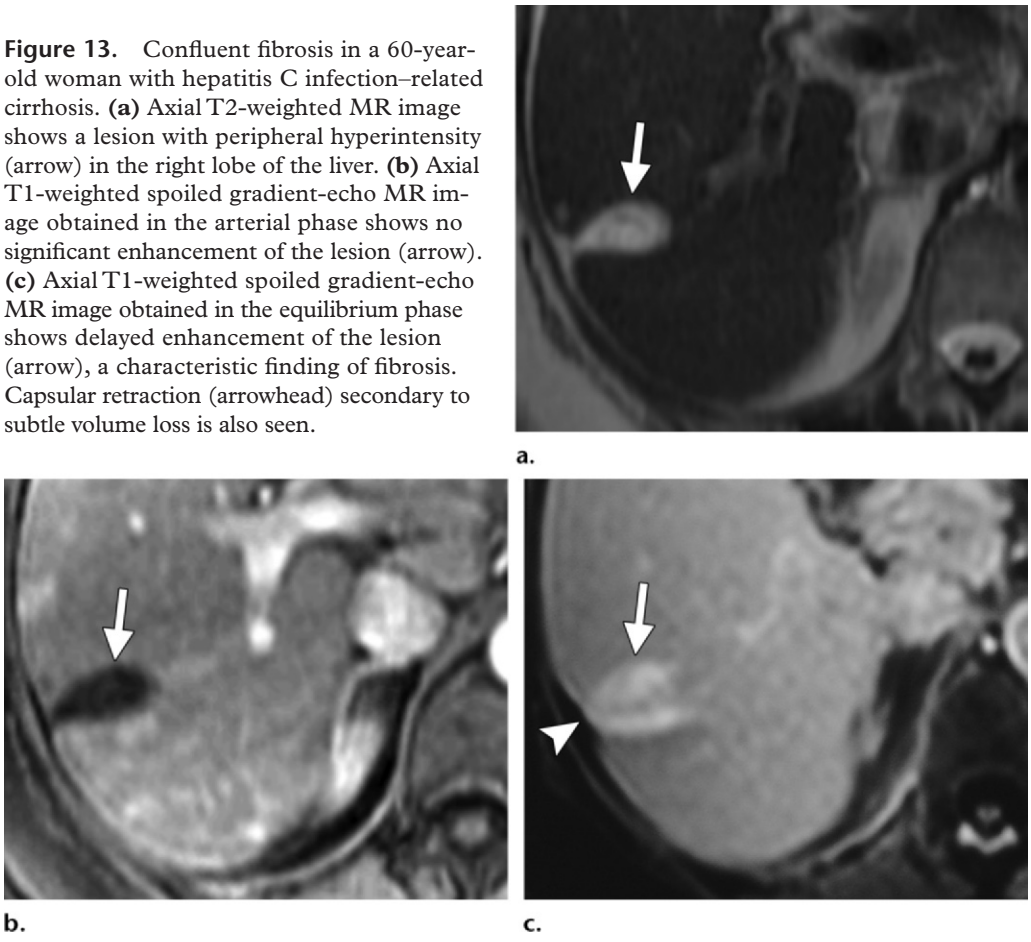


Figure 13. Confluent fibrosis in a 60-year-old woman with hepatitis C infection–related cirrhosis. **(a)** Axial T2-weighted MR image shows a lesion with peripheral hyperintensity (arrow) in the right lobe of the liver. **(b)** Axial T1-weighted spoiled gradient-echo MR image obtained in the arterial phase shows no significant enhancement of the lesion (arrow). **(c)** Axial T1-weighted spoiled gradient-echo MR image obtained in the equilibrium phase shows delayed enhancement of the lesion (arrow), a characteristic finding of fibrosis. Capsular retraction (arrowhead) secondary to subtle volume loss is also seen.

Confluent Fibrosis

Focal confluent hepatic fibrosis occurs in end-stage liver disease and must be differentiated from HCC. It is characteristically wedge shaped, with the wide base oriented toward the liver capsule, and is associated with atrophy of the affected segment and capsular retraction. Typically, fibrotic lesions are located in the anterior and medial segments of the liver. Focal confluent fibrosis is usually hypointense on T1-weighted MR images and hyperintense on T2-weighted images, with delayed contrast enhancement (Fig 13). Infrequently, confluent fibrosis may enhance in the arterial phase, a finding that mimics neoplasm; in such cases, biopsy is necessary to make a diagnosis. The characteristic shape, location, volume loss, and delayed enhancement of confluent fibrosis may help in the diagnosis of this condition (41,63–66). Focal confluent fibrosis also lacks Kupffer cells and may mimic HCC on SPIO contrast-enhanced images (8).

Hemangiomas

Hemangiomas rarely occur in end-stage cirrhosis, probably because the cirrhosis obliterates existing hemangiomas. When present in the cirrhotic liver, they are often atypical and contain large areas of fibrosis (41). They do not wash out and instead remain isointense relative to the hepatic vasculature in multiple phases (65,67).

Rarely, other types of lesions—such as focal nodular hyperplasia or focal nodular hyperplasia–like nodules, hepatic adenoma, hypervascular metastases, Budd-Chiari–associated nodules, and intrahepatic cholangiocarcinoma—complicate the differential diagnosis of cirrhotic liver nodules (68–75). These lesions may be differentiated from HCC on the basis of clinical history and imaging findings (70).

Conclusions

Accurate diagnosis relies on radiologists' familiarity with the multistep process of HCC development and the imaging findings associated with each stage. The major changes that characterize the progression of regenerative nodules through the steps of HCC development are progressive loss of portal vascularity and increased arterial blood flow (40,44,48). Regenerative nodules and low-grade dysplastic nodules are predominantly portally perfused and enhance as much as surrounding liver after administration of gadolinium-based contrast material (8,41). New vessel formation characterizes the progression of nodule development. Vascular patterns change gradually, with some high-grade dysplastic nodules and most HCCs exhibiting an increasing shift from predominantly venous perfusion to predominantly arterial perfusion. The major shift in angiogenesis typically occurs during the transition from low- to high-grade dysplasia (40). Early small HCCs are usually composed of well-differentiated hepatocytes, challenging diagnosis on the basis of dynamic imaging and biopsy results, and are associated with a high rate of false-negative results. Some small HCC nodules demonstrate no hypervascularity. Progressed small HCCs and large HCCs usually have typical imaging findings (hypervascularity followed by washout); however, in the absence of typical findings, differentiating among cirrhotic liver nodules is difficult and remains a challenge, even for experienced radiologists.

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MR Imaging of Hypervascular Lesions in the Cirrhotic Liver: A Diagnostic Dilemma

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Typical HCCs may be diagnosed at imaging. The algorithm for evaluating small nodules found during screening of patients at risk for HCC was recently changed: Now, a nodule larger than 1 cm that demonstrates arterial enhancement followed by washout at computed tomography (CT) or magnetic resonance (MR) imaging may be diagnosed as HCC (7,11,12).

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Early HCCs are the earliest recognizable form of HCC, although they are difficult to differentiate from high-grade dysplastic nodules. Establishing a definitive diagnosis usually requires a biopsy; however, most hypovascular HCCs and those with equivocal imaging findings are early HCCs. Progressed HCCs are small nodular lesions with characteristics similar to those of classic HCCs and usually do not pose a diagnostic problem (40,48).

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When evaluating nodular lesions in patients with cirrhosis, radiologists should recognize that hepatocarcinogenesis is a continuous process that has been arbitrarily divided for practical and didactic purposes. The continuous histologic changes that nodules undergo result in significant overlap of enhancement patterns and findings on T1- and T2-weighted MR images, complicating their imaging and histopathologic differential diagnosis.

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As nodules dedifferentiate, portal vascularization progressively decreases, and blood supply from nontriadal arteries increases. At imaging, this process is seen as a progressive change from enhancement similar to that of the adjacent liver to a loss of portal vascularization that appears as an area of hypoenhancement in the portal phase, followed by an increase in the number of hypervascular nontriadal arteries in the arterial phase. Lesions that exhibit enhancement similar to that of the adjacent liver are probably regenerative and low-grade dysplastic nodules. A diagnosis of HCC may be made when hypervascularity is followed by washout at imaging. However, nodules with a loss of portal supply and development of an insufficient number of nontriadal arteries to produce hypervascularity are difficult to diagnose. These equivocal findings of high-grade dysplastic nodule and early HCC are responsible for the high rate of false-negative imaging and histologic results.

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The likelihood of a nodule being HCC increases with its size; nodules smaller than 1 cm have low likelihood. Thus, recently updated guidelines recommend that patients with indeterminate nodules smaller than 1 cm should be monitored. Nodules larger than 2 cm are likely malignant, whereas those between 1 and 2 cm should be closely monitored with imaging and repeated biopsy (Fig 8) (5,7).