Radiology

CT and MR Imaging Diagnosis and Staging of Hepatocellular Carcinoma. Part II. Extracellular Agents, Hepatobiliary Agents, and Ancillary Imaging Features[1]

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Computed tomography (CT) and magnetic resonance (MR) imaging play critical roles in the diagnosis and staging of hepatocellular carcinoma (HCC). The second article of this two-part review discusses basic concepts of diagnosis and staging, reviews the diagnostic performance of CT and MR imaging with extracellular contrast agents and of MR imaging with hepatobiliary contrast agents, and examines in depth the major and ancillary imaging features used in the diagnosis and characterization of HCC.

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Learning Objectives:

After reading the article and taking the test, the reader will be able to:

- Describe the essential elements for diagnosis and staging of hepatocellular carcinoma (HCC)
- Describe the major and ancillary CT and MR imaging features used in the diagnosis and characterization of HCC
- Discuss the advantages and disadvantages of extracellular and hepatobiliary agents for diagnosis and staging of HCC

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This two-part review discusses the current state of the art for computed tomography (CT)- and magnetic resonance (MR) imaging–based diagnosis and staging of hepatocellular carcinoma (HCC). The first article reviewed basic background material including HCC epidemiology, key concepts in hepatocarcinogenesis, CT and MR imaging technique, and the CT and MR imaging appearance of cirrhotic nodules, low-grade dysplastic nodules, and high-grade dysplastic nodules. This second article builds on these concepts and reviews in detail the diagnosis and staging of HCC using CT and MR imaging. In the article, we focus on CT and MR imaging because these currently are the most important modalities for HCC diagnosis and staging. Other imaging methods have been advocated for these purposes, including contrast material–enhanced ultrasonography (1), CT hepatic angiography and CT arterial portography (2), MR imaging with Kupffer cell agents (3), and positron emission tomography (4), but these modalities are utilized mainly as supplementary tests for select indications, not performed in many parts of the world, and hence not discussed here. While the emphasis is on diagnosis and staging, this article also reviews emerging roles of CT and MR imaging for predicting HCC tumor grade and other important biologic properties.

Essentials

- Current management guidelines recommend multiphasic CT or MR imaging with extracellular agents for diagnosis and staging of hepatocellular carcinoma (HCC); unlike most cancers, in which imaging findings are confirmed by tissue sampling prior to therapy, imaging may be used to establish diagnosis of HCC noninvasively, and treatment, including major surgical options such as hepatic resection and liver transplantation, may be initiated without confirmatory biopsy.
- The hallmark diagnostic features of HCC at multiphasic CT or MR imaging are arterial phase hyperenhancement followed by portal venous or delayed phase washout appearance; in patients with cirrhosis or other risk factors for HCC, this temporal enhancement pattern provides near 100% specificity for diagnosis of HCC.
- Another imaging feature characteristic of progressed HCC is capsule appearance; the combination of arterial phase hyperenhancement and capsule appearance strongly suggests the diagnosis of HCC, even in the absence of washout appearance.
- Cirrhosis-associated nodules that are hypointense in the hepatobiliary phase are likely to be malignant or premalignant, even in the absence of arterial phase hyperenhancement or venous phase "washout."
- Accumulating evidence suggests MR imaging with hepatobiliary agents may be the most sensitive method for detecting small HCCs and premalignant lesions likely to progress to overt HCC, but confirmatory studies, especially in patients with advanced cirrhosis, are needed.

Diagnosis and Staging: Basic Concepts

Diagnosis

Unlike most cancers, in which imaging findings are confirmed by means of tissue sampling prior to therapy, imaging may be used to establish the diagnosis of HCC noninvasively, and treatment, including major surgical options such as hepatic resection and liver transplantation, may be initiated without confirmatory biopsy (5). The rationale is that in well-defined high-risk populations (eg, patients with cirrhosis), some imaging features permit diagnosis of HCC with a positive predictive value approximating 100%, while biopsy has many limitations for HCC diagnosis and staging such as frequent false-negative results in small HCCs (6,7) and impracticability for evaluating multiple lesions concurrently. It also has a number of attendant risks including needle tract seeding (2.7%) and bleeding complications (0.5%). According to current guidelines (8–11), biopsy is reserved for indeterminate nodules that do not satisfy radiologic criteria for HCC. Implicit in imaging-based diagnosis is the differentiation of HCC from nonmalignant cirrhosis-associated nodules (eg, cirrhotic nodules, low-grade dysplastic nodules, high-grade dysplastic nodules) and benign lesions and pseudolesions that may be encountered in the cirrhotic liver (eg, small hemangiomas, perfusion alterations, focal or confluent fibrosis). Also important is differentiation of HCC from nonhepatocellular malignancies that may occur in the cirrhotic liver (12). Among these, differentiation from mass-forming intrahepatic cholangiocarcinoma (ICC) is particularly important. As mentioned in part I, patients with cirrhosis and viral hepatitis have elevated risk for developing ICC as well as HCC, and ICC may account for up to 5% of cancers in these patients (13). Unlike HCC, however, it tends to disseminate systemically early in its course, and patients with ICC usually are not eligible for liver transplantation (14). Thus, it is not sufficient to use imaging to establish the diagnosis of a malignant liver tumor; it needs to establish the diagnosis of HCC specifically.

Staging

Staging systems are key to predict the prognosis of patients with cancer, to stratify the patients according to prognostic variables in the setting of clinical trials, to allow exchange of information

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Abbreviations:
ADC = apparent diffusion coefficient
GRE = gradient echo
HCC = hepatocellular carcinoma
ICC = intrahepatic cholangiocarcinoma
3D = three-dimensional

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among researchers, and to guide the therapeutic approach (15). In general, the prognosis of solid tumors is greatly affected by tumor stage. In HCC patients, however, prognosis assessment is complicated due to the geographic and biologic heterogeneity of the disease and lack of consensus on how to best classify patients. To assess the prognosis of HCC patients it may be necessary to take into consideration not only the tumor stage but also liver function, physical status, and treatment efficacy (16). Conventionally HCC has been classified by the TNM (tumor-node-metastasis) or Okuda staging systems. The TNM system is based on data from patients who underwent curative resections and its use is limited because liver function is not considered (17). The Okuda classification takes tumor size and the degree of underlying cirrhosis into account, but it has limitations in stratifying patients with early or intermediate stage disease (15,18). Several new systems have been proposed recently to incorporate tumor stage, liver function, and physical status (15). Among them the Barcelona Clinic Liver Cancer (BCLC) staging system links the stage of the disease to a specific treatment strategy (19). There is a corresponding treatment schedule for each stage, ranging from curative therapies to best supportive care. It has been suggested that this system is best suited for treatment guidance and particularly to select patients with early stage disease who could benefit from curative therapies (5). However, a limitation of the BCLC system is lack of discrimination within the intermediate stage (BCLC-B), as this stage encompasses a broad clinical spectrum with potential for prognostic heterogeneity (20).

Although there is no universal agreement on the best staging that can be recommended worldwide, most current systems incorporate radiologic staging. Radiologic staging refers to the imaging-based determination of the number and size of HCC nodules within the liver as well as the presence of macrovascular invasion and extrahepatic metastases (21). Although there are minor differences between the systems in how the stage is determined by the size and number of nodules, radiologic staging is used to inform clinical decision making, optimize treatment strategies, and determine eligibility and priority for liver transplantation (5,22). Patients with macrovascular invasive HCC or extrahepatic metastases are not eligible for liver transplantation, while those with one 2–5-cm HCC nodule or with two to three HCCs nodules measuring up to 3 cm may be assigned priority for transplantation (22). According to Organ Procurement and Transplantation Network policy, only nodules that satisfy imaging criteria for definite HCC or that are proven by means of biopsy to be HCC contribute to the staging (22). Imaging-detected nodules that are suspicious but not diagnostic for HCC usually are ignored for staging purposes. Detection of microvascular invasion and differentiation of the two causes of multifocality (intrahepatic metastasis or multicentric carcinogenesis) are not part of routine radiologic staging, as imaging methods for these purposes have not yet been validated. With emerging understanding of HCC genomics, there is no doubt that personalized approaches will be introduced in clinical practice based on molecular targeted therapies (23,24). Under these new circumstances, it is likely that tumor biology will play an important role in future staging.

Diagnostic Performance of CT and MR Imaging

Currently, all major clinical practice guidelines endorse multiphasic CT and MR imaging with extracellular contrast agents as the first-line modalities for diagnosis and staging of HCC (8–11). As discussed in part I, these examinations should include late hepatic arterial, portal venous, and, at about 3–5 minutes, delayed phase acquisitions. Precontrast imaging is needed for MR imaging but, to reduce radiation dose, usually may be omitted for CT, except in patients previously treated with locoregional embolic or ablative therapies, without loss of significant diagnostic information. While some single-center comparative studies have shown slightly better performance of dynamic MR imaging using extracellular contrast agents than multiphasic CT (25,26), the differences are small. The per-lesion sensitivity of MR imaging for nodular HCC of all sizes is 77%–100%, while that of CT is 68%–91% (25,27–30). The per-lesion sensitivities, stratified by size, are 100% for both modalities for nodular HCCs larger than 2 cm, 44%–47% (MR imaging) and 40%–44% (CT) for 1–2-cm HCCs (25,26,29), and 29%–43% (MR imaging) and 10%–33% (CT) for HCCs smaller than 1 cm (26,27,29). Thus, both modalities provide excellent sensitivity for nodular HCCs larger than 2 cm, modest sensitivity for 1–2-cm HCCs, and poor sensitivity for HCCs smaller than 1 cm, and it is not yet clear which modality is superior. Advantages of CT are that it is widely available, rapid, robust, and compared with MR imaging needs less expertise to perform and to interpret images. Disadvantages include radiation exposure and relatively low soft-tissue contrast. By comparison, MR imaging provides higher soft-tissue contrast and permits assessment of a greater number of tissue properties, which in principle may help in lesion detection and characterization. On the other hand, MR imaging is more time consuming, less robust, and more prone to artifacts. It requires greater expertise to perform and interpret images, and it is less available. Thus, while MR imaging may be preferred over CT at many academic centers, there is insufficient data to recommend MR imaging over CT in community or less-specialized centers.

Although MR imaging with hepatobiliary agents is not yet integrated into most clinical practice guidelines, it is discussed here because it is emerging worldwide as a leading method for diagnosis and staging of HCC, and accumulating evidence suggests that MR imaging with hepatobiliary agents is the most sensitive method for detection of small HCCs and of premalignant lesions likely to progress to overt HCC (31–37). As discussed in part I, these agents per-

mit acquisition of hepatobiliary phase images that provide information on hepatocellular function, thereby supplementing the information provided by the vascular phases. In comparative studies, gadoxetate disodium–enhanced MR imaging had significantly higher per-lesion sensitivity and/or overall accuracy for the diagnosis of HCC than multiphasic CT (38,39), CT hepatic angiography/CT arterial portography (40,41), and MR imaging with extracellular agents (39); in two additional studies, differences between gadoxetate disodium–enhanced MR imaging and multiphasic CT studies were not significant (31). Fewer studies have compared gadobenate dimeglumine–enhanced MR imaging with other modalities: One study found no difference in overall accuracy between gadobenate dimeglumine–enhanced MR imaging and multiphasic CT (27), while another found gadobenate dimeglumine–enhanced MR imaging to have higher sensitivity and accuracy (38). The one study comparing gadoxetate disodium– and gadobenate dimeglumine–enhanced MR imaging found no significant performance differences (42).

Diagnosis and Staging of HCC with Extracellular Agents

Multiphasic CT and MR imaging with extracellular agents permit diagnosis and staging of HCC based mainly on assessment of vascularity. The principles are essentially the same for CT and MR imaging, and so the two modalities are discussed together. Major imaging features of HCC depicted in the vascular phases of CT and MR imaging are summarized in Table 1. MR imaging and, to a lesser extent, CT also allow assessment of ancillary features that may help detect and characterize liver lesions as well as modify reader confidence; these are discussed later.

Using extracellular agents, the hallmark diagnostic features of HCC at multiphasic CT or MR imaging are arterial phase hyperenhancement (Fig 1) followed by portal venous or delayed phase washout appearance (7–12,22,43–45).

Arterial phase hyperenhancement, sometimes termed arterial "wash-in" or arterial "hypervascularity," is defined as enhancement in the arterial phase that unequivocally is greater than that of surrounding liver. The pathophysiologic basis for arterial phase hyperenhancement in HCC is well understood. Intranodular arterial supply increases during hepatocarcinogenesis (46). Hence, most cirrhotic nodules, dysplastic nodules and early HCCs are hypoenhancing or isoenhancing in the arterial phase (41). By comparison, most progressed HCCs are hyperenhancing (47). While arterial phase hyperenhancement is characteristic of progressed HCC, it is nonspecific as it can also be observed in benign perfusion alterations, small hemangiomas, small focal nodular hyperplasia–like lesions (48), some atypical cases of focal or confluent fibrosis, some atypical cirrhotic nodules and dysplastic nodules (49), and non-HCC malignancies such as small ICCs (50) or small hypervascular metastases such as neuroendocrine tumors. In patients with cirrhosis or chronic hepatitis, small vascular pseudolesions attributable to arterioportal shunts are particularly common, and the large majority of focal areas of enhancement seen only in the arterial phase and measuring less than 2 cm are nonneoplastic (51), especially those that are wedge shaped and subcapsular (52).

Washout appearance is defined as a visually assessed temporal reduction in enhancement relative to surrounding liver from an earlier to a later phase, resulting in portal venous or delayed phase hypoenhancement (12). This "washout" may be more conspicuous in the delayed compared with the portal venous phase, and in some lesions, "washout" may be depicted only in the delayed phase (53,54). The mechanisms underlying washout appearance in HCC are not fully understood. Several concurrent factors likely are contributory, including early venous drainage of contrast material from the tumor (true washout), progressive enhancement of background liver (due to retention of contrast material within fibrotic parenchyma), reduced intranodular portal venous blood supply, tumoral hypercellularity with corresponding reduction in extracellular volume, and intrinsic hypoattenuation/hypointensity (44). Thus, the visually assessed temporal reduction in enhancement relative to liver may be caused by factors other than true washout, and for this reason the term *washout appearance* is advocated by the Liver Imaging Reporting and Data System (LI-RADS) (12). Like arterial phase hyperenhancement, washout appearance by itself is not specific for HCC as this feature may be observed in cirrhotic nodules and dysplastic nodules. Additionally, focal areas of parenchymal distortion and enhancing fibrosis may create the perception of "washout" (55). Thus, washout appearance should not be used as a feature of HCC unless the findings are unequivocal (12). Until now, most investigators have evaluated washout appearance subjectively. Recently Liu and colleagues (56) proposed a quantitative definition for washout based on CT attenuation values in user-defined regions of interest in lesion and adjacent liver; studies are needed to compare the accuracy and interreader reliability for HCC diagnosis using quantitative versus subjective definitions of "washout."

Although the individual features are nonspecific, the combination of arterial phase hyperenhancement and portal venous and/or delayed phase washout appearance is highly specific for HCC in patients with cirrhosis or other risk factors for HCC (7,43,45). In such patients, this temporal enhancement pattern has approximately 100% specificity for HCCs 20 mm or larger and approximately 90% specificity for 10- to 19-mm HCC (7,44,55). Importantly, the combination of arterial phase hyperenhancement and washout appearance very rarely is observed in ICC (50). Due to its high specificity, this temporal enhancement pattern is incorporated into all current systems developed for CT- or MR imaging–based diagnosis of HCC in at-risk patients (8–12,22). This temporal enhancement pattern is not specific for the diagnosis of HCC in the general population, however, in which the differential diagnosis includes metastasis,

Table 1

Major Imaging Features of HCC Assessed in the Vascular Phases of CT and MR Imaging

Feature	Comments
Arterial phase hyperenhancement	Characteristic of but not specific for progressed HCC. Differential diagnosis: benign perfusion alterations, small hemangiomas, small focal nodular hyperplasia-like lesions, atypical cases of focal or confluent fibrosis, atypical cirrhotic nodule, atypical dysplastic nodule, and non-HCC malignancy such as small ICC or small hypervascular metastases such as neuroendocrine tumors.
Washout appearance	Characteristic of but not specific for progressed HCC. Differential diagnosis: cirrhotic nodules and dysplastic nodules. Pitfall: Focal areas of parenchymal distortion and enhancing fibrosis may create false perception of "washout." Limitation: Although washout appearance may be assessed in either the portal venous phase or delayed phase with extracellular agents, for definitive diagnosis of HCC washout appearance probably should be evaluated only in the portal venous phase after administration of gadoxetate disodium, because hypointensity relative to liver in the transitional phase may reflect hyperenhancement of liver rather than de-enhancement of a mass.
Capsule appearance	Characteristic of and relatively specific for progressed HCC. Pitfall: peripheral enhancement of intrahepatic cholangiocarcinoma and fibrous tissue surrounding cirrhotic nodules and dysplastic nodules may be mistaken for capsule appearance.
Arterial phase hyperenhancement plus washout or capsule appearance	Diagnostic of HCC (in patients at risk for developing HCC) In patients at risk for developing HCC, the combination of arterial phase hyperenhancement plus washout or capsule appearance has near 100% specificity for HCC. Limitation: While this combination has high specificity, it has low sensitivity, as most early HCCs, many small progressed HCCs, and many infiltrative HCCs do not exhibit this combination of imaging features.

Note.—The information in this table is intended for application in patients at risk for development of HCC due to cirrhosis, chronic viral hepatitis, or other factors. It is not intended for application in the general population.

hepatocellular adenoma, and other lesions.

Another imaging feature characteristic of progressed HCC is capsule appearance (45,55,57–59), which refers to a peripheral rim of smooth hyperenhancement in the portal venous or delayed phase (12) (Fig 1). The degree of enhancement usually increases from early to later phases, and the delayed phase may be superior to the portal venous phase for identifying this feature (57,60). Retrospective studies of resected HCCs have shown that capsule appearance at CT (59) or MR imaging (57,58) correlates with the presence of a tumor capsule at pathologic examination; a tumor capsule is a frequent pathologic feature of progressed HCC but not of early HCC, dysplastic nodules, or cirrhotic nodules. The progressive enhancement has been attributed to slow flow within intracapsular vessels as well as contrast agent retention within the extravascular connective tissue of the capsule (57). While imaging-based capsule appearance correlates with the presence of a tumor capsule at pathologic examination, about one quarter of nodules with radiologically detected "capsules" lack a true capsule at pathologic examination but instead are surrounded by "pseudocapsules" consisting of mixed fibrous tissue and dilated sinusoids (58). Thus, capsule appearance is not pathognomonic for the presence of a true tumor capsule. Nevertheless, because precursor nodules (cirrhotic nodules and dysplastic nodules) and non-HCC tumors usually do not demonstrate progressive rim enhancement, capsule appearance has been shown to be an important predictor of HCC (45,55). Although some investigators have found that capsule appearance does not incrementally increase the sensitivity or specificity for HCC since it usually is seen in HCCs with other hallmark imaging features (45), other investigators have found that capsule appearance is valuable by permitting diagnosis of HCC without definite washout appearance (55) (Fig 1). According to two diagnostic systems (12,22), a mass 2 cm or larger with arterial phase hyperenhancement and capsule appearance can be diagnosed definitively as HCC even in the absence of washout appearance; for 10- to 19-mm masses with arterial phase hyperenhancement, both capsule appearance and washout appearance are required.

A potential pitfall in applying this feature is that some small ICCs show peripheral enhancement in all phases (50), which may be misinterpreted as a "capsule;" a discriminating characteristic is that the peripheral enhancement in ICC tends to peak in the arterial phase and diminish in later phases, rather than progress. Another pitfall is that fibrous tissue surrounding cirrhotic nodules and dysplastic nodules may enhance on delayed phase images, generating the perception of a "capsule" (55); thus, radiologists should apply this feature only if the enhancing rim unequivocally is thicker or more conspicuous than the fibrous tissue surrounding background nodules (12) (Fig 2).

Extracapsular extension with the formation of satellite nodules is frequently seen in large progressed HCC (61). These satellite nodules represent

Figure 1

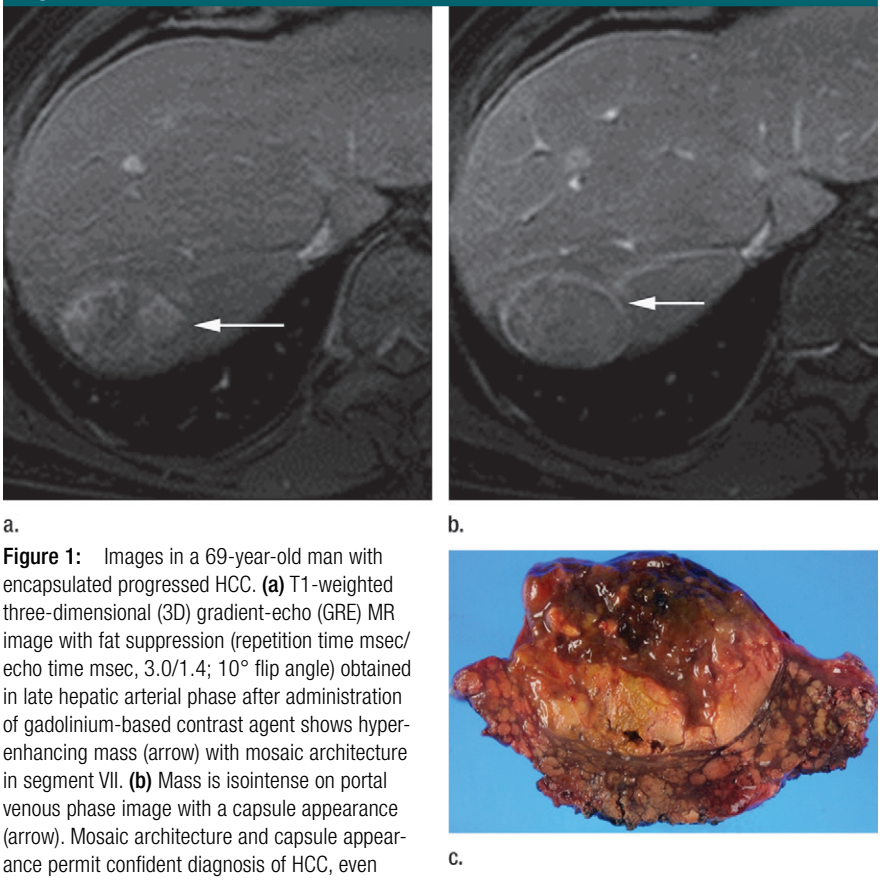


Figure 1: Images in a 69-year-old man with encapsulated progressed HCC. **(a)** T1-weighted three-dimensional (3D) gradient-echo (GRE) MR image with fat suppression (repetition time msec/echo time msec, 3.0/1.4; 10° flip angle) obtained in late hepatic arterial phase after administration of gadolinium-based contrast agent shows hyperenhancing mass (arrow) with mosaic architecture in segment VII. **(b)** Mass is isointense on portal venous phase image with a capsule appearance (arrow). Mosaic architecture and capsule appearance permit confident diagnosis of HCC, even though mass does not appear to wash out to hypointensity relative to liver in portal venous phase. **(c)** Photograph of gross pathologic specimen confirms progressed HCC with fibrous capsule.

intrahepatic metastases within the venous drainage area around the main tumor (62). They often manifest as multiple subcentimeter nodules outside the tumor margins (usually within 2 cm). If corona enhancement (discussed later) is observed, they may be located within the corona enhancement area (63). These satellite nodules are by definition progressed lesions that have developed the ability to invade vessels and metastasize. Hence, despite their small size, they typically manifest arterial phase hyperenhancement, which would not be expected for HCCs of similar size arising through multistep hepatocarcinogenesis from precursor lesions (64). Other features of progressed HCCs such as washout appearance and capsule appearance may or may not be evident, depending on the size of the lesions, the spatial and contrast resolution of the images, and other factors. The presence of satellite nodules has been recognized as predictor of recurrence and lower survival after transplantation, resection, and local ablation (65). Although satellite nodules are frequently observed around progressed HCCs, the sensitivity and specificity of CT or MR imaging for their detection have not been extensively studied and merit further investigation. Also, satellite nodules may occur around ICC; thus, the presence of satellite nodules does not help in the differential diagnosis of HCC and ICC (66).

For nodules that meet diagnostic criteria for HCC, careful analysis of enhancement features may provide prognostic information. Single-center, retrospective studies have suggested that heterogeneous arterial phase enhancement with irregular ringlike structures predicts high tumor grade and posttreatment recurrence (67). A correlation between heterogeneous arterial enhancement and worrisome biologic features has not been consistently observed, however (68). Whether the intensity, as opposed to the heterogeneity, of arterial phase enhancement predicts tumor grade, microvascular invasion, or other prognostic features is controversial (69,70). Additionally, the rate at which tumors appear to "wash out" may be important. According to some single-center retrospective studies, early washout appearance manifesting in the portal venous phase predicts higher tumor grade (71,72) and, at a trend level, higher probability of microvascular invasion (68) than washout appearance manifesting only in the delayed phase. In HCCs with capsule appearance, radiologists should inspect the "capsule" carefully for its integrity, as imaging evidence of capsular disruption suggests the tumor has infiltrated through the capsule into the surrounding tissue, an indicator of poor prognosis (59,73).

In addition to diagnosis of individual HCC nodules, CT and MR imaging with extracellular agents also contribute to tumor staging by permitting diagnosis of macrovascular invasion ("tumor thrombus"). Identification of macrovascular invasion, and differentiation from bland thrombus, which also occurs with high frequency in patients with cirrhosis, is critical: The former usually precludes surgical treatment options such as resection or liver transplantation, while the latter may alter the surgical approach but usually does not exclude surgery from consideration. Specific imaging features of macrovascular invasion include direct extension of a parenchymal tumor mass into an adjacent vessel (74) and the presence within an occluded vein of arterial enhancing neovessels manifesting as defined as thin and punctate hyperenhancing "threads and streaks" within a portal venous or hepatic venous thrombus (Fig 3). Expansion of a thrombosed main portal vein to greater than or equal to 23 mm also suggests intraluminal tumor, with a reported sensitivity and specificity of 63% and 100%, respec-

Figure 2

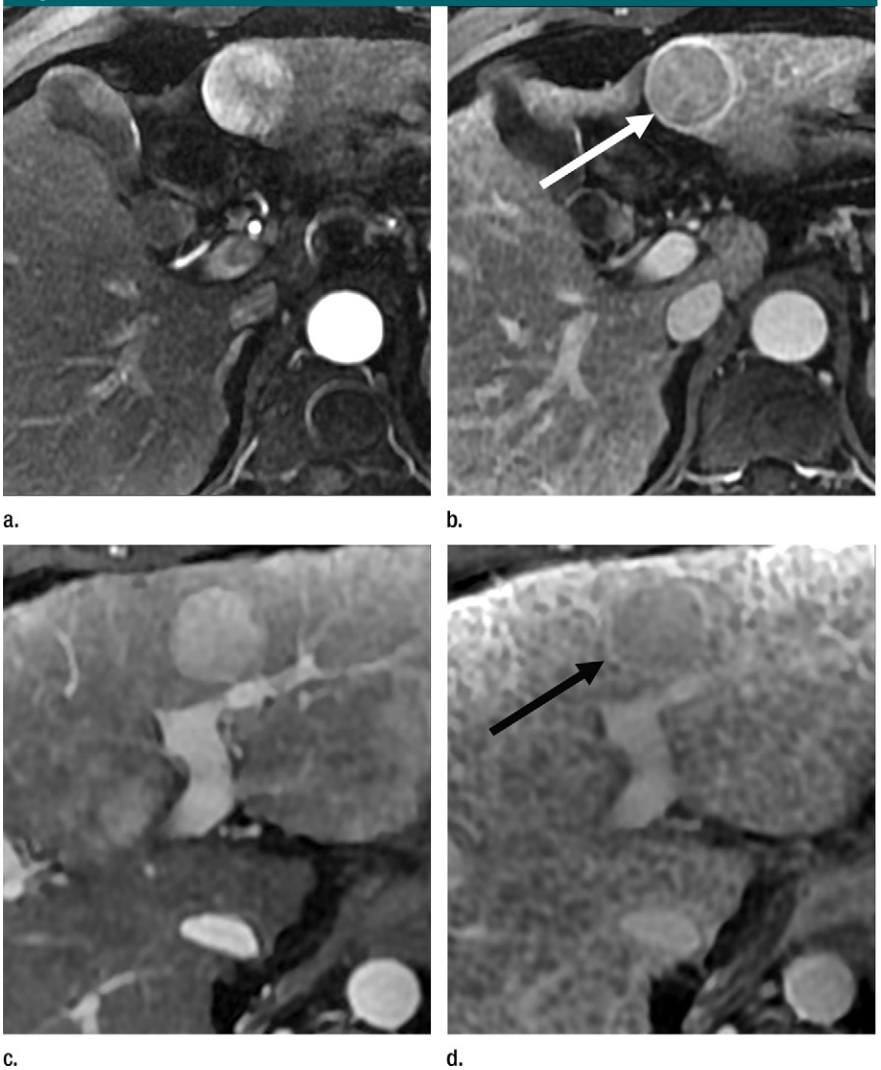


Figure 2: HCCs with and without definite capsule appearance. **(a, b)** HCC with definite capsule appearance in a 54-year-old man with hepatitis C–related cirrhosis. T1-weighted 3D GRE MR images with fat suppression (3.0/1.4; 15° flip angle) obtained in **(a)** late hepatic arterial phase and **(b)** 3-minute delayed phase after administration of gadolinium-based contrast agent show 3.2-cm HCC in left lobe. Peripheral enhancing rim (arrow) in delayed phase is unequivocally thicker and more conspicuous than enhancing fibrosis surrounding background nodules, consistent with capsule appearance. **(c, d)** HCC without definite capsule appearance in 35-year-old man with hepatitis C–related cirrhosis. T1-weighted 3D GRE MR images with fat suppression (3.0/1.4; 15° flip angle) obtained in **(c)** late hepatic arterial phase and **(d)** 3-minute delayed phase after administration of gadolinium-based contrast agent show 2.5-cm HCC in left lobe. Peripheral enhancing rim (arrow) in delayed phase is of similar thickness and conspicuity as enhancing fibrosis surrounding background nodules.

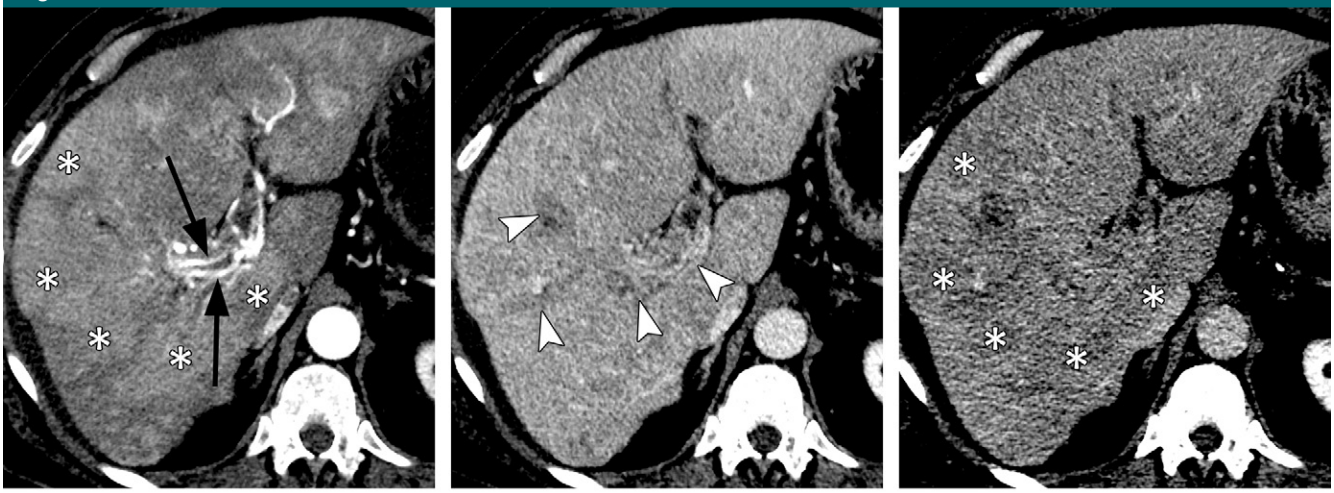
tively (75); caution should be exercised in interpretation of this feature, however, as acute bland thrombosis also may result in luminal expansion. Despite the importance of macrovascular invasion for tumor staging, treatment planning, and prognosis, the sensitivity and specificity of state-of-the-art CT and MR imaging for its diagnosis is not well known due to paucity of studies on this subject since 2000. In one recent study, Sorrentino and colleagues (76) evaluated the diagnostic performance of arterial phase hyperenhancement of the thrombus at CT and found a sensitivity of 87%. As mentioned later, in retrospective studies, diffusion-weighted MR imaging has been shown by some investigators to aid in the differentiation of macrovascular invasion from bland venous thrombus (77), but other investigators have not found diffusion-weighted imaging to be helpful (78). Larger prospective studies are needed to evaluate diffusion-weighted imaging for this purpose.

The main limitation of CT and MR imaging with extracellular contrast agents for diagnosis and staging of HCC is low per-lesion sensitivity. Only HCCs that have developed sufficient neoangiogenesis to show arterial phase hyperenhancement and that also exhibit washout or capsule appearance can be unequivocally diagnosed. In general, these are progressed, moderately differentiated HCCs. Other HCCs may be difficult to diagnose. Up to approximately 40% of HCCs lack arterial phase hyperenhancement (41,79) and cannot be diagnosed as definite HCC using extracellular agents. These include most early HCCs (80); poorly differentiated, infiltrative HCCs, which may have weak, patchy arterial phase hyperenhancement (81); some nodular HCCs with tiny hypervascular foci too small to be perceived at CT or MR imaging (41); and HCCs in which true hyperenhancement is missed due to arterial phase mistiming or imaging artifacts. Additionally, approximately 40%–60% of small HCCs, even if hyperenhanced in the arterial phase, do not exhibit a washout or capsule appearance in the venous phases (29,55), and so cannot be diagnosed as definite HCC with extracellular agents.

Diagnosis and Staging of HCC with Hepatobiliary Agents

Hepatobiliary agents permit assessment not only of tumor vascularity but also of hepatocellular function based mainly on signal intensity relative to liver in the hepatobiliary phase. While the signal intensity of lesions relative to the liver in the hepatobiliary phase de-

Figure 3



a. b. c.

Figure 3: Images in a 64-year-old man with infiltrative HCC and macrovascular invasion. Axial CT images obtained in the **(a)** late arterial, **(b)** portal venous, and **(c)** 3-minute delayed phases after administration of an iodinated contrast agent reveal heterogeneously enhancing soft tissue expanding the lumen of the right portal vein and its branches consistent (arrowheads) with macrovascular invasion by HCC. Note arterial phase hyperenhancing tumoral arteries (arrows), sometimes described as "threads and streaks," within the intraluminal tissue. Note patchy areas (*) of arterial phase hyperenhancement and delayed phase partial washout appearance in the liver parenchyma, consistent with infiltrative HCC.

Table 2

Hepatobiliary Phase Imaging Features of HCC

Feature	Comments
T1 hypointensity	Characteristic of HCC (including both early and progressed forms), but not specific for HCC. Differential diagnosis: high-grade dysplastic nodule, low-grade dysplastic nodule (uncommon), large cirrhotic nodule (uncommon), siderotic nodule (due to T2* shortening effects of iron), nodular or confluent area of fibrosis, intrahepatic cholangiocarcinoma, and hemangioma. Limitations: HCCs may be difficult to recognize in the hepatobiliary phase in patients with severe liver dysfunction, cholestasis, iron overload, or marked fibrosis. Even in the absence of these conditions, infiltrative HCCs may be difficult to identify in the hepatobiliary phase.
T1 hyperintensity	Observed in 5%–12% of HCCs (most are moderately differentiated) Differential diagnosis: nonmalignant nodule (eg, focal nodular hyperplasia-like lesion). In the differential diagnosis of hepatobiliary phase hyperintense HCC versus nonmalignant nodule, features that favor HCC include focal defect(s) in contrast agent uptake, presence of hypointense rim, and absence of architectural features of focal nodular hyperplasia (central scar and radiating fibrous septa)

Note.—The information in this table is intended for application in patients at risk for development of HCC due to cirrhosis, chronic viral hepatitis, or other factors. It is not intended for application in the general population.

pends on a complex interplay between numerous incompletely understood factors (82), the dominant determinant is OATP8 expression (83,84). Thus, nodules with low or no OATP expression do not uptake hepatobiliary agents and appear hypointense in the hepatobiliary phase (83,84), while nodules with preserved or elevated OATP expression uptake the agents and tend to be isointense or hyperintense (83,84). The role of MRP2 and MRP3 (the transporters that excrete gadoxetate disodium and gadobenate dimeglumine into the bile [MRP2] and back into the sinusoids [MRP3]) in determining hepatobiliary phase signal intensity remains controversial (83,84). Hepatobiliary phase imaging features of HCC are summarized in Table 2 and are discussed below.

Since OATP expression declines during hepatocarcinogenesis, the assessment of signal intensity in the hepatobiliary phase helps in the detection and characterization of hepatocellular nodules in the cirrhotic liver. Most HCCs, including many early HCCs, and some high-grade dysplastic nodules are hypointense in the hepatobiliary phase (41) due to underexpression of OATP. By comparison, most cirrhotic nodules, most low-grade dysplastic nodules, some high-grade dysplastic nodules,

Figure 4

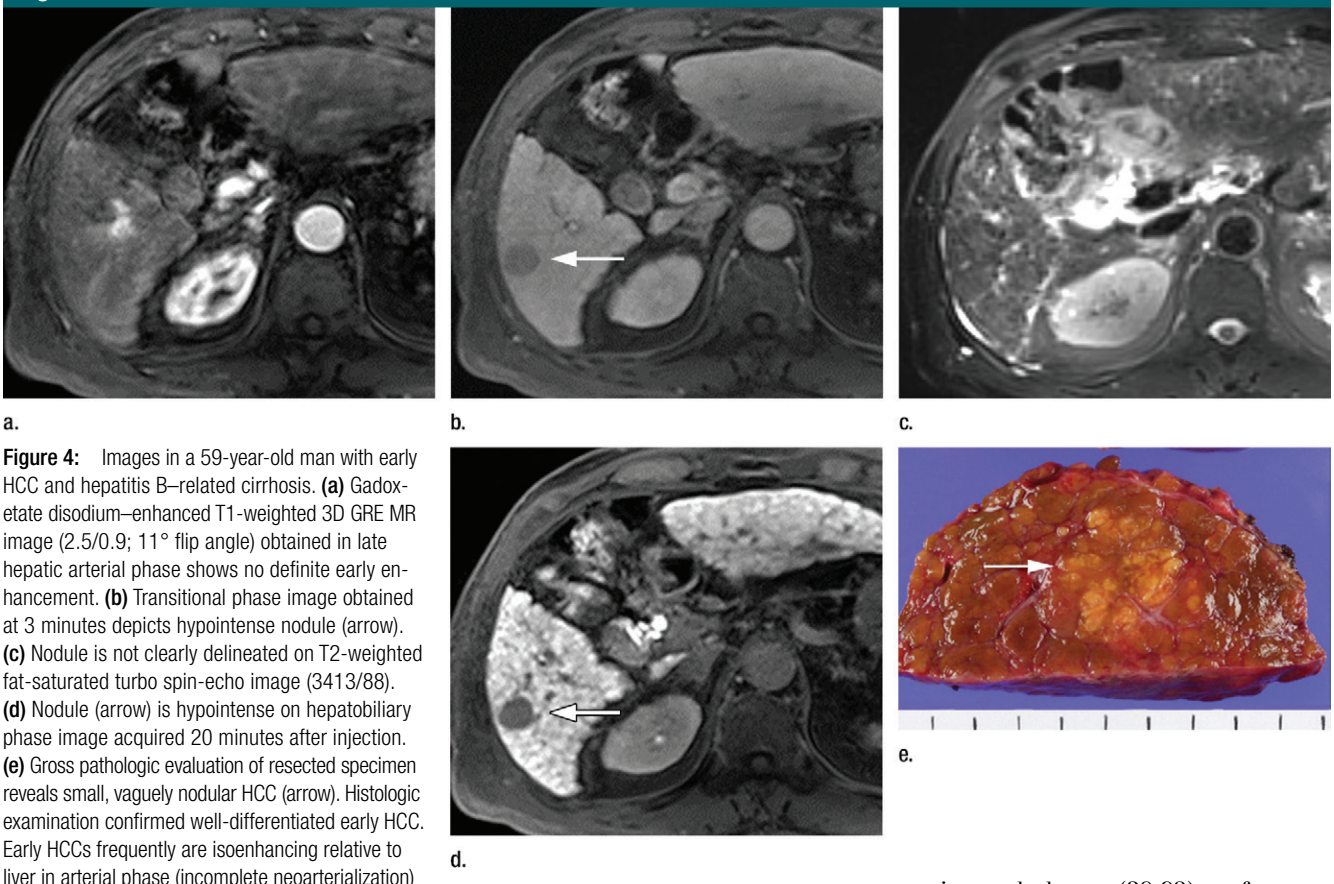


Figure 4: Images in a 59-year-old man with early HCC and hepatitis B–related cirrhosis. **(a)** Gadoxetate disodium–enhanced T1-weighted 3D GRE MR image (2.5/0.9; 11° flip angle) obtained in late hepatic arterial phase shows no definite early enhancement. **(b)** Transitional phase image obtained at 3 minutes depicts hypointense nodule (arrow). **(c)** Nodule is not clearly delineated on T2-weighted fat-saturated turbo spin-echo image (3413/88). **(d)** Nodule (arrow) is hypointense on hepatobiliary phase image acquired 20 minutes after injection. **(e)** Gross pathologic evaluation of resected specimen reveals small, vaguely nodular HCC (arrow). Histologic examination confirmed well-differentiated early HCC. Early HCCs frequently are isoenhancing relative to liver in arterial phase (incomplete neoarterialization) but seen clearly as hypointense nodules in the hepatobiliary phase (underexpression of OATP transporters). Note motion artifact in the arterial phase.

and only a minority of HCCs are isointense or hyperintense due to preserved expression (85). As a corollary, cirrhosis-associated nodules that are hypointense in the hepatobiliary phase are likely to be malignant or premalignant (86), even in the absence of arterial phase hyperenhancement or venous phase "washout."

These concepts can be exploited for diagnostic benefit (Fig 4). In patients with cirrhosis or chronic hepatitis, the addition of hepatobiliary phase images improves the per-lesion sensitivity for the diagnosis of HCC by 6%–15% for gadoxetate disodium (87–89) and by 9% for gadobenate dimeglumine (38). By depicting HCCs as easily discernible hypointense nodules against a strongly enhanced background parenchyma (90), the hepatobiliary phase can increase HCC conspicuity and delineation. This facilitates detection and improves reader confidence for HCC nodules that otherwise may be difficult to visualize due to subtle features at other phases and sequences (90). Another benefit is in the interpretation of small nodular lesions characterized by arterial phase hyperenhancement and venous phase isoenhancement. Such lesions are indeterminate if evaluated only in the vascular phases but, after exclusion of hemangiomas, these are highly suspicious for malignancy if they demonstrate hypointensity in the hepatobiliary phase (10,91), with the major differential diagnosis including HCC and ICC. A related benefit is in the differentiation of hypervascular HCCs from hypervascular pseudolesions such as focal perfusion alterations due to arterioportal shunts (38,92), a frequent source of diagnostic confusion using extracellular agents. For most vascular pseudolesions, the underlying OATP expression is preserved and the hepatobiliary phase signal intensity is the same as that of background liver, in contradistinction to HCCs, which characteristically appear hypointense. Although the hepatobiliary phase helps in the differentiation of HCC from some benign entities such as arterioportal shunts, it may complicate the differentiation of HCC from other benign entities such as confluent fibrosis, which also appears hypointense in this phase and conceivably could be misinterpreted as HCC.

Perhaps the most important benefit of imaging the hepatobiliary phase is that it helps to identify early HCCs (41) (Fig 4). These HCCs have incomplete neoarterialization, frequently are isoenhancing in the vascular phases, and so cannot be reliably detected with extracellular agents. However, since OATP8

expression level decreases during hepatocarcinogenesis prior to complete neoarterialization and to elevation of arterial flow, such HCCs may be visible in the hepatobiliary phase as hypointense nodules (93,94), and some early HCCs are visible only in the hepatobiliary phase (40,95). The differential diagnosis for arterial phase hypoenhancing or isoenhancing nodules with hepatobiliary phase hypointensity includes high-grade dysplastic nodules (88,94), occasional low-grade dysplastic nodules (88), occasional large cirrhotic nodules (96), and nodular areas of fibrosis, so this finding is not specific for HCC, however. A recent retrospective study suggested that diffusion-weighted hyperintensity may be used to discriminate early HCCs from nonmalignant isovascular or hypovascular hepatobiliary phase hypointense nodules (97), but further studies are needed to validate diffusion-weighted imaging for this purpose. Other investigators have shown that if followed, many arterial phase hypoenhancing or isoenhancing nodules with hepatobiliary phase hypointensity will progress to hypervascular HCC over 12 months (33–37,98). The frequency of progression depends on baseline nodule size (36,37,98): Most nodules smaller than 1 cm with this appearance do not progress or progress only slowly (36,37), while nodules 1 cm or larger are more likely to progress. Other suggested predictors of progression include degree of hepatobiliary phase hypointensity (34), diffusion-weighted hyperintensity (34), T2 hyperintensity (33,34), and intralesional fat (33). The optimal management of arterial phase isoenhancing or hypoenhancing nodules with hepatobiliary phase hypointensity has not yet been determined. Depending on their size it may be reasonable to follow them with imaging or to biopsy them (91). They probably should not be ignored, however. In one study of patients who underwent resection for HCC, the presence of such nodules in the unresected liver remnant was a strong predictor of postoperative multicentric recurrence (99).

Although most HCCs are hypointense in the hepatobiliary phase, about 5%–12% HCCs are hyperintense (83,100,101), owing to overexpression of OATP (83,84). As mentioned in part I, the overexpression of OATP in some HCCs may be due to a genomic alteration during hepatocarcinogenesis or a distinct cell of origin (102). Histologically, most such HCCs are moderately differentiated and some are well differentiated (83,101,103). HCCs with isointensity or hyperintensity in the hepatobiliary phase may cause diagnostic confusion and be misinterpreted as nonmalignant. Other hepatobiliary phase features that favor HCC include focal defect(s) in contrast material uptake, presence of a hypointense rim ("capsule") (Fig 5), and absence of architectural features of focal nodular hyperplasia (central scar and radiating fibrous septa) (100).

Beyond making a diagnosis of HCC, an emerging role of hepatobiliary agent–enhanced MR imaging is to characterize HCC tumor biology and thereby provide prognostic information. In single-center retrospective studies, some investigators

Figure 5

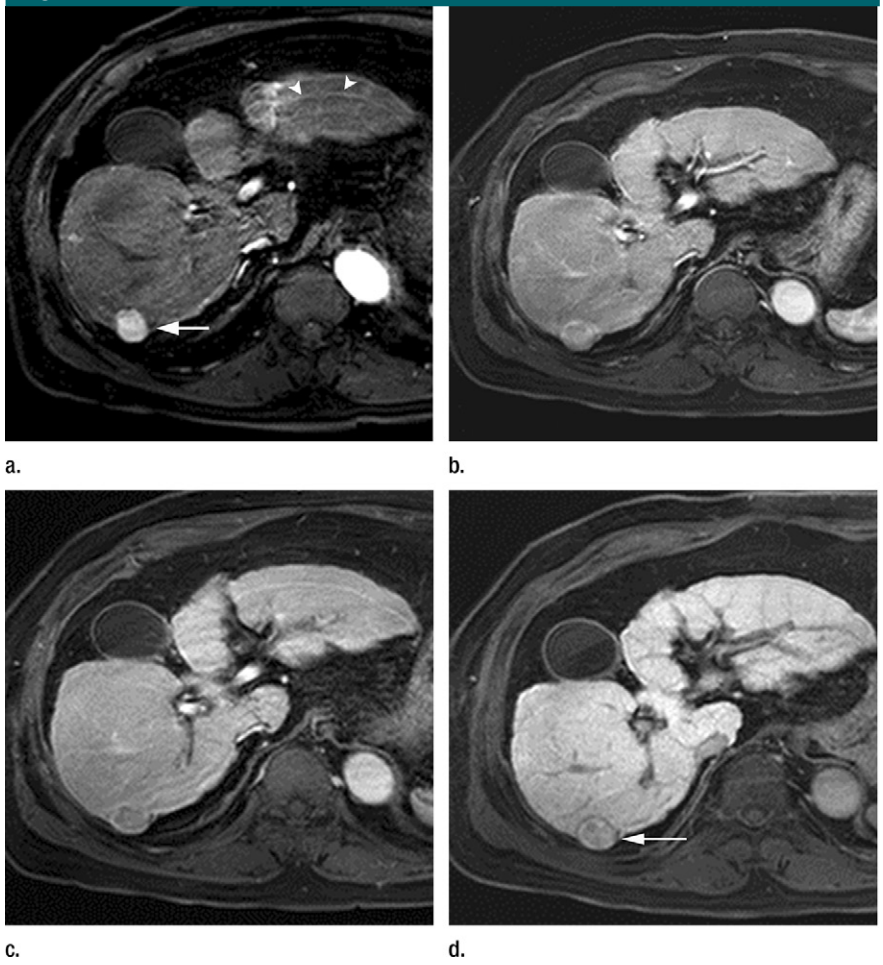


Figure 5: MR images in a 70-year-old man with HCC show hyperintensity in the hepatobiliary phase. **(a)** Gadoxetate disodium–enhanced T1-weighted 3D GRE image (2.5/0.9; 11° flip angle) in late hepatic arterial phase shows hyperenhancing mass (arrow) in right posterior liver. **(b, c)** Relative to liver, mass is slightly hyperintense in **(b)** portal venous phase and mildly hypointense in **(c)** transitional phase. **(d)** In the hepatobiliary phase, mass is hyperintense with hypointense rim, likely representing tumor capsule (arrow). Presence of hypointense rim permits confident diagnosis of HCC despite hyperintensity of lesion. Note motion artifact on arterial phase image (arrowheads).

have found that, after excluding HCCs with hepatobiliary phase isoenhancement or hyperenhancement (ie, those with presumed OATP overexpression), the degree of nodule enhancement in the hepatobiliary phase after injection of gadoxetate disodium (93,102) or gadobenate (104) correlates inversely with tumor grade. The inverse correlation has been attributed to the progressive decline in OATP expression during hepatocarcinogenesis and suggests that quantitative analysis of nodule enhancement in the hepatobiliary phase may help to noninvasively predict this important histologic and prognostic feature (105). Other investigators have found that the degree of nodule enhancement does not correlate with tumor grade (69,106), however, or only correlates in the subset of patients with Child-Pugh class A liver disease and relatively preserved hepatocellular function in the background parenchyma (105). Other single-center retrospective studies have found that the degree of nodule enhancement in the hepatobiliary phase after injection of gadoxetate disodium was significantly lower in HCCs with biliary (106) or progenitor cell (107) markers; if validated by independent studies, this would be important, since HCCs with such markers have more aggressive biology and worse outcome clinically (108,109). Compared with hepatobiliary phase hypointense HCCs, HCCs with isointensity or hyperintensity in the hepatobiliary phase (ie, those with preserved OATP expression) may be biologically more indolent, with lower grade (101), less frequent vascular invasion (101,103,110), and longer recurrence-free survival after resection (47,101,110). Other investigators have analyzed tumor morphology in the hepatobiliary phase. In a retrospective study, nonsmooth tumor margin depicted in the hepatobiliary phase after injection of gadoxetate disodium was shown to correlate with microvascular invasion, intrahepatic metastasis, and early recurrence (111). The same finding after injection of gadobenate was found to predict microvascular invasion in univariate but not in multivariate analyses (112). Finally, peritumoral hypointensity seen on gadoxetate disodium–enhanced hepatobiliary phase images was shown in a retrospective study to be a specific, although insensitive, marker for microvascular invasion; the authors attributed the peritumoral hypointensity to altered expression of OATP or MRP2 receptors in the hepatic parenchyma caused by hemodynamic changes associated with tumor obstruction of minute portal veins (113).

The main disadvantage of the hepatobiliary phase alone for HCC diagnosis and staging is its nonspecificity. Any lesion not composed of functioning hepatocytes may appear hypointense, including benign entities (eg, hemangiomas, nodular or confluent areas of fibrosis, some atypical perfusion alterations) and non-HCC malignancies (eg, ICCs, metastases). Also, even though they are composed of nonmalignant hepatocytes, siderotic nodules may appear hypointense due to the T2* shortening effects of iron. Moreover, some lesions with large extracellular spaces (eg, fibrotic tumors including ICCs) may have paradoxical intermediate or mixed signal intensity due to extracellular contrast agent pooling (66), which may be misinterpreted as intracellular uptake. For these reasons, the hepatobiliary phase must be evaluated in conjunction with other phases and sequences—such a T1-weighted dual-echo, T2-weighted, or diffusion-weighted imaging—to differentiate HCC from other entities that may appear hypointense in the hepatobiliary phase. Careful analysis of the hepatobiliary phase enhancement pattern also may be helpful in the differentiation of HCC and ICC: A target appearance in the hepatobiliary phase, characterized by central enhancement with a peripheral hypointense rim, favors the diagnosis of ICC (114). The central enhancement has been attributed to pooling of the contrast agent within the dense fibrous stroma of the ICC tumor core.

In addition to the lack of specificity of the hepatobiliary phase, another challenge is that many conditions reduce contrast between lesions and liver, thereby limiting the efficacy of the hepatobiliary phase for lesion detection and characterization. Patients with severe hepatic dysfunction or cholestasis have limited uptake of hepatobiliary agents (82). Recent studies report that the diagnostic performance of gadoxetate disodium–enhanced MR imaging for HCC deteriorates with increasing severity of cirrhosis (115) and may be modest in patients with advanced cirrhosis on the liver transplant list (116). In addition, both iron overload and marked fibrosis may reduce hepatobiliary phase enhancement of the liver or they may give the parenchyma a heterogeneous appearance, factors that potentially lower the detectability of HCC. Finally, infiltrative HCC may be difficult to identify due to ill-defined margins and poor contrast between tumor and background liver. The optimal strategies for addressing these limitations have not yet been identified.

A potential pitfall unique to gadoxetate disodium is that this agent does not provide a conventional delayed vascular phase and instead provides a transitional phase; this phase overlaps with the portal venous phase and the hepatobiliary phase, lasts for several minutes, and represents a transition from extracellular-dominant to intracellular-dominant enhancement (117). The interpretation of signal intensity in the transitional phase is not yet well understood, and it possible that hypointensity relative to liver in the transitional phase may reflect hyperenhancement of liver rather than de-enhancement of a mass. Most nodules with arterial phase hyperintensity, portal venous phase isointensity, and transitional phase hypointensity probably are HCC, but the specificity of this pattern for HCC has not been established. Caution should be used in the interpretation of such nodules as the differential diagnosis may include atypical hemangioma and ICC in addition to HCC. For definitive diagnosis of HCC, therefore, washout appearance probably should be evaluated only in the portal venous phase after administration of gadoxetate disodium. Another challenge associated with the transitional phase is that the relatively high enhancement of the background parenchyma may obscure "capsular" enhancement and reduce the frequency or confidence with which this important feature can be perceived.

Table 3

Ancillary Imaging Features of HCC

Feature	Comments
Favors diagnosis of HCC	
Intralesional fat	Characteristic of but not specific for early HCC. Differential diagnosis: low-grade and high-grade dysplastic nodule. Some progressed HCCs also may be fatty, such as the steatohepatitic variant. Limitation: incremental value of intralesional fat for diagnosis of HCC is limited since this feature often coincides with other more discriminatory imaging features.
Corona enhancement	Characteristic of progressed, hypervascular HCC. Helps to differentiate progressed, hypervascular HCC from vascular pseudolesions such as arterioportal shunts and thought to represent a frequent site of perilesional satellite metastases. Limitations: May be difficult to recognize at CT or MR imaging; hence, incremental value of this feature for diagnosis of progressed HCC may be modest. Not characteristic of and therefore does not help in diagnosis of early HCC. Pitfall: May overlap and blend with tumor enhancement, causing tumor to appear larger than it really is.
Nodule-in-nodule architecture	Corresponds to nodule-in-nodule growth pattern observed at histology and suggests emergence of progressed HCC within dysplastic nodule or early HCC. Limitation: nodule-in-nodule architecture is uncommonly depicted in HCCs at CT or MR imaging; hence, incremental value of this feature for diagnosis of HCC may be modest.
Mosaic architecture	Characteristic of and frequently observed in large HCCs. Helps in the differentiation of HCC from ICC. Limitation: mosaic architecture is uncommon in small HCCs; hence, incremental value of this feature for diagnosis of small HCC may be modest.
Favors diagnosis of malignancy but not specific for HCC	
Mild-moderate T2 hyperintensity	Highly suggestive of malignancy if present. Differential diagnosis: early HCC, progressed HCC, and intrahepatic cholangiocarcinoma. Limitation: feature has limited sensitivity for HCC, as many HCCs are T2 iso- or hypointense.
Restricted diffusion	Highly suggestive of malignancy if present. Differential diagnosis: early HCC, progressed HCC, and intrahepatic cholangiocarcinoma. Limitation: feature has limited sensitivity for HCC, as many HCCs do not show restricted diffusion. Pitfall: small hemangiomas may have high signal on diffusion-weighted images and be mistaken for HCC.
Lesional iron sparing	Highly suggestive of premalignancy or malignancy if present. Differential diagnosis: high-grade dysplastic nodule, early HCC, progressed HCC, and intrahepatic cholangiocarcinoma. Limitation: feature is applicable only to solid nodules in iron-overloaded livers. Pitfall: confluent fibrosis is iron free and may be mistaken for HCC based on this imaging feature.

Note.—The information in this table is intended for application in patients at risk for development of HCC due to cirrhosis, chronic viral hepatitis, or other factors. It is not intended for application in the general population.

Other limitations unique to gadoxetate disodium–enhanced MR imaging include relatively weak arterial phase hyperenhancement (if the agent is used at its approved dose of 0.025 mmol gadolinium per kilogram of body weight) and relatively high frequency of arterial phase artifacts (mainly due to transient dyspnea associated with this agent [118]). The impact of these factors on diagnostic performance has not been determined and merits further study.

The accuracy of gadoxetate disodium–enhanced MR imaging for diagnosis of macrovascular invasion has not been reported in the published literature to our knowledge but is expected to be lower than that of MR imaging with extracellular agents. The reason is that gadoxetate disodium tends to generate relatively weak contrast between vessels and surrounding liver, attributable in part to its low dose and in part to strong parenchymal enhancement.

Ancillary Imaging Features for Diagnosis of HCC

As discussed in the previous two sections, the CT and MR imaging diagnosis of HCC is based mainly on assessment of vascularity, capsule appearance, and, if hepatobiliary agents are administered, signal intensity in the hepatobiliary phase. MR imaging and, to a lesser extent, CT also permit assessment of ancillary imaging features. While these ancillary imaging features usually do not permit definitive diagnosis of HCC, they provide incremental information that helps to characterize nodules and may improve the sensitivity for HCC. As summarized in Table 3 and discussed below, these ancillary features can be divided into those that favor the

diagnosis of HCC specifically (intralesional fat, corona enhancement, nodule-in-nodule architecture, and mosaic architecture) and those that favor the diagnosis of malignancy but are not specific for HCC (mild-moderate T2 hyperintensity, restricted diffusion, and, if other features confirm a solid mass, lesional iron sparing).

Ancillary Features That Favor the Diagnosis of HCC

Intralesional fat refers to the presence of lipid within a mass in higher concentration than in the background liver (12). This feature can be detected at MR imaging by observing signal loss on out-of-phase compared with in-phase T1-weighted GRE images (12,45) (Fig 6). Although precontrast CT attenuation values correlate with fat content in HCC nodules (119), the detection of intralesional fat can be problematic at CT, because many factors other than fat affect the attenuation. Intralesional fat is frequently observed histologically in early HCC (41) and its detection at imaging favors the diagnosis of HCC. This imaging feature does not establish the diagnosis of HCC, however, as the differential diagnosis includes high-grade dysplastic nodule and occasionally low-grade dysplastic nodule (120). Nevertheless, in a patient with cirrhosis or other risk factor for HCC, the imaging-based identification of intralesional fat in a solid nodule raises concern for malignancy or premalignancy. Importantly, intralesional fat is extremely rare in non-HCC hepatic malignancies; thus, the detection of fat may help to exclude ICC in problematic cases. Despite these potential benefits, the incremental value of intralesional fat for the diagnosis of HCC has not yet been determined. In two separate multivariate analyses of MR imaging using extracellular agents, intralesional fat was shown to be noncontributory for the imaging-based diagnosis of HCC, in part because the presence of fat coincided with other more discriminatory imaging features (43,45). Intralesional fat may have value as a prognostic feature, however. Since intralesional fat is characteristic of early but—with the exception of the steatohepatitic variant of HCC (121)—not progressed HCC (41), HCCs with this feature may have more favorable prognosis, with longer time to progression and less risk of developing metastases, than non–fat-containing HCCs (122). Steatohepatitic HCC is a newly described variant of HCC with histologic features that resemble those of steatohepatitis in nonneoplastic liver (eg, steatosis, inflammation, evidence of hepatocyte injury, and pericellular fibrosis) (123). Emerging data suggest this variant occurs most commonly in persons with underlying steatohepatitis. Although confirmatory studies are needed, it appears that steatohepatitic HCCs may have pronounced intralesional fat even if they are progressed cancers with advanced tumor grade (123).

Figure 6

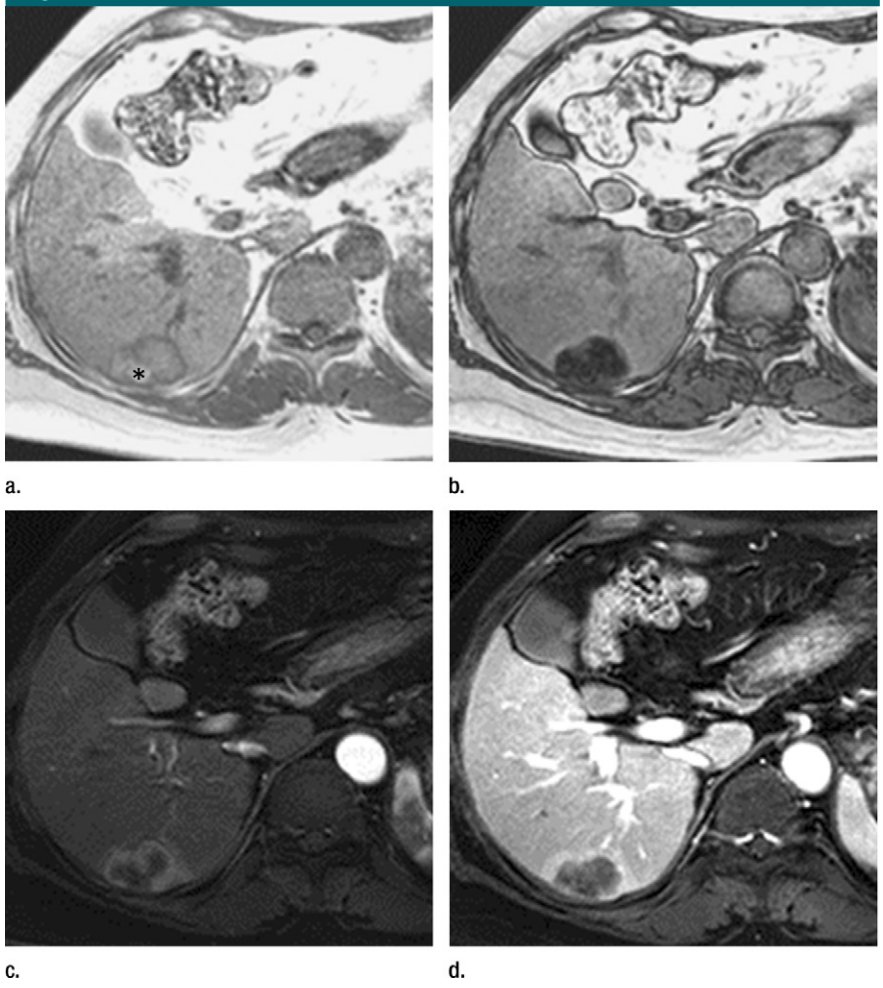


Figure 6: MR images in a 66-year-old woman with fat-containing HCC and hepatitis B–related cirrhosis. **(a, b)** Axial dual-echo GRE images show mass in segment VI of liver. Signal loss of mass on **(b)** out-of-phase compared with **(a)** in-phase image indicates intralesional fat. Note also nodule-in-nodule architecture on in-phase image with hyperintense inner nodule (*). **(c)** Mass shows heterogeneous predominantly peripheral enhancement in late hepatic arterial phase of gadoxetate disodium–enhanced T1-weighted 3D GRE image (3.0/1.4; 10° flip angle). **(d)** Mass is hypointense relative to liver in the portal venous phase. Surgical specimen confirmed moderately differentiated (Edmondson grade II) HCC with 80% fatty change. Although peripheral rim enhancement is somewhat unusual for HCC and can be observed in ICC and metastasis from extrahepatic primary, presence of intralesional fat permits confident radiologic diagnosis of HCC.

Figure 7

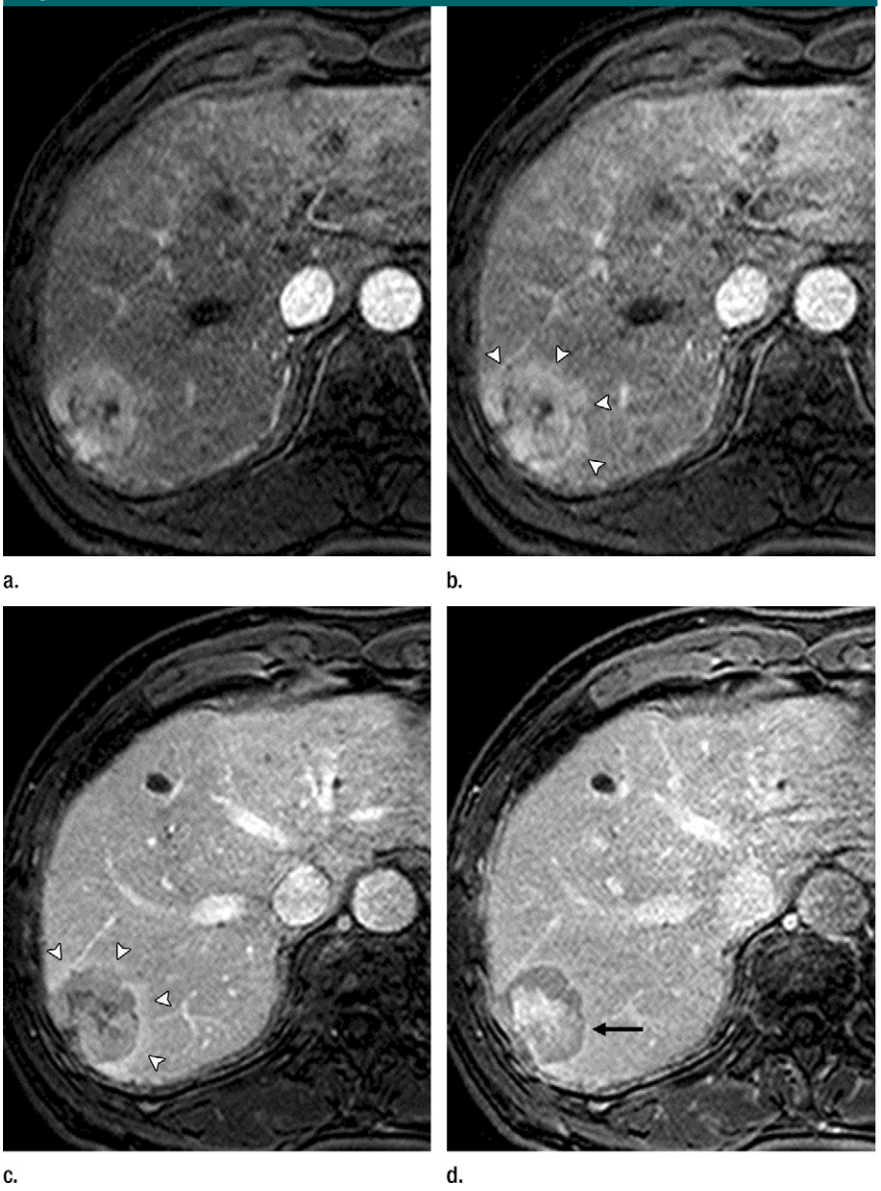


Figure 7: MR images in a 66-year-old man with HCC show corona enhancement and capsule appearance. T1-weighted 3D GRE images with fat suppression (3.2/1.6; 10° flip angle) obtained in **(a)** early and **(b)** late hepatic arterial phase after administration of gadolinium-based contrast agent show hyperenhancing mass in segment VII. Note partially circumferential enhancement (arrowheads) of variable thickness in the liver parenchyma around the mass in the late hepatic arterial phase. The enhancement of the perilesional parenchyma (arrowheads) fades in **(c)** the portal venous phase and is resolved by **(d)** the 3-minute delayed phase. The transient enhancement of the perilesional parenchyma is known as corona enhancement; this is thought to represent the area of liver parenchyma receiving venous drainage from progressed HCC and to be a frequent site of satellite metastases. Note the mass also has capsule appearance (arrow, **d**); as opposed to corona enhancement, which fades in the venous phases, capsule appearance manifests as progressively enhancing rim.

Corona enhancement is a feature of hypervascular, progressed HCC and refers to enhancement of the venous drainage area in the peritumoral parenchyma (124,125). As discussed in part I, venous drainage evolves during multistep hepatocarcinogenesis from hepatic veins (cirrhotic nodules, dysplastic nodules, and early HCCs) to sinusoids (unencapsulated progressed HCCs) to portal venules (encapsulated progressed HCCs). The sinusoids and portal venules draining progressed HCCs communicate with the sinusoids in the perinodular hepatic parenchyma; these drainage vessels carry contrast material from the tumor into the surrounding sinusoids, resulting in corona-shaped perinodular enhancement a few seconds after the tumor itself begins to enhance. Corona enhancement initially was described at CT during hepatic arteriography (126) but it also can be seen at multiphasic CT or MR imaging (127). It manifests as a transient zone or rim ("corona") of enhancement around a progressed, hypervascular HCC in the late arterial phase or early portal venous phase, with fading to isoenhancement at subsequent phases (Fig 7). Although corona enhancement begins a few seconds after tumor enhancement, corona and tumor enhancement may appear to overlap if only a single acquisition is obtained during the arterial phase, and the corona may blend into the tumor. This overlap and blending may cause the tumor to appear larger than it really is at conventional CT or MR imaging (128) and also makes recognition of corona enhancement difficult; some investigators have proposed the use of high-temporal-resolution multiarterial phasic imaging from early to late hepatic arterial phase to facilitate its recognition (127). Corona enhancement may have variable thickness and uniformity, and it may be circumferential or eccentric. Its presence helps to differentiate small hypervascular HCCs from pseudolesions, such as arterioportal shunts, which are not associated with this feature (120). The sensitivity and specificity at multiphasic CT and MR imaging of corona enhancement for the diagnosis of progressed HCC has not been studied prospectively, however. Corona enhancement is not a feature of early HCC, which is drained by hepatic veins, and so does not help in the diagnosis of early HCC (128).

Beyond its potential contribution to the diagnosis of progressed, hypervascular HCC, corona enhancement may convey prognostic information. Single-center retrospective studies have suggested that large (129) or irregular and/or distorted (112) corona enhancement predicts microvascular invasion. Also, metastatic satellite nodules and local recurrences after resection or ablation frequently develop in the corona enhancement areas (63). To more effectively treat such metastases and reduce the risk of recurrence, some authors have recommended that the corona enhancement areas be included within the surgical resection margin or ablation zone (63,125).

Nodule-in-nodule architecture refers to the presence of a nodule within a larger nodule or mass (12). This imaging appearance corresponds to the nodule-in-nodule growth pattern observed at histologic evaluation (130) and suggests the emergence of a progressed HCC within a dysplastic nodule or early HCC (131). The subnodule, corresponding to the progressed HCC, typically shows arterial phase hyperenhancement as well as hyperintensity on T2-weighted images (41) and, if a hepatobiliary agent is given, hypointensity in the hepatobiliary phase (Fig 8). The surrounding parent nodule, corresponding to more well-differentiated tissue, typically is T1 hyperintense, T2 hypointense (132), and arterial phase hypo- or isoenhancing (85). The parent nodule may be fatty or iron rich (siderotic); the inner nodule usually contains less fat and, reflecting the iron "resistance" of neoplastic hepatocytes, less iron (133), While nodule-in-nodule configuration is characteristic of HCC, it is seen infrequently at CT and MR imaging (131), and the sensitivity and specificity of this feature for the diagnosis of HCC has not been established.

Mosaic architecture refers to the presence within a mass of randomly distributed internal nodules or compartments differing in enhancement (in the dynamic vascular phases or, if a hepatobiliary agent is administered, in the hepatobiliary phase), attenuation, intensity, shape, and size and often separated by fibrous septations (12,134) (Fig 1). The appearance is characteristic of and frequently observed in large HCCs (135) and reflects the mosaic configuration observed at pathologic examination (132). Although heterogeneity is a common characteristic of many liver lesions, mosaic architecture is unusual in tumors other than HCC, and so this feature helps in the differentiation of HCC from ICC. As mosaic architecture is uncommon in small HCCs (46,131), the incremental value of this feature for the diagnosis of small HCC is uncertain.

Figure 8

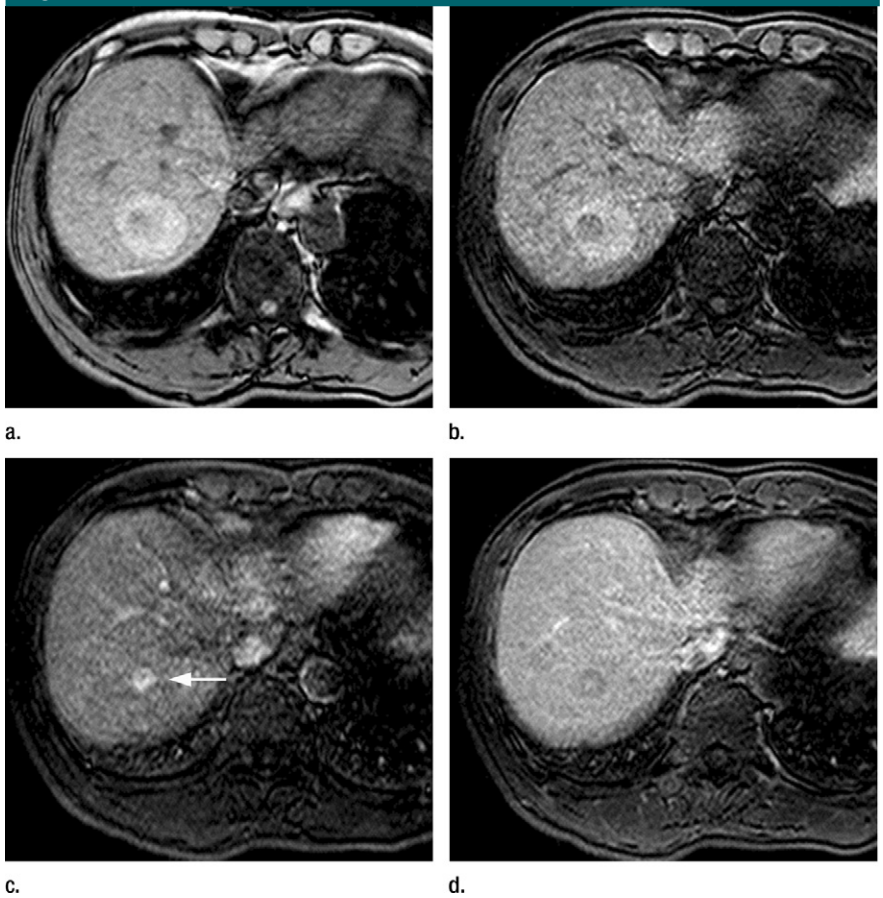


Figure 8: MR images in a 68-year-old man with HCC show nodule-in-nodule architecture. **(a)** Axial opposed-phase T1-weighted fast field echo image (181.3/2.3; 80° flip angle) and **(b)** precontrast T1-weighted 3D GRE image show hypointense inner nodule (1.5 cm) within hyperintense outer nodule (3.7 cm), consistent with nodule-in-nodule architecture. **(c)** Gadolinium-enhanced 3D GRE image in late hepatic arterial phase shows arterial hyperenhancement of inner nodule (arrow); outer nodule is isointense to liver. **(d)** Inner nodule shows washout appearance on 3-minute delayed phase image and, except for a small central area, is hypointense relative to outer nodule and surrounding liver; outer nodule remains isointense and is imperceptible on this image. Arterial phase hyperenhancement and venous phase washout appearance of inner nodule suggest progressed HCC arising within more well-differentiated parent nodule.

Ancillary Features That Favor the Diagnosis of Malignancy but Are Not Specific for HCC

Mild-moderate T2 hyperintensity refers to signal intensity on T2-weighted images that unequivocally is greater than that of background liver but less than that of bile ducts or other simple–fluid-filled structures (12). This feature is typical of HCC and has been described

Figure 9

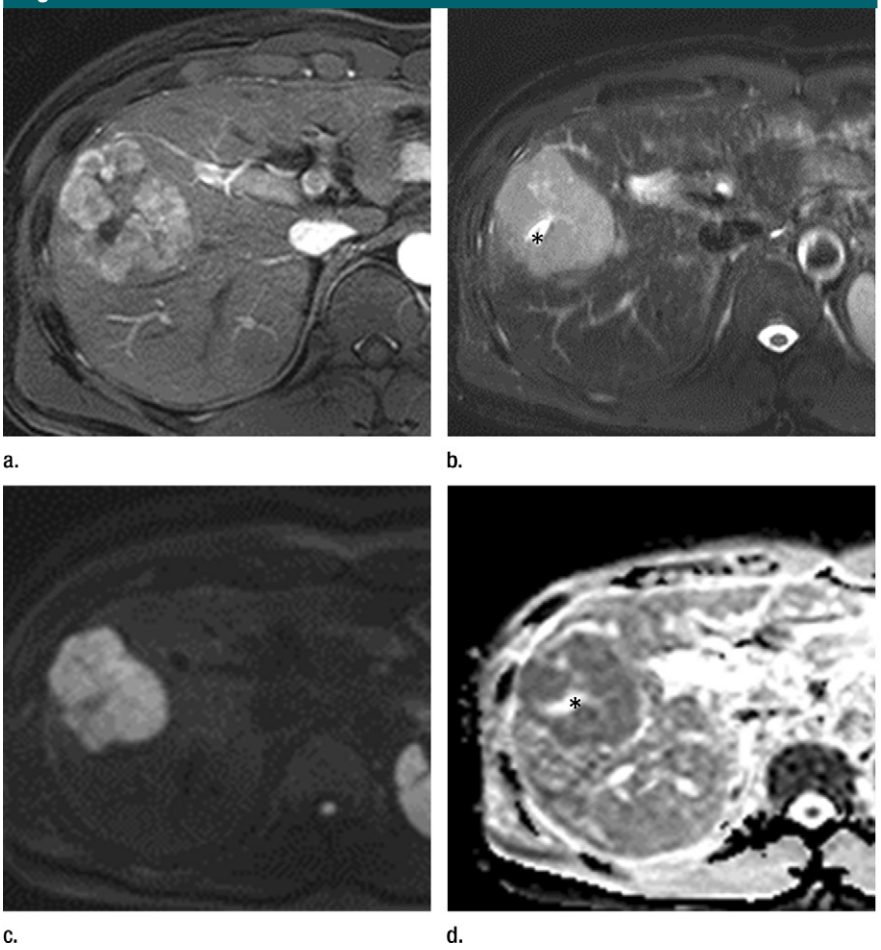


Figure 9: MR images in a 46-year-old man with hepatitis B–related cirrhosis and HCC show restricted diffusion. **(a)** Gadoxetate disodium–enhanced T1-weighted 3D GRE image (3.0/1.4; 10° flip angle) acquired in late hepatic arterial phase shows large heterogeneous mass with mosaic architecture measuring 6 cm in right lobe of liver. **(b)** Mass is moderately hyperintense on T2-weighted turbo spin-echo image (951/80). **(c)** Diffusion-weighted image (b = 800 sec/mm^2) shows hyperintensity, suggesting restricted diffusion, confirmed on **(d)** ADC map. Estimated ADC is 1010 mm^2/sec. Restricted diffusion is highly suggestive of malignancy but not specific for HCC. Mosaic architecture in arterial phase and washout appearance in venous phases (not shown) permit specific diagnosis of HCC. Note central necrotic component within tumor (*). Necrotic component is markedly hyperintense on T2-weighted image (**b**), and has relatively unrestricted diffusion (**d**).

in 77% of HCCs larger than 3 cm (136). By comparison, cirrhotic nodules and dysplastic nodules characteristically are isointense or hypointense on T2-weighted images and rarely show mild-moderate T2 hyperintensity (137). Thus, mild-moderate hyperintensity in a nodule in a cirrhotic liver on T2-weighted images is highly suggestive of malignancy (137). However, this feature is not specific for HCC per se, as ICCs and metastases to the liver typically are T2 hyperintense as well. Thus, the presence of mild-moderate T2 hyperintensity cannot be used to establish the diagnosis of HCC in the absence of HCC-specific features. Moreover, mild-moderate T2 hyperintensity lacks sensitivity for HCC diagnosis. Many well-differentiated HCCs and some small moderately differentiated HCCs are T2 isointense or hypointense (136,138), while those with mild-moderate T2 hyperintensity may be obscured on T2-weighted images by parenchymal fibrosis (132). Finally, the incremental value of mild-moderate T2 hyperintensity for the diagnosis of HCC is modest, as most HCCs with this feature are progressed lesions that can be detected based on vascular or hepatobiliary phase imaging features. As a corollary, mild-moderate T2 hyperintensity suggests advanced tumor grade and so may have prognostic significance (136,139).

As opposed to mild-moderate T2 hyperintensity, diffuse marked T2 hyperintensity favors a benign etiology (12), as this signal pattern is characteristic of cysts and hemangiomas but not HCC. Similarly, although mild T2 hypointensity is nonspecific—with the differential diagnosis including dysplastic nodules and some cirrhotic nodules as well as HCCs—marked uniform hypointensity on T2-weighted images indicates the presence of iron, which as discussed in part I suggests a nonmalignant etiology (12).

Restricted diffusion refers to the presence of higher signal intensity than background liver, not attributable solely to T2 shine-through, on diffusion-weighted images acquired with at least moderate diffusion weighting (eg, b value ≥ 400 sec/mm^2) (12). If an apparent diffusion coefficient (ADC) map is generated, the ADC of the lesion should be similar to or lower than that of liver by visual estimation (Fig 9). For masses that cannot be categorized as definite HCC based on other features, the presence of diffusion restriction favors the diagnosis of malignancy and helps differentiate HCC from dysplastic nodule (140). The underlying basis for diffusion restriction in malignant tumors is not completely understood; however, hypercellularity is assumed to be the main cause (141). Restricted diffusion also helps differentiate small hypervascular HCCs from hypervascular pseudolesions, which usually are isointense on diffusion-weighted images (142). Diffusion-weighted imaging also may increase the conspicuity of HCC nodules that on images from other sequences have low lesion-liver contrast or are obscured by high-signal-intensity vessels. Many but not all (143) studies have shown that the addition of diffusion-weighted imaging to MR imaging

examinations incrementally increases the detection rate of HCC (32,142) and intrahepatic HCC metastases (144). The sensitivity of diffusion-weighted imaging for HCC detection is low, however. Many HCCs, particularly those with well-differentiated components, have no or only minimal diffusion restriction (143). Moreover, the background fibrotic/cirrhotic parenchyma frequently has reduced diffusivity compared with normal liver, thereby reducing lesion-liver contrast on diffusion-weighted images (32,141). Thus, in a mass with other imaging features of HCC, absence of diffusion restriction should not downgrade the suspicion level for HCC (132). Another challenge is that restricted diffusion is not specific for HCC as it may be observed in ICCs and other non-HCC malignancies (145). Similarly, small HCCs and hemangiomas may overlap in diffusion-weighted signal intensity (146). Thus diffusion-weighted images need to be interpreted in conjunction with other images. Unfortunately, diffusion-weighted images are prone to spatial distortion and other artifacts, which complicates the co-localization and interpretation of small nodules.

In nodules that can be diagnosed as HCC based on other imaging features, restricted diffusion may be of prognostic value. Retrospective studies have suggested that restricted diffusion, as assessed by signal intensity ratio or ADC measurement, can be used to predict higher tumor grade (69,147,148), presence of progenitor cell markers (107), microvascular invasion (149), and early recurrence after resection (150). Results have been inconsistent, however, and some investigators have found no correlation between ADC and HCC tumor grade (151). It should be emphasized, moreover, that ADC and diffusion-weighted signal-intensity ratios are technique, field strength, and scanner dependent; hence, diffusion-weighted–based prediction thresholds may not be generalizable. Additionally, some investigators have suggested that restricted diffusion may aid in the differentiation of macrovascular invasion from bland venous thrombus (77); however, other investigators have found that restricted diffusion does not aid in this differentiation due to substantial overlap in ADCs between bland thrombus and macrovascular invasion (78). Owing to these conflicting results, caution should be exercised in using diffusion-weighted images for differentiating bland from malignant thrombus.

Lesional iron sparing refers to relative paucity of iron in a solid mass compared with that of background iron-overloaded liver (12). This feature can be detected on T2- or T2*-weighted MR images by observing hyperintensity in a solid mass relative to hypointense, siderotic hepatic parenchyma. Lesional iron sparing raises concern for premalignancy or malignancy because high-grade dysplastic nodules and HCCs characteristically are iron "resistant." Thus, any iron-free solid nodule in an otherwise iron-overloaded liver should be regarded as suspicious for high-grade dysplastic nodule or HCC (152). This feature is not specific for high-grade dysplastic nodule/HCC, however, as it also is observed in ICC and other non-HCC malignancies. Also, confluent fibrosis tends to be iron-free and, if masslike in configuration, conceivably could be mistaken for a tumor.

As discussed above, unenhanced T1-weighted imaging may contribute to the assessment of ancillary features such as intralesional fat, nodule-in-nodule architecture, and mosaic architecture. Otherwise, unenhanced T1-weighted imaging plays a relatively minor role in the diagnosis of HCC, because HCCs and nonmalignant hepatic nodules have variable and overlapping T1 signal intensity (134,137). However, the signal intensity on T1-weighted images may help in characterizing nodules that can be diagnosed as definite HCC based on other features. Studies have shown that T1-hypointense HCC nodules tend to have higher tumor grade (71) while T1-hyperintense HCC nodules tend to have lower tumor grade (71,139).

Conclusion

Currently all clinical practice guidelines recommend multiphasic CT and MR imaging with extracellular agents for diagnosis and staging of HCC; these modalities provide valuable information regarding vascularity and have excellent accuracy for diagnosis of large nodular HCCs, but they have limited sensitivity for early HCCs as well as for small and progressed HCCs. Emerging evidence suggests that MR imaging with hepatobiliary agents may be the most sensitive technique for detection of such HCCs, but confirmatory studies, especially in patients with advanced cirrhosis, are needed. Despite the importance of macrovascular invasion for tumor staging, treatment planning, and prognosis, the sensitivity and specificity of state-of-the-art CT and MR imaging for its diagnosis is not well known due to paucity of studies on this subject. Ancillary imaging features provide incremental information that helps to characterize nodules and may improve the sensitivity for HCC. Some ancillary imaging features show promise for predicting tumor grade or microvascular invasion, but independent confirmatory studies are needed to validate these features for these purposes.

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