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.

Watery 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

**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.
The authors concluded that routine 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 enhanced 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-
Contrast-Enhanced MRI in Liver Cirrhosis

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-DTPA 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 arterial phase timing. 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 dose, 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 dose, 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 dose, 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 dose, 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 dose, 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 dose, 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 dose, 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
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-

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**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 patients with cirrhosis (B–H). Textural alterations in cirrhosis include fine reticulations (B), coarse reticulations (C), parenchymal heterogeneity (D), discrete mildly hyperintense nodules (E), discrete markedly hyperintense nodules (F), 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).

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**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.
Contrast-Enhanced MRI in Liver Cirrhosis

Fig. 6—56-year-old man with hepatitis C virus cirrhosis. A–L, 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 $b = 0 \text{ s/mm}^2$ (H) and $b = 500 \text{ s/mm}^2$ (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
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 CIRROTIC 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 PARENCHYMVA), HEPATOCYTE PHASE IMAGING FEATRES OF HEPATIC PARENCHYMVA AND OF FOCAL LESIONS IN THE CIRRHOTIC LIVER ARE DESCRIBED. IN GENERAL, FOCAL LESIONS MAY BE PROMINENTLY HYPINTENSE, 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 PARENCHYMVA (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 PARENCHYMVA 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**

<table>
<thead>
<tr>
<th>Condition</th>
<th>T2 Weighted</th>
<th>T1-Weighted Precontrast</th>
<th>Arterial Phase</th>
<th>Hepatocyte Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple cyst</td>
<td>![Image]</td>
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<td>![Image]</td>
<td>![Image]</td>
</tr>
<tr>
<td>Hemangioma</td>
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<td>![Image]</td>
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<tr>
<td>Benign (e.g., RN)</td>
<td>![Image]</td>
<td>![Image]</td>
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<tr>
<td>Benign (e.g., DN)</td>
<td>![Image]</td>
<td>![Image]</td>
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<tr>
<td>Probably benign (e.g., DN)</td>
<td>![Image]</td>
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<td>![Image]</td>
<td>![Image]</td>
</tr>
<tr>
<td>Probably benign (e.g., DN)</td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
<tr>
<td>Probably HCC (early)</td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
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<tr>
<td>Definitely HCC</td>
<td>![Image]</td>
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<tr>
<td>Probably HCC (hypovascular)</td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
<tr>
<td>Confluent fibrosis</td>
<td>![Image]</td>
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</table>

**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.
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 hypointense 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...
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by tumor differentiation [30]. From the fore-
going, the pathophysiologic characteristics of
HCCs that take up Gd-EOB-DTPA in the he-
patocyte phase, the mechanism of this uptake,
and the clinical relevance of this enhance-
ment pattern are not fully elucidated. In ad-
dition, the vast majority of hyperintense hep-
atocyte phase nodules in the cirrhotic liver are
probably not HCCs but rather benign regen-
erative nodules or dysplastic nodules. Further
research is therefore needed to better under-
stand hepatocyte phase hyperintense nod-
ules and to inform management guidelines for
their workup.

Although unusual, hemangiomas can oc-
casionally be encountered in cirrhosis and
should be considered in the differential diag-
osis of lesions that are hypervascular in the
dynamic phases. However, the dynamic en-
hancement pattern of hemangiomas typically
follows the blood-pool (Fig. 8), which helps
differentiate them from HCCs that show rap-
id washout. Because not all HCCs show rapid
washout, correlation with signal intensity on
T2-weighted imaging is often necessary. He-
mandiomas tend to be moderately to mark-
edly 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 he-
paticcellular 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 regenera-
tive nodules and contain atypical hepatocytes
but do not have definite features of malignan-
cy on histology [31]. They are present in 15–
25% of cirrhotic livers [33] and are histologi-
cally classified as low-grade or high-grade
depending on the degree of dedifferentiation.
High-grade dysplastic nodules are considered
premalignant [34] and can undergo mali-
gnant transformation in a duration as short as
4 months [35]. Nevertheless, the clinical sig-
nificance of dysplastic nodules is unclear, and

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).

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.
In cirrhosis, fibrosis is present as a lattice-like framework of fibrotic septa surrounding hepatocellular nodules throughout the liver parenchyma. 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 arteriportal 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).

Arteriportal 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 phase.
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 arterioporal 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.
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 be compared head-to-head with that of extracellular gadolinium-based contrast agent–enhanced MRI and of contrast-enhanced CT.

References

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