AJR FOCUS ON:

Gadoxetate Disodium–Enhanced MRI of the Liver: Part 2, Protocol Optimization and Lesion Appearance in the Cirrhotic Liver

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OBJECTIVE. The purpose of this article is to review the use of gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (gadoxetate disodium [Gd-EOB-DTPA]) in the cirrhotic liver and illustrate the imaging appearance of lesions commonly encountered in the cirrhotic liver.

CONCLUSION. Gd-EOB-DTPA shows promise as a problem-solving tool in the cirrhotic liver because it provides additional information that may be helpful in lesion detection and characterization. Further research is needed to optimize Gd-EOB-DTPA imaging protocols in cirrhosis and develop diagnostic criteria for liver lesions in the cirrhotic liver.

Keywords: cirrhosis, gadoxetate disodium (Gd-EOB-DTPA), hepatocellular carcinoma, MRI, nodules

DOI:10.2214/AJR.10.4538

Received March 2, 2010; accepted after revision April 28, 2010.

Supported by a grant from the Comprehensive Research Center in Health Disparities.

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AJR 2010; 195:29–41

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As in the noncirrhotic liver, MRI has evolved into an important technique in the evaluation of focal and diffuse abnormalities in the cirrhotic liver. Historically, extracellular gadolinium-based contrast agents have played a critical role in MRI of the cirrhotic liver because these agents help to detect and characterize important abnormalities, including benign and malignant nodules. Detection and characterization of abnormalities using gadolinium-based contrast agents is based mainly on assessment of vascularity. Such assessment may be limited, however, because some abnormalities in the cirrhotic liver may not be associated with vascular alteration, whereas others may have nonspecific features at vascular imaging. Combined extracellular–hepatobiliary gadolinium-based contrast agents recently have been developed. These agents assess hepatocellular function in addition to vascularity and hence may overcome some of the limitations of pure extracellular agents for lesion detection and characterization in the cirrhotic liver (Fig. 1). Two combined agents are now available, gadobenate dimeglumine (MultiHance, Bracco), and gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid (Gd-EOB-DTPA), also known as gadoxetate disodium, gadoxetic acid, or gadoxetate disodium (Eovist, Bayer HealthCare and Primovist, Bayer Schering Pharma). This article will focus on the use of Gd-EOB-DTPA in the cirrhotic liver. Although many of the principles of Gd-EOB-DTPA use in the cirrhotic liver are similar to those discussed in the companion article (also in this issue) on the noncirrhotic liver, the cirrhotic liver presents unique challenges that may require modifications in image acquisition technique or image interpretation. In parallel with the companion article, this article will review the pharmacokinetic and pharmacodynamic properties of this agent peculiar to the cirrhotic liver, discuss issues relevant to MRI protocol optimization for the cirrhotic liver, and illustrate the imaging appearance of common lesions in the cirrhotic liver. Emphasis will be placed on areas in which the cirrhotic liver and its assessment differ from those of the noncirrhotic liver.

Pharmacokinetic and Pharmacodynamic Properties of Gd-EOB-DTPA in Cirrhosis

In patients with early or well-compensated cirrhosis, the pharmacokinetics and pharmacodynamics of Gd-EOB-DTPA are similar to those in noncirrhotic livers, as discussed in the companion article. In patients with advanced or decompensated cirrhosis, however, three important differences may be present: diminished and delayed liver parenchymal enhancement with Gd-EOB-DTPA, diminished and delayed biliary excretion of Gd-EOB-DTPA, and prolonged blood pool enhancement with Gd-EOB-DTPA.

Diminished and Delayed Liver Parenchymal Enhancement With Gd-EOB-DTPA

Compared with the noncirrhotic liver, the cirrhotic liver may have diminished parenchymal enhancement in the hepatocyte phase after Gd-EOB-DTPA injection, and the time to peak

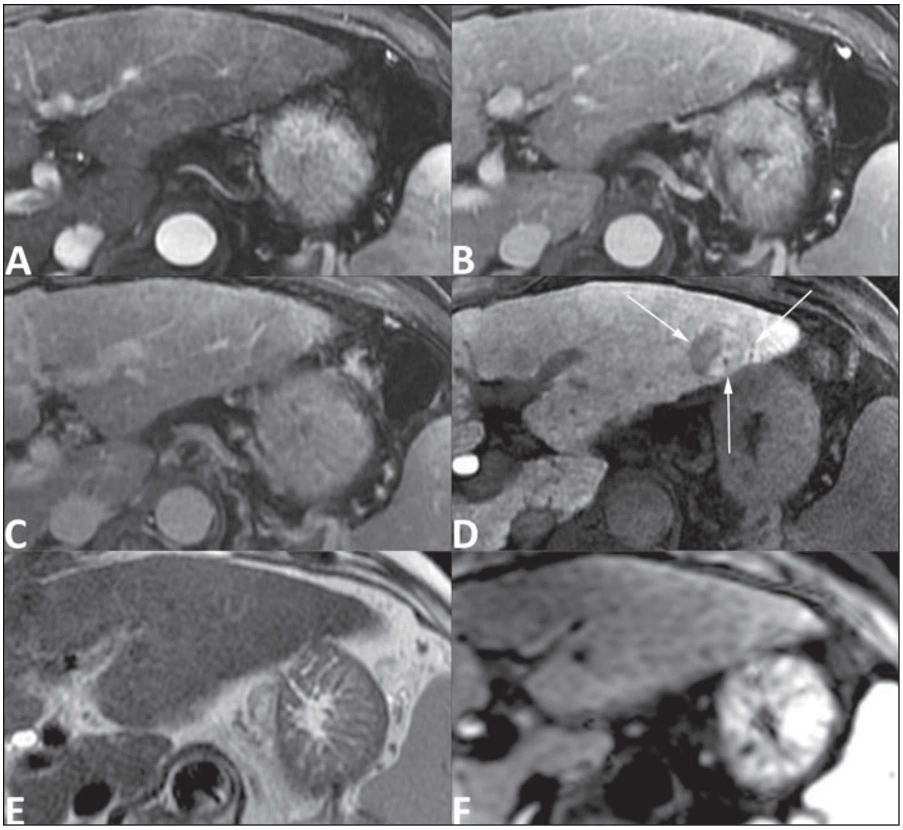


Fig. 1—57-year-old man with cirrhosis secondary to hepatitis B virus infection. This case illustrates advantage of hepatocyte phase of gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) over dynamic phases in both detection and characterization of lesions.
A–C, T1-weighted 3D gradient-echo images obtained at 3 T using extracellular gadolinium-based contrast agent in hepatic arterial phase (**A**), portal venous phase (**B**), and delayed phase (**C**) show no obvious lesion in left lobe of liver.
D–F, Images acquired 2 days later show 2-cm mass in lateral segment of left lobe (*arrows*) visible only in hepatocyte phase of Gd-EOB-DTPA (**D**). On hepatocyte phase, mass has heterogeneous appearance due to mixed cellular components, some of which accumulate contrast agent and thus appear hyperintense whereas others do not and thus appear hypointense. Mass is isointense to liver on T2-weighted single-shot fast spin-echo image (**E**) and on b = 500 s/mm^2 diffusion-weighted image (**F**). At follow-up imaging 1 year later, mass was stable both in size and imaging features. Given imaging features and stability over time, mass is thought to represent dysplastic nodule with varying degrees of cellular atypia, although indolent HCC cannot be excluded.

enhancement may be delayed. Thus, whereas Gd-EOB-DTPA produces peak parenchymal enhancement of the normal liver by 20 minutes [1], enhancement of the cirrhotic liver may be modest and the peak may not be achieved for 40 or more minutes. The reason for the diminished and delayed enhancement is that hepatic signal intensity in the hepatocyte phase depends on uptake of Gd-EOB-DTPA from the extracellular space into hepatocytes by the ATP-dependent organic anion transporting polypeptide 1 (OATP1) and subsequent excretion into the biliary canaliculi by the canalicular multispecific organic anion transporter (cMOAT). These transport mechanisms may be impaired in patients with cirrhosis [2–4], presumably due to reduced functional hepatocellular mass or dysfunctional transporters.

The uptake of Gd-EOB-DTPA in cirrhotic livers is variable and may be difficult to predict. Motosugi et al. [5] showed that Child-Pugh classifications and indocyanine green clearance tests 15 minutes after injection significantly correlated with liver enhancement in the hepatocyte phase, but bilirubin levels, albumin, prothrombin activity, aminotransferase levels, alkaline phosphatase, and γ-glutamyl transpeptidase did not [5]. The authors concluded that routine serum liver chemistry tests might not be helpful in predicting adequate liver enhancement on the hepatocyte phase. The limited efficacy of routine liver serum chemistries to predict enhancement is not unexpected. Bilirubin levels are markers of hepatocellular excretory function but not of uptake. Whereas albumin and prothrombin activity are markers of synthetic function, aminotransferase levels relate to hepatocellular injury, alkaline phosphatase levels relate to cholestasis, and γ-glutamyl transpeptidase levels relate to cell membrane damage and cellular regeneration [6]. The cause of cirrhosis conceivably may impact the degree of enhancement, and this possibility merits further investigation.

Diminished and Delayed Biliary Excretion of Gd-EOB-DTPA

In the noncirrhotic liver, Gd-EOB-DTPA produces intense biliary luminal enhancement that begins as early as 5 minutes after contrast injection [7]. This enhancement is due to uptake of the agent by hepatocytes, with subsequent excretion into the biliary system. Because of impaired hepatocellular uptake and excretion of Gd-EOB-DTPA in cirrhosis, enhancement of bile ducts in the cirrhotic liver may be delayed and of limited intensity.

Prolonged Blood Pool Enhancement With Gd-EOB-DTPA

In patients without cirrhosis, the signal intensity of the vascular lumen declines rapidly after peak enhancement after Gd-EOB-DTPA injection, returning to the baseline unenhanced signal after 10 minutes [8]. A plausible explanation for the rapid signal decline is that the agent is cleared from the blood via two elimination pathways, with 50% of the administered dose of Gd-EOB-DTPA cleared by the liver and the remainder via the kidneys [9]. In patients with advanced cirrhosis or cholestasis, the hepatic elimination pathway is impaired, resulting in slower clearance from the blood. Thus, Gd-EOB-DTPA tends to have a more prolonged plasma half-life in patients with cirrhosis or cholestasis compared with those with normal livers, and blood vessels may appear hyperintense for a longer duration (Fig. 2). Concomitant renal insufficiency, which is quite common in patients with advanced liver disease, may exacerbate prolongation of the vascular dwell time.

Although blood pool enhancement may be relatively prolonged in cirrhosis, the peak enhancement of hepatic and portal veins is still shorter in duration and lower in intensity using Gd-EOB-DTPA than using con-

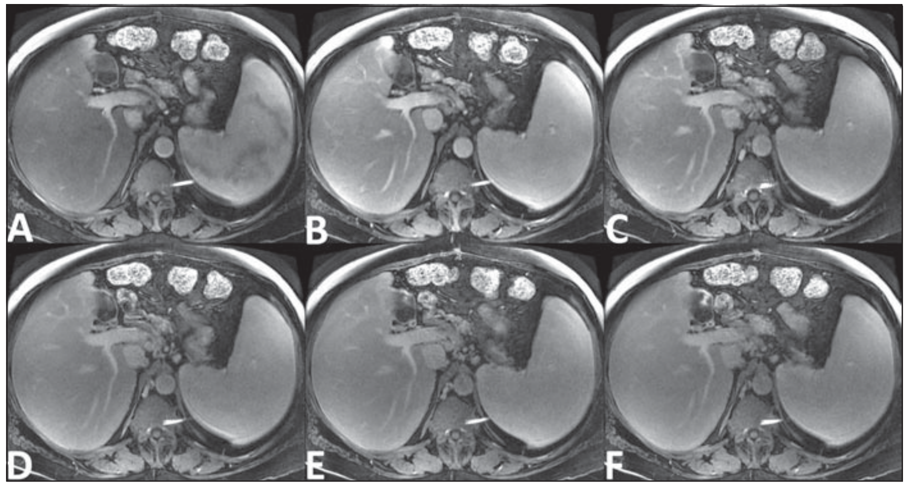


Fig. 2—57-year-old man with cirrhosis secondary to hepatitis C virus infection and alcohol consumption, with biliary cholestasis.
A–F, T1-weighted 3D gradient-echo images obtained at 3 T using gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) at 22 seconds (**A**), 1 minute (**B**), 3 minutes (**C**), 14 minutes (**D**), 20 minutes (**E**), and 32 minutes (**F**) after contrast injection show prolonged blood pool dwell time of contrast agent, with vessels hyperintense even at 32 minutes after contrast injection. Also note liver parenchyma has signal intensity similar to that of spleen, indicative of poor uptake of Gd-EOB-DTPA by hepatocytes. In patients with normal liver, liver parenchyma is hyperintense and blood vessels hypointense in hepatocyte phase (see Fig. 3).

ventional extracellular gadolinium-based contrast agents. The relatively low contrast enhancement of veins is relevant because assessment of venous patency is an important aspect of radiologic interpretation in the cirrhotic liver. In principle, diminished venous enhancement using Gd-EOB-DTA may reduce sensitivity for detecting venous obstruction, but this potential limitation has not been verified in the published literature to our knowledge.

Protocol Optimization for Hepatobiliary Imaging With Gd-EOB-DTPA in Cirrhotic Liver

The technical aspects of Gd-EOB-DTPA administration and protocol optimization have been covered in part 1 of this article. Similar concepts apply in the cirrhotic liver and a similar protocol can be used, with the following additional considerations.

Acquisition of an adequately enhanced hepatic arterial phase is particularly important in cirrhosis because lesion vascularity is a key feature for detecting hepatocellular carcinomas (HCCs) and differentiating HCCs from most benign hepatocellular nodules [10]. A concern in using Gd-EOB-DTPA for HCC assessment in cirrhotic liver is it may be more difficult to achieve optimal hepatic arterial phase enhancement. Studies have shown the signal intensity of vessels in the dynamic phase is less with Gd-EOB-DTPA than extracellular gadolinium-based contrast agents [8]. The on-label approved dose of Gd-EOB-DTPA is 0.025 mmol/kg. Because this dose is one fourth of the recommended standard dose of conventional extracellular gadolinium-based contrast agents, Gd-EOB-DTPA provides a shorter peak arterial perfusion time window, which makes the selection of an appropriate scanning delay difficult. Because of these factors, the hepatic arterial phase using Gd-EOB-DTPA at its approved dose tends to provide low sensitivity for detection of hypervascular HCC lesions [11–13] despite the higher T1 relaxivity of the agent compared with other gadolinium-based contrast agents.

As discussed in the companion article on the noncirrhotic liver, one solution for achieving optimal arterial phase timing is to acquire several consecutive arterial phase data sets using a fixed delay. A second solution is to stretch the contrast bolus by diluting the contrast agent or injecting at a slower rate. In the cirrhotic liver, a third solution may be to administer the agent at a higher off-label dose (e.g., 0.0375–0.05 mmol/kg), although this may increase the incurred cost of the agent. Even though this dose (0.0375–0.05 mmol/kg) is 50–100% higher than the approved

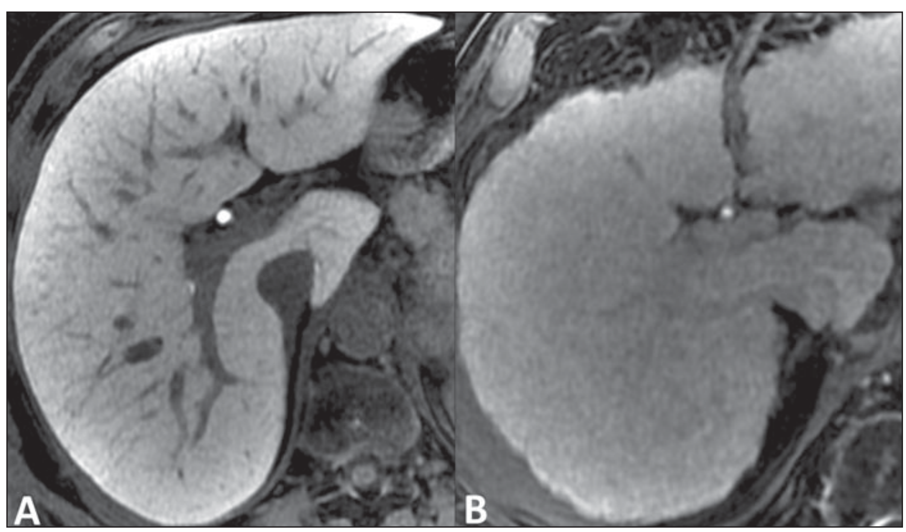


Fig. 3—Compensated and decompensated cirrhosis.
A and **B,** 44-year-old man with compensated, biopsy-proven cirrhosis secondary to hepatitis C virus (HCV) (**A**) and 65-year-old man with decompensated biopsy-proven cirrhosis secondary to HCV cirrhosis (**B**). Shown are gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)–enhanced T1-weighted 3D gradient-echo hepatocyte phase images obtained at 3 T. In patient with compensated cirrhosis (**A**), liver parenchyma is hyperintense due to preserved hepatocellular Gd-EOB-DTPA uptake mechanism. There is mild hypointense reticulation due to fibrotic septa, which do not take up contrast agent. Blood vessels are hypointense because of rapid clearance of agent from blood pool via both hepatobiliary and renal excretory pathways. There is intense enhancement of common bile duct because of hyperconcentration of contrast agent within lumen (compare with **B**). In patient with decompensated cirrhosis (**B**), liver is relatively featureless; blood vessels and liver parenchyma have intermediate signal intensity due to reduced clearance of Gd-EOB-DTPA from blood pool and diminished hepatocellular uptake, respectively. Also, enhancement of common bile duct is less intense than in patient with compensated cirrhosis, presumably reflecting lower intraluminal concentration of agent.

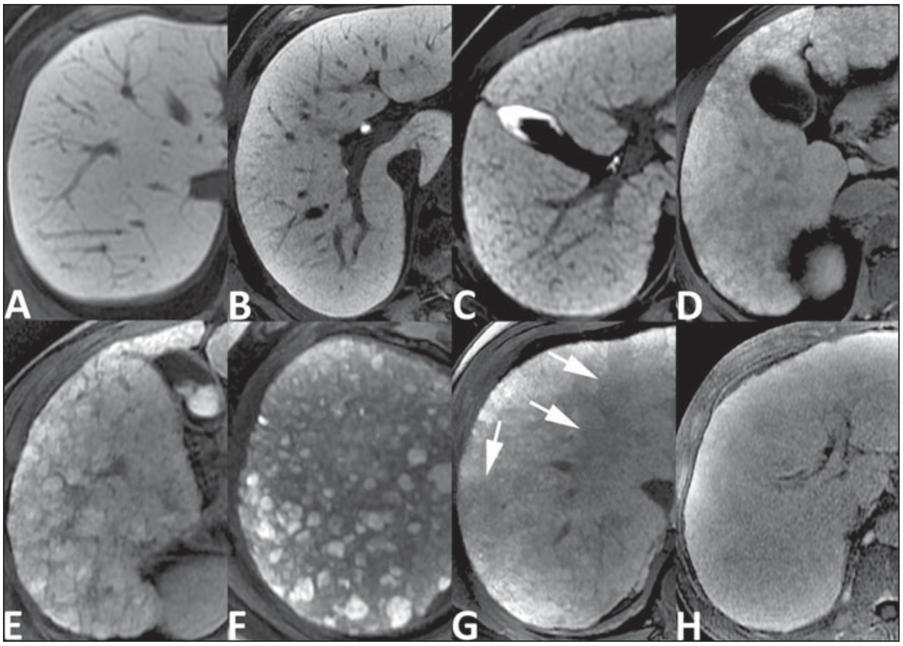


Fig. 4—Cirrhotic livers in different patients show broad spectrum of textural alterations in hepatocyte phase after gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) injection.
A–H, Shown are Gd-EOB-DTPA hepatocyte-phase T1-weighted 3D gradient-echo images obtained at 3 T in patient with a normal liver (**A**, same patient as in Fig. 3) and in patients with cirrhosis (**B–H**). Textural alterations in cirrhosis include fine reticulations (**B**), coarse reticulations (**C**, same patient as in Fig. 4A), parenchymal heterogeneity (**D**), discrete mildly hyperintense nodules (**E**), discrete markedly hyperintense nodules (**F**, same patient as in Fig. 10), broad bands of hypointensity representative of confluent fibrosis (*arrows*) (**G**), and featureless liver parenchyma (**H**). Note that normal liver has homogeneous texture without parenchymal reticulations (**A**).

dose (0.025 mmol/kg) of Gd-EOB-DTPA, it is still lower than the approved dose of any other gadolinium-based contrast agent. Thus, administering Gd-EOB-DTPA at an off-label, higher-than-approved dose, in principle, may help overcome the potential limitations of the agent when imaging the cirrhotic liver, while at the same time using a lower dose than with conventional gadolinium-based contrast agents. This off-label approach would prolong the peak arterial perfusion time window, thereby facilitating optimal arterial phase timing; increase the degree of arterial phase enhancement of hypervascular lesions; provide more intense luminal enhancement of portal and hepatic veins; and increase the degree of liver parenchymal enhancement in the hepatocyte phase. Further investigation is needed, however, to confirm that increasing the dose of Gd-EOB-DTPA improves diagnostic accuracy for malignant nodules or venous obstruction in the cirrhotic liver.

In addition to giving a larger dose, it may be helpful in cirrhotic livers to increase the delay at which hepatocyte phase images are acquired. Whereas a 20-minute delay is adequate for hepatocyte phase imaging in the normal liver, a greater delay may be beneficial in the cirrhotic liver for reasons previously discussed, although a prolonged delay may be impractical in clinical practice. The optimal delay for hepatocyte phase imaging in patients with cirrhosis requires further investigation.

Gd-EOB-DTPA has been shown to be useful in contrast-enhanced MR cholangiography (MRC) in patients with normal livers [7, 14], although the agent is not FDA approved for this purpose. Whereas intense signal enhancement of the common bile duct in noncirrhotic livers begins at 5–15 minutes after Gd-EOB-DTPA injection [7], peak intensity may be reduced and the onset delayed in patients with cirrhosis, as discussed earlier. In one study, only 40% of patients with cirrhosis had sufficient biliary visualization for anatomic diagnosis within 30 minutes of Gd-EOB-DTPA injection, and only 52% had sufficient visualization at 3 hours, compared with 100% visualization after 20 minutes in the control noncirrhotic group [2]. Use of Gd-EOB-DTPA in patients with cirrhosis for contrast-enhanced MRC is therefore likely to be challenging because optimal biliary tree visualization is infrequent and the degree and timing of biliary excretion are unpredict-

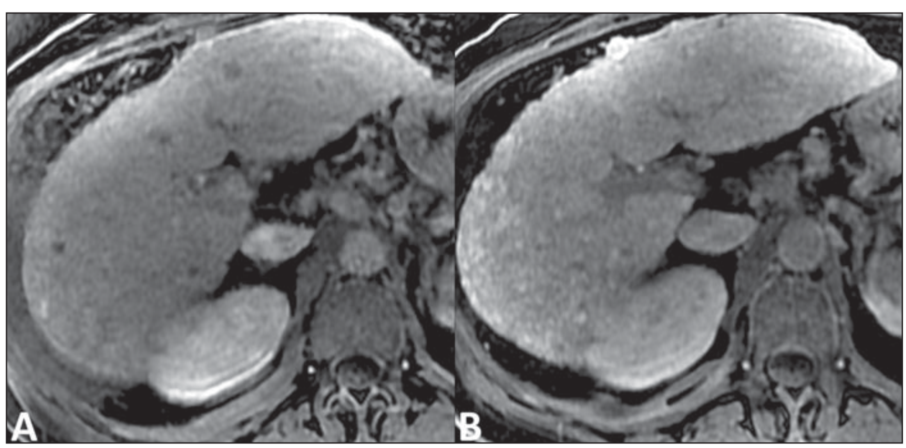


Fig. 5—48-year-old woman with alcohol-induced cirrhosis.
A and **B,** Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)–enhanced T1-weighted 3D gradient-echo hepatocyte phase images obtained at 3 T in same patient 1 year apart. Soon after initial study (**A**), patient stopped consuming alcohol. On both imaging studies, identical dose of Gd-EOB-DTPA was administered, and hepatocyte phase images were obtained 30 minutes after contrast agent injection. On initial study (**A**), patient had decompensated cirrhosis with Model of End-Stage Liver Disease (MELD) score > 30. On follow-up image (**B**), patient's cirrhosis was well compensated with MELD score < 10. Decompensated cirrhotic liver is featureless with both liver parenchyma and blood vessels having intermediate signal. Note liver parenchyma is hypointense to kidney. By comparison, compensated cirrhotic liver parenchyma is hyperintense relative to vessels and nearly isointense to kidney. Numerous hyperintense hepatocellular nodules are now evident.

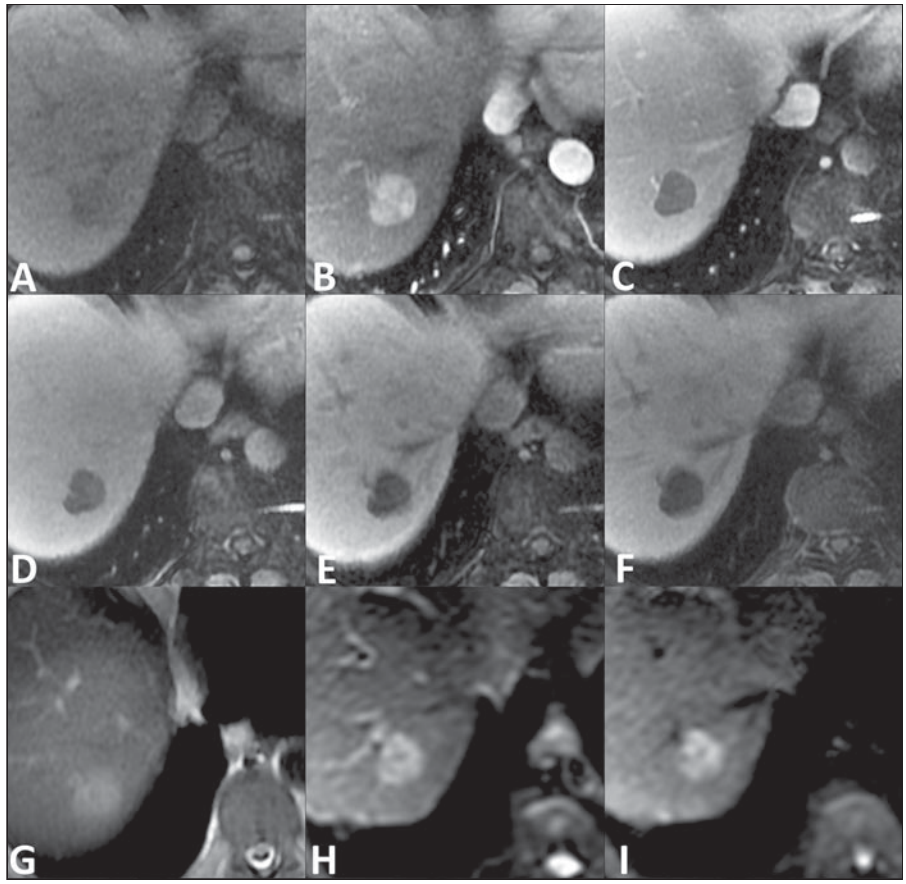


Fig. 6—56-year-old man with hepatitis C virus cirrhosis.
A–I, T1-weighted 3D gradient-echo images obtained at 3 T prior to contrast administration (**A**) and 22 seconds (**B**), 1 minute (**C**), 5 minutes (**D**), 15 minutes (**E**), and 20 minutes (**F**) after gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) administration. Also shown are T2-weighted single-shot fast spin-echo image (**G**) and diffusion-weighted images at b = 0 s/mm^2 (**H**) and b = 500 s/mm^2 (**I**). Note 25-mm hepatocellular carcinoma nodule is visible in segment VI of liver. It avidly enhances in hepatic arterial phase (**B**) then rapidly washes out in portal venous phase (**C**) and remains hypointense in hepatocyte phase images (**D**–**F**) because it lacks functional hepatocytes. Background liver parenchyma progressively enhances because of hepatocellular uptake of Gd-EOB-DTPA, which accentuates apparent washout of lesion relative to liver. Nodule is mildly hyperintense to background liver on T2-weighted image (**G**) and moderately hyperintense on diffusion-weighted images (**H** and **I**).

able. By comparison, acquisition of T2-weighted MRC images may be less problematic after Gd-EOB-DTPA administration in patients with cirrhosis because there is delayed contrast excretion into the bile ducts and the degree of T2 shortening is not as pronounced. The efficacy of T2-weighted MRC images after Gd-EOB-DTPA administration in cirrhosis has not been studied, however, and the routine acquisition of such images is not recommended.

At our institution, we initially used Gd-EOB-DTPA as a problem-solving tool in cirrhosis, but with accruing experience, we now use the agent routinely in cirrhosis with the following exceptions: evaluation of vascular patency, assessment of ablated lesions for residual or recurrent disease, and in patients whose bilirubin level is above 3 mg/dL. For these exceptions, we use extracellular gadolinium-based contrast agents rather than Gd-EOB-DTPA.

Our Gd-EOB-DTPA MR sequence protocol for patients with cirrhosis is evolving. The current protocol starts with acquisition of a multiplanar localizer followed by unenhanced 2D coronal T2-weighted single shot fast spin-echo and 2D axial T1-weighted in- and out-of-phase fast spoiled gradient-echo images. Heavily T2-weighted MRCP sequences, if indicated, are performed before contrast administration.

For Gd-EOB-DTPA–enhanced imaging, we administer a weight-adjusted dose of Gd-EOB-DTPA rounded up to the nearest bottle in patients with normal renal function—that is, patients receive either 10 or 20 mL of Gd-EOB-DTPA depending on their weight. For patients with an estimated glomerular filtration rate of less than 60 mL/min, however, a weight-adjusted dose is administered without rounding. The contrast agent is injected at a rate of 1 mL/s, followed by 20 mL of saline chaser injected at a rate of 2 mL/s. In all patients, we use a fixed delay of 20 seconds between the initiation of the contrast administration and the start of data acquisition for the arterial phase. We acquire two consecutive arterial phases (double arterial) in a single 20- to 30-second breath-hold using an axial fat-suppressed 3D T1-weighted gradient-echo sequence with parallel imaging and a 1.5–2 acceleration factor. A single portal venous phase is acquired as soon as the patient is ready for another breath-hold, usually 15–30 seconds after completion of the arterial phase data acquisition. This is acquired with slightly higher spatial resolution than the arterial phase acquisition and without parallel imaging if possible. Late dynamic phase imaging is done 2–3 minutes after contrast injection using the identical sequence as for portal venous phase data acquisition, immediately followed by a single-phase 3D coronal T1-weighted gradient-echo sequence.

We then perform echo-planar diffusion-weighted imaging and 2D axial single-shot spin-echo sequences followed by sequential axial fat-suppressed 3D T1-weighted gradient-echo sequences until the major bile ducts intensely enhance with the contrast agent or until at least 30 minutes after contrast injection, whichever is sooner.

Detection and Characterization of Lesions in Cirrhotic Liver

Conventional MRI criteria that rely primarily on lesion vascularity are prone to false-negative and false-positive findings in cirrhotic livers. Cirrhosis is characterized by variable disturbances in hepatic blood flow because of progressive disruption of normal liver vascular anatomy and physiology, which makes interpretation of blood supply to hepatocellular

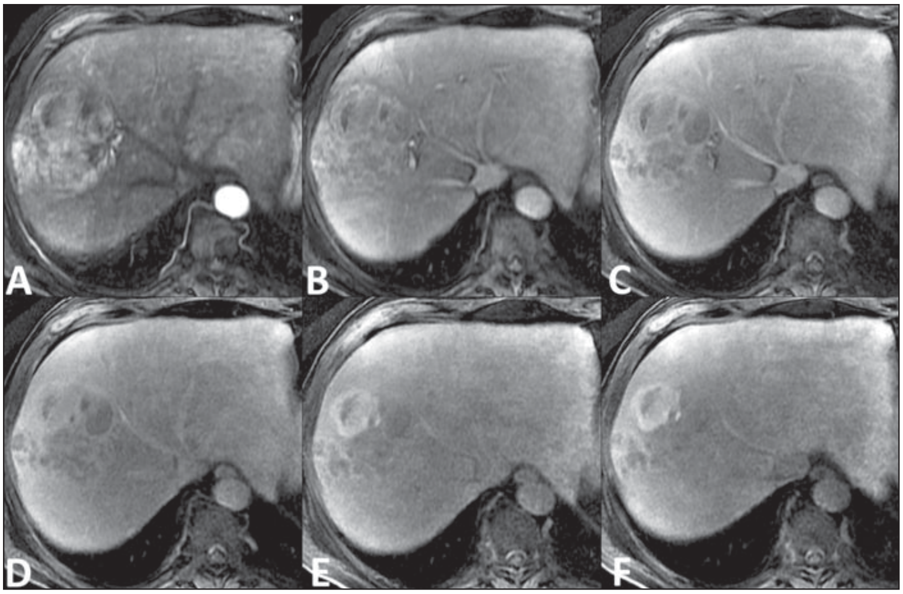


Fig. 7—65-year-old man with alcohol-induced cirrhosis.
A–F, Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) enhanced T1-weighted 3D gradient-echo images obtained at 3 T 24 seconds (**A**), 1 minute (**B**), 3 minutes (**C**), 7 minutes (**D**), 15 minutes (**E**), and 22 minutes (**F**) after contrast administration show 9-cm mass in right lobe of liver that has mosaic pattern of enhancement in arterial phase followed by washout at 1, 3, and 7 minutes. Mass then progressively accumulates Gd-EOB-DTPA starting at 15 minutes after contrast injection, giving it heterogeneous appearance in hepatocyte phase (**E** and **F**). Parts of mass appear iso-, hyper-, or hypointense to background liver parenchyma, suggesting variable degrees of cellular atypia in different parts of mass. Percutaneous biopsy of lesion was performed. Histological analysis revealed well-differentiated hepatocellular carcinoma. Because only one biopsy specimen was obtained, variable intralesional cellular atypia suggested by MR images could not be confirmed. At follow-up imaging 6 months later, initial mass had grown to 15 cm in diameter and cancer had become multifocal, indicating aggressive biologic behavior.

nodules difficult. For instance, well-differentiated HCCs may be portally perfused and show hypo- or isoenhancement; such HCCs thus evade detection or may be confused for benign nodules in the arterial imaging phase. As a corollary, benign cirrhotic tissue with altered vascularity may show arterial hyperenhancement and be confused for or obscure underlying HCC. Also, in a background of cirrhosis, the presence or absence of washout may be difficult to assess in small (< 2 cm) arterially enhancing lesions, and differentiation of malignant nodules from benign nodules and pseudolesions may be problematic.

The hepatocyte phase of Gd-EOB-DTPA may be useful in detecting iso- and hypovascular HCCs and in characterizing hypervascular lesions that are nonspecific in the vascular dynamic phases.

In the next section (Cirrhotic Liver Parenchyma), hepatocyte phase imaging features of hepatic parenchyma and of focal lesions in the cirrhotic liver are described. In general, focal lesions may be predominantly hypointense, isointense, hyperintense, or heterogeneous with a combination of various signal intensities in the hepatocyte phase, depending on the cellular composition of the lesions as well as the appearance of the background liver parenchyma (Table 1). Interpretation of Gd-EOB-DTPA–enhanced hepatocyte phase images should not be done in isolation but should be done in conjunction with both dynamic and unenhanced images (e.g., T1-, T2-, and diffusion-weighted images), while taking into account lesion size. Discussion of unenhanced features of liver parenchyma and liver lesions is beyond the scope of this review, however, because these features are unaffected by contrast agents. Interpretation of dynamic images (i.e., hepatic arterial phase, portal venous phase, and delayed phase) is similar to that of extracellular gadolinium-based contrast agents. As with extracellular agents, subtraction of baseline from dynamic Gd-EOB-DTPA–enhanced images may be helpful to assess enhancement of intrinsic T1-hyperintense nodules and lesions that have been treated with transarterial chemoembolization. However, subtraction should only be performed on well-registered images obtained with identical imaging parameters and calibration settings.

Cirrhotic Liver Parenchyma

As opposed to normal liver parenchyma, which typically is homogeneously hyperintense in the hepatocyte phase, the cirrhotic liver parenchyma has a variable appearance. In patients with advanced or decompensated cirrhosis and reduced hepatocellular uptake of Gd-EOB-DTPA, the liver may seem featureless, with liver parenchyma, vessels, and bile ducts all having intermediate signal intensity. In comparison, in patients with early or compensated cirrhosis and preserved hepatocellular uptake of Gd-EOB-DTPA, the liver parenchyma may appear hyperintense but heterogeneous (Fig. 3). The heterogeneity is due to the presence of cirrhosis-associated hepatocellular nodules of variable sizes and signal intensity interspersed in a meshwork of hypointense fibrotic scars that may be fine, coarse, nodular, or confluent. Depending on the size and signal intensity of the hepatocellular nodules and the thickness and density of the fibrotic septa, cirrhotic livers may manifest a broad spectrum of textural alterations in the hepatocyte phase (Fig. 4).

In cirrhotic patients who decompensate or recover function between serial MR examinations, longitudinal changes in the appearance of the liver parenchyma may be observed in the hepatocyte phase (Fig. 5).

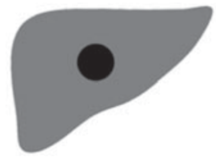
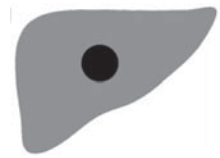
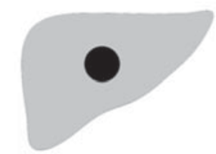
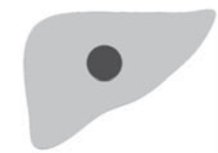
In principle, the variable enhancement of cirrhotic liver parenchyma and potentially heterogeneous parenchymal texture may complicate the detection and characterization of nodules in the hepatocyte phase. Research is needed to define the impact on diagnostic performance of the variable appearance of the cirrhotic liver parenchyma in the hepatocyte phase after Gd-EOB-DTPA administration.

Although the variable, potentially heterogeneous parenchymal enhancement may complicate nodule evaluation, it could potentially be exploited for novel diagnostic purposes. As suggested in animal studies by Tsuda et al. [15, 16], quantitative analysis of Gd-EOB-DTPA uptake by the liver may permit noninvasive assessment of segmental liver function as well as histologic alterations, such as fibrosis in the precirrhotic phases of diffuse liver disease. Further research on the use of Gd-EOB-DTPA–enhanced MRI as a biomarker in diffuse liver disease is warranted.

HCC

HCC is a malignant neoplasm composed of dedifferentiated hepatocytes. In cirrhotic

TABLE 1: Proposed Algorithm for Assessment of Liver Lesions in Cirrhotic Liver Using Gd-EOB-DTPA

	T2 Weighted	T1-Weighted Precontrast	Arterial Phase	Hepatocyte Phase
Simple cyst				
Hemangioma				
Benign (e.g., RN)				
Benign (e.g., DN)				
Probably benign (e.g., DN)				
Probably benign (e.g., DN)				
Probably HCC (early)				
Definitely HCC				
Probably HCC (hypovascular)				
Confluent fibrosis				

Note—The proposed algorithm is based on the authors' anecdotal experience. It is meant as a provisional guide and should be applied cautiously in clinical care. Confirmatory studies are required, with revision of the algorithm as appropriate. Gd-EOB-DTPA = gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid; RN = regenerative nodule ; DN = dysplastic nodule; HCC = hepatocellular carcinoma.

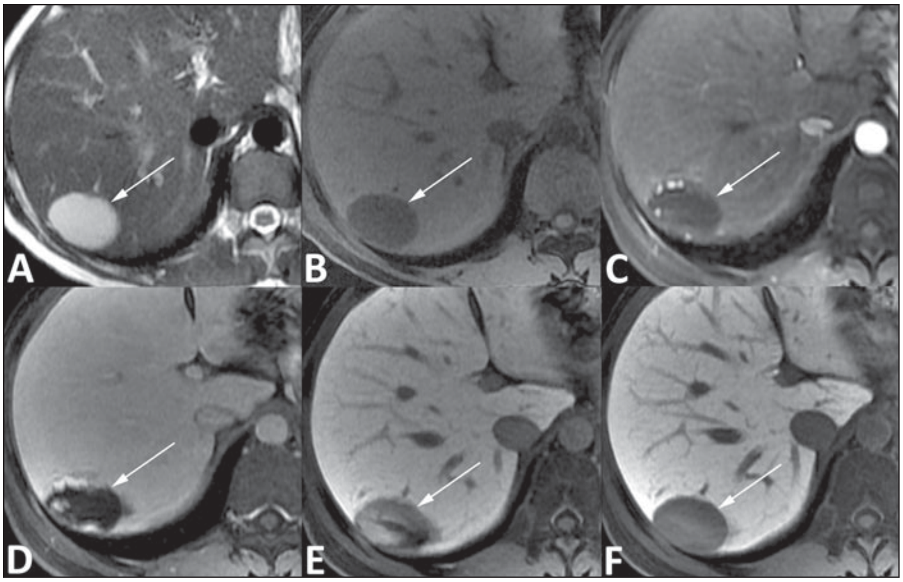


Fig. 8—46-year-old woman with chronic hepatitis C viral infection but without cirrhosis.
A–F, T2-weighted single-shot fast spin echo image (**A**) and T1-weighted 3D gradient-echo images obtained at 3 T prior to contrast administration (**B**) and 20 seconds (**C**), 1 minute (**D**), 5 minutes (**E**), and 25 minutes (**F**) after gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid administration show 4.5-cm mass in segment VII of liver (*arrows*) that is light-bulb bright on T2-weighted image (**A**) and hypointense on T1-weighted image (**B**). After contrast administration, mass has peripheral puddles of contrast enhancement on arterial phase (**A**) that progressively coalesce at 1 minute (**D**) and 5 minutes (**E**) while following blood pool signal. In the hepatocyte phase, mass is hypointense, with similar signal intensity to blood vessels. Imaging features are characteristic of hemangioma.

livers, HCC usually develops from dysplastic nodules [17]. HCC is solitary in about 50%, multifocal in approximately 40%, and diffuse in less than 10% of cases [18].

The vascular supply of HCCs is mainly arterial through neoangiogenesis, with markedly reduced or absent portal supply [19]. Approximately 80–90% of HCCs show arterial hypervascularity at MRI after a bolus injection of a gadolinium-based contrast agent [20]. After arterial phase hyperenhancement, HCCs typically show washout in the delayed phases, with signal intensity lower than that of background liver parenchyma. Some hypervascular HCCs, however, may not show washout and so may be difficult to see on delayed phases. A peripheral rim of delayed enhancement may be observed, lasting for more than 5 minutes after contrast injection [20].

From 10% to 20% of HCCs are hypovascular and enhance less than surrounding liver parenchyma in the arterial phase. This is presumably from loss of arterial and portal blood supply and the absence of arterial neoangiogenesis [21]. Typically, hypovascular HCCS are small, well-differentiated tumors. Although poorly differentiated, infiltrating HCCs also may be hypovascular. Such hypovascular tumors may be difficult to detect on dynamic gadolinium-based contrast agent–enhanced MR images despite their large size and aggressive biologic behavior.

On Gd-EOB-DTPA administration, the contrast behavior of typical HCCs in the dynamic phases (arterial, portovenous, and equilibrium phases) is comparable to that with extracellular gadolinium-based contrast agents, i.e., arterial hyperenhancement followed by rapid washout [20, 22], except that washout may appear more rapid with Gd-EOB-DTPA because the background liver parenchyma progressively enhances (Fig. 6).

The degree of peripheral rim enhancement may be similar to or lower than that seen with extracellular gadolinium-based contrast agents, depending on the Gd-EOB-DTPA dose used [20]. In the hepatocyte phase, typical HCCs are well delineated as areas of low signal intensity relative to surrounding liver parenchyma because they do not have the ability to take up Gd-EOB-DTPA. Liver-to-lesion contrast enhancement typically peaks in the hepatocyte phase, when it may exceed arterial phase contrast enhancement by 50% [23]. In addition, tumor margins are most clearly delineated in the hepatocyte phase [23], potentially improving detection of HCCs not readily visible in the dynamic imaging phases [23]. If the liver parenchyma does not enhance intensely or homogeneously, however, liver-to-lesion contrast ratio may be low and lesion margins may be difficult to define in the hepatocyte phase.

From 2.5% to 8.5% of HCCs [24, 25] may show paradoxical uptake of Gd-EOB-DTPA in the hepatocyte phase, appearing as iso- or hyperintense lesions relative to surrounding liver parenchyma [11, 26] (Fig. 7). In an animal study, paradoxical uptake of Gd-EOB-DTPA by HCCs was observed in well-differentiated HCCs [24], but additional experimental and clinical studies [12, 20, 23, 25–28] have not confirmed a correlation between HCC grade and Gd-EOB-DTPA uptake. Previous reports have suggested that liver enzymes, such as glutathione-S-transferase (an intracellular transport protein for Gd-EOB-DTPA [7]) play a role in the paradoxical contrast uptake by HCCs [29], whereas a more recent small human study suggested that the uptake is determined by expression of OATP1B3 receptors, rather than

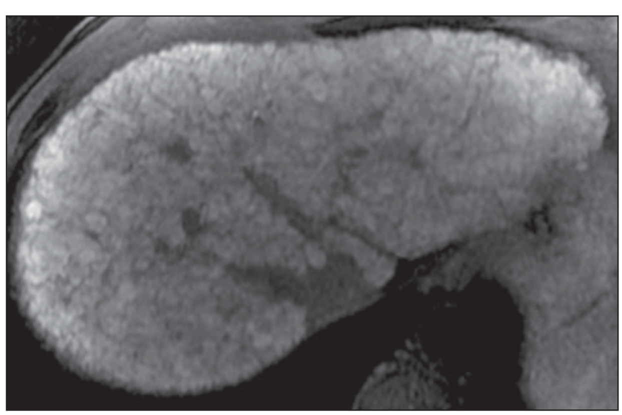


Fig. 9—57-year-old man with hepatitis C virus cirrhosis. Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid–enhanced T1-weighted 3D gradient-echo hepatocyte phase image obtained at 3 T shows heterogeneous liver parenchyma. Liver parenchyma is carved into intermediate-signal intensity regenerative nodules with preserved hepatocellular function by meshwork of hypointense fibrotic septa devoid of functional hepatocytes. Note hypointense vessels.

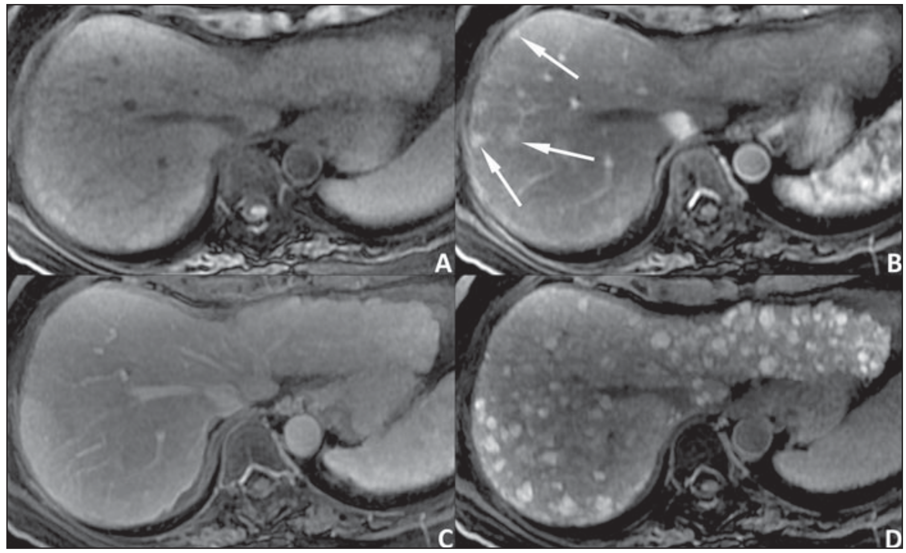


Fig. 10—54-year-old man with hepatitis C virus cirrhosis.
A–D, T1-weighted 3D gradient-echo images obtained at 3 T prior to contrast administration (**A**) and 20 seconds (**B**), 1 minute (**C**), and 25 minutes (**D**) after gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) administration. Hepatocyte phase image (**D**) shows innumerable T1-hyperintense nodules against background of intermediate signal liver parenchyma. Hyperintense nodules may be dysplastic nodules with retained ability to take up Gd-EOB-DTPA but reduced excretory capacity, resulting in intracellular cholestasis and T1 shortening. Nodules neither arterially hyperenhance nor washout on dynamic phase images. Note focal areas of perfusional alteration on hepatic arterial phase (*arrows*, **B**).

by tumor differentiation [30]. From the foregoing, the pathophysiologic characteristics of HCCs that take up Gd-EOB-DTPA in the hepatocyte phase, the mechanism of this uptake, and the clinical relevance of this enhancement pattern are not fully elucidated. In addition, the vast majority of hyperintense hepatocyte phase nodules in the cirrhotic liver are probably not HCCs but rather benign regenerative nodules or dysplastic nodules. Further research is therefore needed to better understand hepatocyte phase hyperintense nodules and to inform management guidelines for their workup.

Although unusual, hemangiomas can occasionally be encountered in cirrhosis and should be considered in the differential diagnosis of lesions that are hypervascular in the dynamic phases. However, the dynamic enhancement pattern of hemangiomas typically follows the blood-pool (Fig. 8), which helps differentiate them from HCCs that show rapid washout. Because not all HCCs show rapid washout, correlation with signal intensity on T2-weighted imaging is often necessary. Hemangiomas tend to be moderately to markedly hyperintense on T2-weighted images (Fig. 8), whereas HCCs tend to be isointense or only mildly hyperintense.

Regenerative and Dysplastic Nodules

Regenerative nodules represent focal hepatocellular proliferations that contain one or more portal tracts [31] surrounded by fibrous septa. They may be micronodular (≤ 3 mm) or macronodular (> 3 mm) [31]. The major blood supply to regenerative nodules is the portal vein [32].

In the hepatocyte phase of Gd-EOB-DTPA, regenerative nodules generally show contrast uptake and excretion because of preserved hepatocellular function and intact organic ion transporters, with signal intensity similar to that of background liver (Fig. 9).

Dysplastic nodules develop from regenerative nodules and contain atypical hepatocytes but do not have definite features of malignancy on histology [31]. They are present in 15–25% of cirrhotic livers [33] and are histologically classified as low-grade or high-grade depending on the degree of dedifferentiation. High-grade dysplastic nodules are considered premalignant [34] and can undergo malignant transformation in a duration as short as 4 months [35]. Nevertheless, the clinical significance of dysplastic nodules is unclear, and

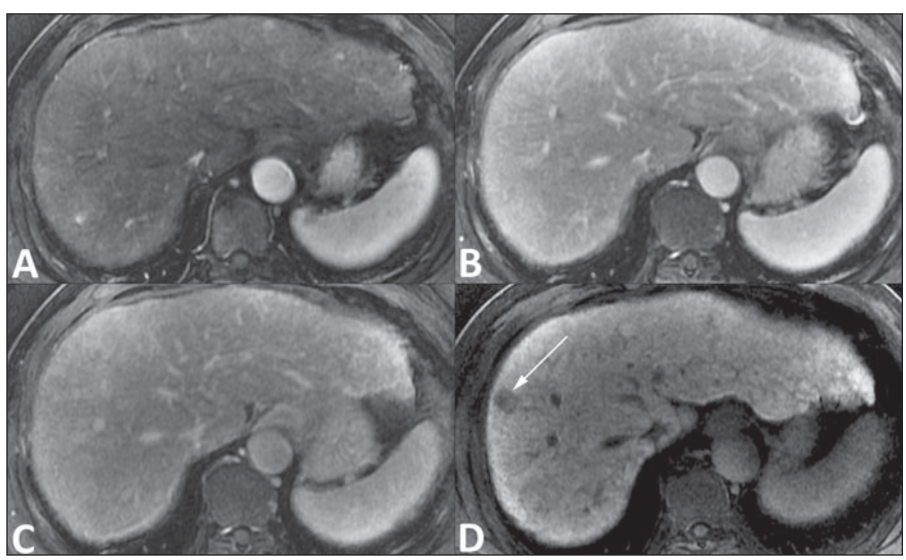


Fig. 11—57-year-old man with hepatitis B virus cirrhosis.
A–D, Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid–enhanced T1-weighted 3D gradient-echo images obtained at 3 T 22 seconds (**A**), 1 minute (**B**), 5 minutes (**C**), and 20 minutes (**D**) after contrast administration show 1-cm hypointense nodule in hepatocyte phase (*arrow*, **D**). Nodule shows no discernible vascular enhancement or washout. It is presumed to represent dysplastic nodule with reduced uptake of contrast agent, although hypovascular hepatocellular carcinoma cannot be excluded. As illustrated in this case, interpretation of such nodules is not fully understood.

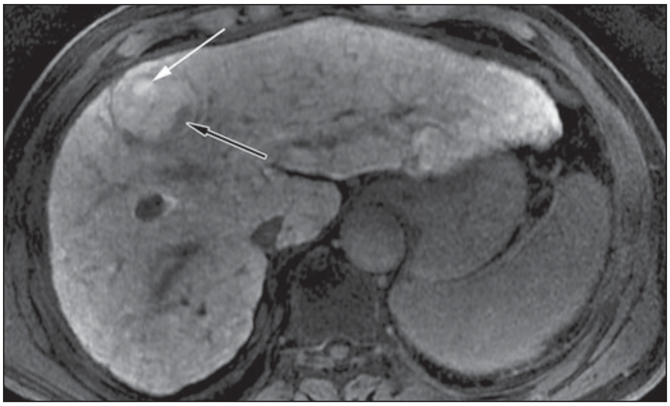


Fig. 12—57-year-old man with hepatitis B virus cirrhosis. Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid–enhanced T1-weighted 3D gradient-echo hepatocyte phase image obtained at 3 T shows 3.5-cm mass in right lobe of liver. Mass is predominantly isointense to background liver parenchyma but contains hyperintense (*white arrow*) and hypointense (*black arrow*) components. Because of its large size, mass was empirically treated as hepatocellular carcinoma (HCC) using transarterial chemoembolization, but it did not take up chemoembolic material. At follow-up imaging 8 months later, mass was stable in size and imaging features. Mass probably represents well-differentiated HCC or macroregenerative nodule with foci of cellular dysplasia and atypia. As illustrated in this case, interpretation of such masses is not fully understood.

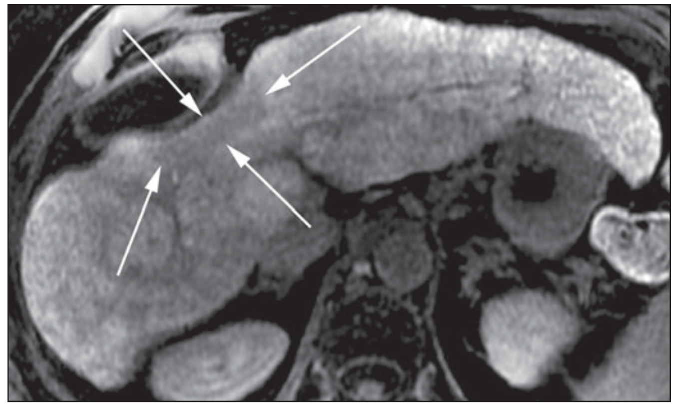


Fig. 13—56-year-old woman with alcohol-induced cirrhosis. Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid–enhanced T1-weighted 3D gradient-echo hepatocyte phase image obtained at 3 T shows areas of confluent hypointensity relative to background liver parenchyma (*arrows*). Hypointense areas are wedge-shaped, with base toward liver capsule and associated with volume loss and capsular retraction. These features are consistent with confluent fibrosis.

current management guidelines do not advocate aggressive workup of suspected dysplastic nodules.

Like regenerative nodules, dysplastic nodules receive their blood supply mainly from the portal vein, although high-grade dysplastic nodules may develop arterial hypervascularity [36]. With progression of atypia, the number of expressed organic ion transporters in dysplastic nodules decreases, which reduces their ability to take up Gd-EOB-DTPA.

In the hepatocyte phase of Gd-EOB-DTPA, dysplastic nodules that retain their ability to take up the agent but not to excrete it appear homogeneously or heterogeneously hyperintense due to intracellular cholestasis (Fig. 10), whereas nodules that have lost their ability to take up the agent appear hypointense [26] (Fig. 11). However, such hypointense nodules can be mistaken for HCCs in the hepatocyte phase [26], and their interpretation is not fully understood. Occasionally, a nodule-within-a-nodule appearance may be seen in the hepatocyte phase representing nodules with foci of cellular dysplasia or atypia (Fig. 12).

Fibrosis

In cirrhosis, fibrosis is present as a lattice-like framework of fibrotic septa surrounding hepatocellular nodules throughout the liver parenchyma. Because the fibrotic septa do not contain hepatocytes, they appear hypointense in the hepatocyte phase. Depending on their thickness and density, fibrotic septa may manifest as fine or coarse reticulations. Occasionally confluent fibrosis may occur with a diffuse or focal distribution. Focal confluent fibrosis has a masslike appearance that can be mistaken for HCC. Morphologically, it is wedge-shaped with the base toward the liver capsule, often associated with parenchymal atrophy and capsular retraction and usually located in the anterior and medial segments of the liver [37, 38]. After administration of an extracellular gadolinium-based contrast agent, delayed contrast enhancement of fibrosis is characteristic, which is in contradistinction to the hypointensity seen on the hepatocyte phase of Gd-EOB-DTPA (Fig. 13).

Confluent fibrosis can be differentiated from hepatocyte phase tumoral hypointensity on the basis of morphology [39]. Confluent fibrosis also usually does not hyperenhance in the arterial phase. In difficult cases, follow-up imaging may be helpful.

Arterially Enhancing Pseudolesions

Arterially enhancing pseudolesions represent 72–87% of arterially hyperenhancing lesions seen in cirrhotic livers [40]. Such pseudolesions may be mistaken for HCC at dynamic imaging because assessment of washout may be difficult in the cirrhotic liver and the absence of washout does not exclude malignancy because some tumors with residual portal venous blood supply remain isointense to liver parenchyma on delayed images [40]. The hepatocyte phase of Gd-EOB-DTPA provides additional information that may help characterize such lesions.

Transient arterial enhancement may result from arterioportal shunts [41] compensating for reduced portal supply. Such shunts are due to either occlusion or compression of the portal vein or focal obstruction of a distal parenchymal portal vein as is often seen in the cirrhotic liver. Areas of transient arterial enhancement commonly are peripheral and wedge shaped, do not displace adjacent structures, and correspond to the segment or lobe of reduced portal supply [42]. Infrequently, these areas can be nodular or irregularly shaped [41]. In the hepatocyte phase of Gd-EOB-DTPA, areas of transient arterial enhancement are usually isointense to background liver parenchyma because they contain functional hepatocytes (Figs. 14A–14D). Occasionally, some hepatocytes in adjacent liver parenchyma may be dysfunctional and show relatively reduced uptake of Gd-EOB-DTPA (Figs. 14E–14H).

Arterioportal fistulas may occur as a complication of liver biopsy. Occasionally, these may be associated with a pseudoaneurysm. The enhancement of the pseudoaneurysm matches that of the blood pool after contrast administration [38]. Accordingly, pseudoaneurysms appear hypointense to the background liver parenchyma on the hepatocyte

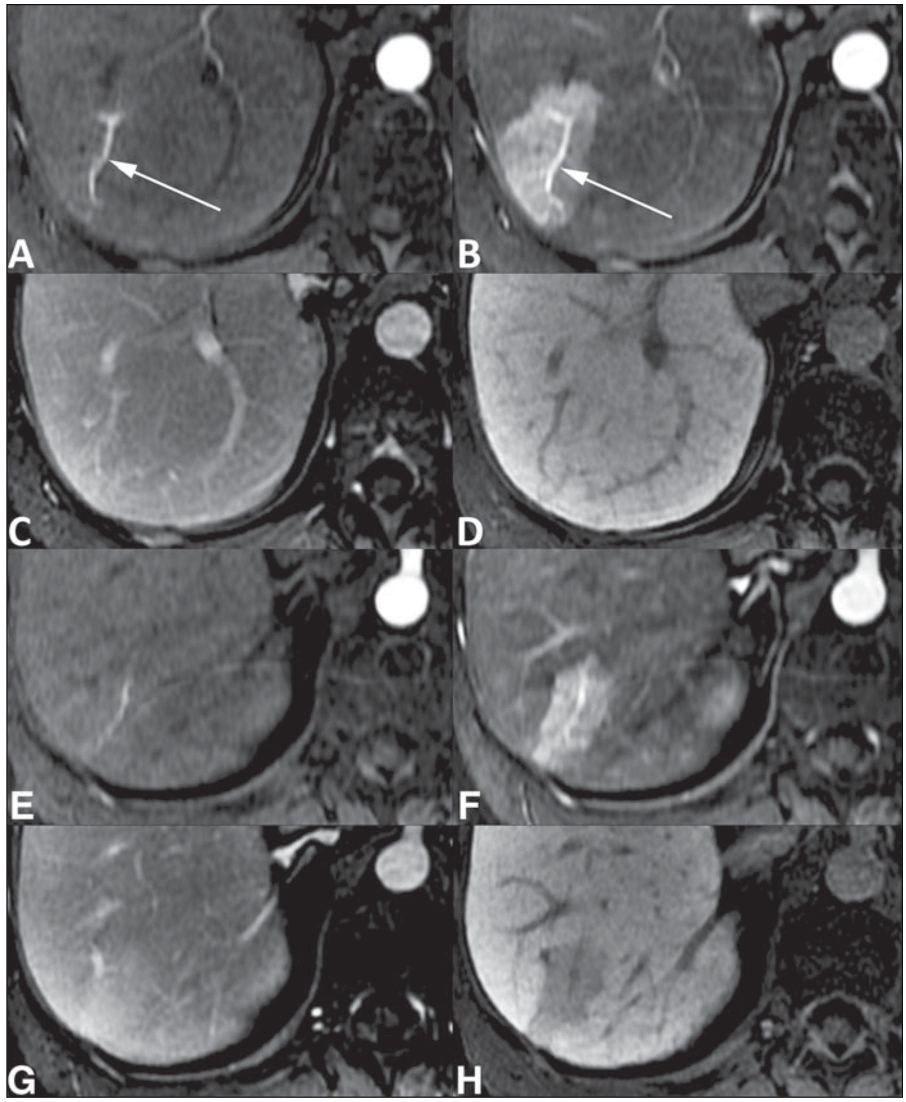


Fig. 14—41-year-old man with cirrhosis secondary to nonalcoholic liver disease who underwent liver biopsy.
A–D, Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)–enhanced T1-weighted 3D gradient-echo images obtained at 3 T 15 seconds (**A**), 23 seconds (**B**), 31 seconds (**C**), and 20 minutes (**D**) after contrast administration show wedge-shaped area of arterial hyperenhancement that fades to isointensity by 31 seconds and remains isointense in hepatocyte phase. Notice early enhancement of portal vein branch (*arrow*, **A** and **B**) within hyperenhancing area due to postbiopsy arterioportal fistula. Lack of architectural distortion favors diagnosis of pseudolesion.
E–H, Images obtained at more caudal slice level show inferior aspect of wedge-shaped area of perfusion alteration. At this slice level, area of altered perfusion is hypointense in hepatocyte phase, indicating diminished uptake of Gd-EOB-DTPA, plausibly due to dysfunctional hepatocytes. Lack of architectural distortion favors diagnosis of pseudolesion.

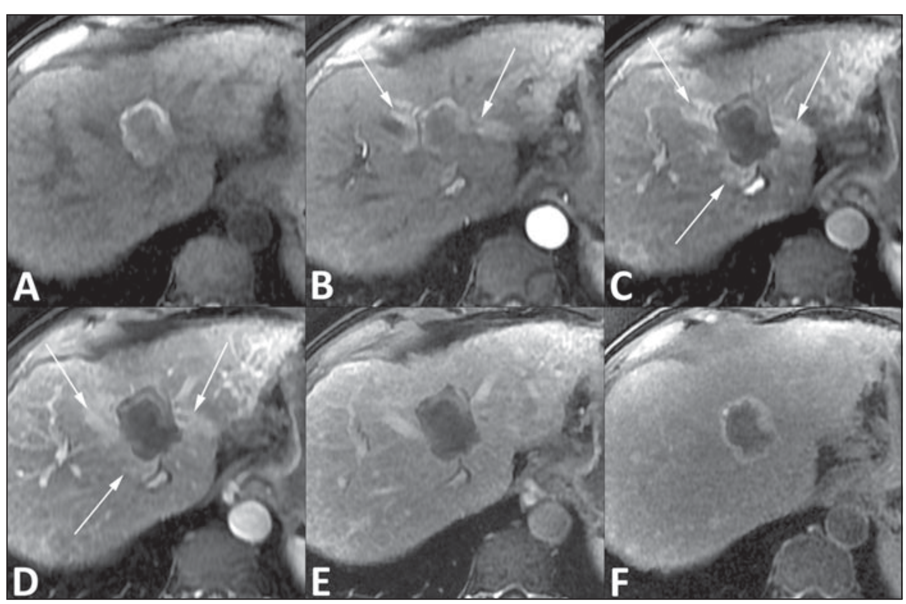


Fig. 15—61-year-old man with hepatitis C virus cirrhosis who underwent transarterial chemoembolization (TACE) of hepatocellular carcinoma in right lobe of liver. T1-weighted 3D gradient-echo images obtained at 3 T are shown.
A, Unenhanced image shows T1-hyperintense rim around lesion, presumably from TACE procedure.
B–D, Images acquired 15 seconds (**B**), 22 seconds (**C**), and 29 seconds (**D**) after contrast administration show perilesional hyperenhancement (*arrows*, **B–D**) that may represent residual or recurrent disease along tumor margins.
E and **F,** On images acquired in hepatocyte phase, however, perilesional tissue is isointense to surrounding liver parenchyma, indicating presence of functional hepatocytes and helping to exclude presence of tumor. Arterial phase hyperenhancement likely represents benign post-TACE perfusion alteration.

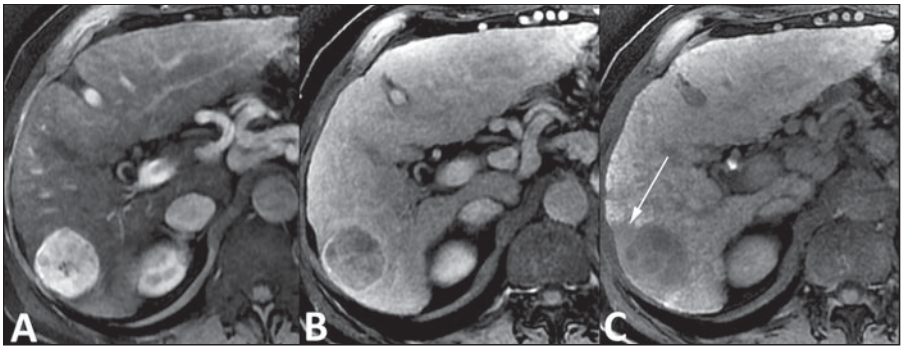


Fig. 16—62-year-old woman with hepatitis C virus cirrhosis.
A–C, Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid–enhanced T1-weighted 3D gradient-echo images obtained at 3 T 22 seconds (**A**), 1 minute (**B**), and 20 minutes (**C**) after contrast administration show 3.9-cm arterially hyperenhancing mass that washes out in portal venous phase, has delayed rim of enhancement, and is hypointense in hepatocyte phase, findings consistent with hepatocellular carcinoma. Wedge-shaped hypointense area (*arrow*, **C**) adjacent to tumor likely represents perilesional hepatocellular dysfunction rather than tumoral extension on basis of lack of arterial vascularity and findings on other imaging sequences (not shown).

phase of Gd-EOB-DTPA. Arterioportal fistulas and pseudoaneurysms can be differentiated from HCC on the basis of their morphology, location, and clinical history.

Peritumoral Arterial Enhancement

Peritumoral enhancement is usually secondary to arterioportal shunting, such as occurs spontaneously with HCC or after interventional procedures such as biopsy or ablation. It is important to differentiate such enhancement from tumoral extension or residual disease because overestimation of lesion size may falsely influence treatment decisions. Gd-EOB-DTPA may be helpful in this regard. In the hepatocyte phase of Gd-EOB-DTPA, areas of peritumoral enhancement are usually isointense to background liver parenchyma because they contain functional hepatocytes (Fig. 15).

Occasionally, however, peritumoral hepatocytes may be dysfunctional and show reduced uptake of Gd-EOB-DTPA compared with parenchyma remote from the tumor (Fig. 16). Further research is needed is to define the frequency and differentiating characteristics of peritumoral hypointensity caused by benign hepatocyte dysfunction versus neoplastic extension.

Summary

Gd-EOB-DTPA provides diagnostic information regarding lesion blood supply and hepatocellular function, which helps in detection and characterization of liver lesions. Because regenerative nodules, dysplastic nodules, and HCCs constitute a spectrum with gradual dedifferentiation [17], it may be difficult to distinguish among these entities on the basis of vascular imaging features [26]. The hepatocyte phase of Gd-EOB-DTPA may help differentiate benign (regenerative and dysplastic) nodules from HCC because benign nodules usually show Gd-EOB-DTPA uptake unlike HCC [43], a distinction that is of clinical importance. In addition, Gd-EOB may allow a more confident evaluation and characterization of pseudolesions and peritumoral areas of arterial hyperenhancement.

Although early results using Gd-EOB-DTPA in the cirrhotic liver are promising, the agent should be used with caution in the cirrhotic liver. For radiologists using Gd-EOB-DTPA for the first time to evaluate patients with cirrhosis, it may be prudent to use the agent initially in select cases as a problem-solving tool rather than routinely until experience accrues. Optimized Gd-EOB-DTPA imaging protocols and diagnostic criteria for liver lesions in the cirrhotic liver need to be developed, and the diagnostic performance of Gd-EOB-DTPA–enhanced MRI for HCC diagnosis and staging needs to compared head-to-head with that of extracellular gadolinium-based contrast agent–enhanced MRI and of contrast-enhanced CT.

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FOR YOUR INFORMATION

The reader's attention is directed to part 1 accompanying this article, titled "Gadoxetate Disodium–Enhanced MRI of the Liver: Part I, Protocol Optimization and Lesion Appearance in the Noncirrhotic Liver," which begins on page 13.