

Hepatobiliary-specific MR Contrast Agents: Role in Imaging the Liver and Biliary Tree¹

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LEARNING OBJECTIVES

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

- Describe the mechanism of action of hepatobiliary-specific contrast agents.
- Discuss indications for the use of hepatobiliary-specific contrast agents for MR imaging of the liver and the biliary tree.
- Identify the pitfalls and current limitations of liver imaging with hepatobiliary-specific contrast agents.

TEACHING POINTS

See last page

Hepatobiliary-specific contrast agents are one of several classes of contrast agents available for magnetic resonance (MR) imaging of the liver. These agents are taken up by functioning hepatocytes and excreted in the bile, and their paramagnetic properties cause shortening of the longitudinal relaxation time (T1) of the liver and biliary tree. The three contrast agents that have been developed are mangafodipir trisodium (Mn-DPDP), gadobenate dimeglumine (Gd-BOPTA), and gadoxetic acid (Gd-EOB-DTPA). These three MR contrast agents vary in mode of administration and dose, mechanism of cellular uptake, degree of excretion through the biliary pathway, and imaging characteristics. In the liver, hepatobiliary-specific agents can be used to improve lesion detection, to characterize lesions as hepatocellular or nonhepatocellular, and to specifically characterize some hepatocellular lesions, notably focal nodular hyperplasia. Biliary excretion of these agents can be used to evaluate the anatomic structure and function of the biliary tree. In the future, hepatobiliary-specific contrast agents may have wider applications, such as grading of cirrhosis and quantification of liver function.

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Abbreviations: FDG = fluorine 18 fluorodeoxyglucose, Gd-BOPTA = gadobenate dimeglumine, Gd-EOB-DTPA = gadoxetic acid, Mn-DPDP = mangafodipir trisodium, T1 = longitudinal relaxation time, T2 = transverse relaxation time

RadioGraphics 2009; 29:1725–1748 • Published online 10.1148/rg.296095515 • Content Codes: **GI** **MR**

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Introduction

Contrast agents currently available for magnetic resonance (MR) imaging of the liver can be divided into five categories: (a) extracellular fluid agents, (b) hepatobiliary-specific agents, (c) combined agents, (d) reticuloendothelial agents, and (e) blood-pool agents (1). Agents in the first three categories are covered in detail in this article.

Contrast agent-enhanced MR imaging of the liver and biliary tree is routinely performed for lesion detection and characterization and for mapping vascular and biliary anatomic structures. Research has shown that hepatobiliary-specific agents improve lesion detection and in some situations can facilitate characterization of hepatocellular lesions. In addition, the biliary tree can be depicted because of the excretion of these agents via the biliary tree.

In this article, the extracellular fluid contrast agents are briefly presented. Then the hepatobiliary-specific contrast agents that are currently in clinical use are introduced, and the uses of these agents for imaging the liver and the biliary tree are discussed, followed by a brief discussion of their potential future applications.

Extracellular Fluid Agents

Extracellular fluid agents are the contrast agents that have been in clinical use for the longest period of time in contrast-enhanced MR imaging of the liver, and they are still the most widely used and best-documented of such agents (2,3). Extracellular fluid agents are composed of gadolinium chelated to an organic compound. Gadolinium shortens the longitudinal relaxation time (T1) and the transverse relaxation time (T2), predominantly the former, which leads to increased signal intensity on T1-weighted images. The pharmacokinetics of gadolinium chelates is similar to the pharmacokinetics of iodinated contrast agents for computed tomography (CT)—the contrast agent circulates and then freely distributes in the extracellular fluid compartment. Elimination of extracellular fluid agents is predominantly renal. Typically, liver imaging with extracellular fluid

agents relies on differential blood flow between the liver and the tumor for lesion detection and characterization.

Extracellular fluid agents are generally considered safe when administered at low dosage but may be nephrotoxic at high dosage. In patients with normal renal function, side effects are uncommon and are generally mild (eg, headache, nausea, vomiting). However, one case report of fatal anaphylaxis is found in the literature (1). Patients with renal impairment are at risk of nephrogenic systemic fibrosis (4). Risk appears to increase with the degree of renal impairment and the cumulative dose of gadolinium. The extracellular fluid agents in clinical use are listed in Table 1.

Pitfalls of Extracellular Fluid Agents

Contrast-enhanced MR imaging of the liver with extracellular fluid agents relies on well-performed dynamic imaging because the enhancement of many lesions is transient. Correct timing for initiating imaging after contrast agent injection can be difficult to achieve accurately, especially in patients who are unable to hold their breath or who have poor cardiac status. A test bolus may be used to optimize imaging, but this is a time-consuming process. For practical purposes, most institutions use fixed time delays for dynamic imaging, which may not always result in optimal hepatic arterial and venous enhancement.

Rapid imaging is required to cover the liver in the arterial phase, which limits anatomic coverage and spatial resolution. Patient cooperation is required, particularly during dynamic imaging with breath-hold sequences, to limit movement and respiratory artifacts.

Because of the nonspecific nature of extracellular fluid agents, many benign and malignant liver lesions have considerable morphologic overlap and exhibit similar enhancement patterns with use of these agents. For example, one of the typical features of focal nodular hyperplasia is the central scar, but a central scar may also be seen in fibrolamellar hepatocellular carcinoma, hepatocellular adenoma, and hemangioma. In addition, a central scar may be absent in as many as 20% of focal nodular hyperplasia lesions, particularly when they are small (5).

Table 1
Extracellular Fluid Contrast Agents Used for Liver MR Imaging

Generic Name	Abbreviated Name	Trade Name	Manufacturer
Gadopentetate dimeglumine	Gd-DTPA	Magnevist	Berlex
Gadodiamide	Gd-DTPA-BMA	Omniscan	Nycomed Amersham
Gadoteridol	Gd-HP-DO3A	ProHance	Bracco
Gadoversetamide	Gd-DTPA-BMEA	Optimark	Mallinckrodt
Gadoterate meglumine	Gd-DOTA	Dotarem	Guerbet
Gadobutrol	Gd-BT-DO3A	Gadovist	Schering

Table 2
Hepatobiliary-specific Contrast Agents Used for Liver MR Imaging

Generic Name	Abbreviated Name	Trade Name	Manufacturer
Mangafodipir trisodium	Mn-DPDP	Teslascan	GE Healthcare
Gadobenate dimeglumine	Gd-BOPTA	MultiHance	Bracco
Gadoxetic acid (or gadoxetate disodium)	Gd-EOB-DTPA	Eovist (United States), Primovist (EU, Australia)	Bayer

Note.—EU = European Union.

In the cirrhotic liver, altered hemodynamics may cause heterogeneous hepatic enhancement, obscuring lesions. In addition, some dysplastic nodules and even well-differentiated hepatocellular carcinoma may not be hypervascular (6) and hence may not be depicted.

Hepatobiliary-specific Agents

Several hepatobiliary-specific agents have been developed during the past 2 decades, with the aim of overcoming some of the limitations of nonspecific extracellular fluid agents. **These hepatobiliary-specific agents are taken up to varying degrees by functioning hepatocytes and are excreted in the bile.** Because of their paramagnetic properties, the agents cause T1 shortening of the liver and biliary tree. This results in an increased contrast-to-noise ratio for nonhepatocellular lesions compared with that of the background liver, thereby increasing lesion conspicuity on delayed T1-weighted images.

The hepatobiliary-specific agents for which clinical trials have been successfully completed

are mangafodipir trisodium (Mn-DPDP), gadobenate dimeglumine (Gd-BOPTA), and gadoxetic acid (Gd-EOB-DTPA) (Tables 2, 3) (1,7–9). Mn-DPDP has recently been removed from the market in the United States, but Gd-BOPTA and Gd-EOB-DTPA are approved by the Food and Drug Administration for clinical use. Although Mn-DPDP is no longer available for clinical use in the United States, it is included in the discussion because much of the experience with hepatobiliary-specific agents has been with this agent, and imaging in the delayed “hepatobiliary” phase has many similar features with all hepatobiliary-specific agents.

These hepatobiliary-specific agents are based on manganese (Mn-DPDP) or gadolinium (Gd-BOPTA and Gd-EOB-DTPA); manganese and gadolinium have five and seven unpaired electrons, respectively, which give the agents their paramagnetic properties. All hepatobiliary-specific agents are administered intravenously, although their

Table 3
Pharmacologic and Radiologic Features of Hepatobiliary-specific Contrast Agents

Feature	Mn-DPDP	Gd-BOPTA	Gd-EOB-DTPA
Uptake	Via vitamin B ₆ receptors on hepatocytes	Via organic anion transporter on hepatocytes*	Via organic anion transporter on hepatocytes*
Excretion	>50% biliary; remainder, renal	3%–5% biliary, 95% renal	50% biliary, 50% renal
Method of administration	Slow infusion (1–2 minutes)	Bolus injection (2 mL/sec)	Bolus injection (2 mL/sec)
Manufacturer's recommended dose	0.5 μmol/kg	0.1 mmol/kg	0.025 mmol/kg
Timing of imaging after start of contrast agent injection			
Dynamic imaging	Not applicable	As for ECF agents	As for ECF agents
Delayed phase	15 minutes to several hours	1–2 hours	10 minutes to hours
FDA status	Previously approved, no longer available in United States	Available in United States, EU, and Australia	Recently made available in United States, available in EU and Australia
Side effects	Mild (eg, flushing, nausea, dizziness, raised blood pressure and heart rate) (1,7)	Mild (eg, nausea, flushing, injection site pain, taste perversion) (8)†	Mild (eg, nausea, flushing, headache, injection site pain, taste perversion most commonly) (7)
Limitations	Cannot be used for dynamic imaging; possible paradoxical uptake in some metastases (9)	Hepatobiliary-specific phase is late compared with that of Gd-EOB-DTPA; possible uptake in well-differentiated HCC	Possible uptake in well-differentiated HCC
Other comments	Small amount of uptake in pancreas, renal cortex, and adrenal glands	T1 relaxivity double that of Gd-DTPA (7)	T1 relaxivity higher than that of Gd-DTPA but much smaller dose used

Note.—ECF = extracellular fluid, EU = European Union, FDA = Food and Drug Administration, HCC = hepatocellular carcinoma.

*Same transport protein as bilirubin.

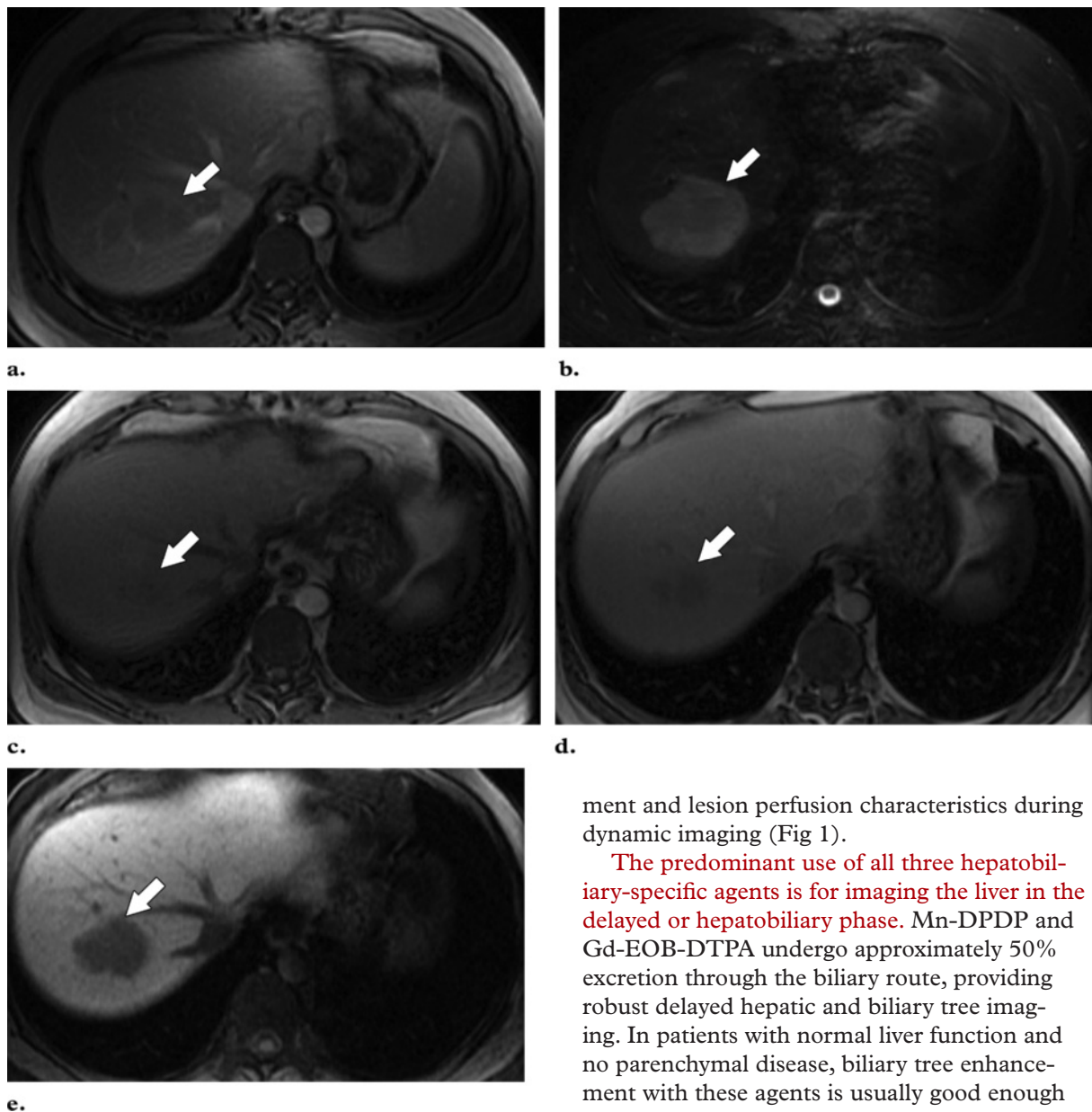
†Mild side effects reported in less than 0.03% after 100,000 clinical doses; serious adverse events occurred in less than 0.005% (8).

doses and the duration of injection are different. The two gadolinium-based hepatobiliary-specific agents initially distribute in the extracellular fluid compartment, just as extracellular fluid agents do, and are subsequently taken up by hepatocytes. Hence these two agents provide the dual benefit of dynamic imaging capability as well as delayed hepatobiliary phase imaging.

When Gd-BOPTA is given at the manufacturer's recommended dose of 0.1 mmol/kg, which is equimolar to the standard dose of gadopentetate

dimeglumine, Gd-BOPTA has twofold greater T1 relaxivity (7). This is due to weak transient interaction with serum albumin (7). The subsequent increased T1 shortening that occurs with Gd-BOPTA has been shown to cause earlier and stronger enhancement of central nervous system lesions, which is manifest as improved lesion conspicuity and better depiction of tumor margins (10). Although not validated in clinical studies, a similar effect is likely to occur in the dynamic phase of liver imaging (11). In addition, the increased signal of hepatic vessels can be exploited to improve the performance of MR angiography, enabling better delineation of small hepatic vessels (1).

Figure 1. Hepatic lymphoma in a 51-year-old woman. **(a)** Axial contrast-enhanced portal venous phase MR image obtained with a nonspecific contrast agent (gadopentetate dimeglumine) demonstrates a poorly enhancing lesion (arrow) in segment VII of the liver. MR imaging with Gd-EOB-DTPA was subsequently performed for further characterization of the lesion. **(b)** Axial T2-weighted MR image shows that the lesion (arrow) is hyperintense compared with the liver. **(c)** On the axial contrast-enhanced arterial phase MR image, the lesion is nonenhancing (arrow). **(d)** Axial contrast-enhanced portal venous phase MR image shows low-grade enhancement of the lesion (arrow). **(e)** Axial contrast-enhanced hepatobiliary phase MR image shows the hypointense lesion (arrow). Note that hepatic parenchymal enhancement during dynamic imaging is better with the nonspecific contrast agent than with Gd-EOB-DTPA because of the comparatively small dose of Gd-EOB-DTPA. The findings from biopsy of the lesion confirmed lymphoma.



The T1 relaxivity of Gd-EOB-DTPA is also slightly higher than that of gadopentetate dimeglumine (7), but the recommended dose of 0.025 mmol/kg is one-quarter those of gadopentetate dimeglumine and Gd-BOPTA, and the resultant T1-shortening effect for dynamic imaging is relatively weaker, particularly for vascular enhance-

ment and lesion perfusion characteristics during dynamic imaging (Fig 1).

The predominant use of all three hepatobiliary-specific agents is for imaging the liver in the delayed or hepatobiliary phase. Mn-DPDP and Gd-EOB-DTPA undergo approximately 50% excretion through the biliary route, providing robust delayed hepatic and biliary tree imaging. In patients with normal liver function and no parenchymal disease, biliary tree enhancement with these agents is usually good enough to confidently depict small intrahepatic ducts to third-order branching. Gd-BOPTA, on the other hand, undergoes only 3%–5% biliary excretion (7), which results in relatively weaker liver signal intensity and biliary tree enhancement. Although the main right and left ducts and the common bile duct can be confidently depicted in most cases with the use of Gd-BOPTA, smaller branch

Teaching
Point

Table 4
Suggested Protocols for Liver MR Imaging with Hepatobiliary-specific Contrast Agents

Protocol Step	Mn-DPDP	Gd-BOPTA	Gd-EOB-DTPA
Precontrast imaging	(a) T1-weighted in- and opposed-phase GRE* (b) T2-weighted FS fast SE† (c) T2-weighted MRCP‡	(a) T1-weighted in- and opposed-phase GRE* (b) T2-weighted FS fast SE† (c) T2-weighted MRCP‡	(a) T1-weighted in- and opposed-phase GRE* (b) T2-weighted FS fast SE† (c) T2-weighted MRCP‡
Contrast agent injection	0.5 μmol/kg (slow infusion, 2–3 mL/min)	0.1–mmol/kg bolus (2 mL/sec)	0.025–mmol/kg bolus (2 mL/sec)
Dynamic imaging	Not applicable	2D or 3D T1-weighted FS GRE§	2D or 3D T1-weighted FS GRE§
Hepatobiliary phase imaging			
Time of imaging (min)¶	10–30#	60–120**	10–60
Parenchymal assessment and lesion detection/characterization	Axial and/or coronal 2D or 3D T1-weighted FS spoiled GRE	Axial and/or coronal 2D or 3D T1-weighted FS spoiled GRE	Axial and/or coronal 2D or 3D T1-weighted FS spoiled GRE
T1-weighted contrast-enhanced MR cholangiography	Axial and oblique coronal 2D or 3D T1-weighted FS GRE	Axial and oblique coronal 2D or 3D T1-weighted FS GRE	Axial and oblique coronal 2D or 3D T1-weighted FS GRE

Note.—FS = fat-suppressed, GRE = gradient echo, MRCP = MR cholangiopancreatography, SE = spin echo, 2D = two-dimensional, 3D = three-dimensional.

*Axial images (150–200/4.2 [repetition time msec/echo time (TE) msec]; second TE, 1.8–2.1 msec; flip angle, 60°–80°; section thickness, 5–8 mm).

†Axial images (4000–6000/102–135; echo train length, 16; section thickness, 5–8 mm).

‡Oblique coronal heavily T2-weighted thick-slab turbo SE (2800–3300/900–1100; section thickness, 60 mm).

§Performed at 15, 60, and 180 seconds after the start of contrast agent injection (hepatic arterial, portal venous, and hepatic venous phases).

¶Time after the start of contrast agent injection.

#Because dynamic imaging is not performed, the patient receives contrast agent 10–30 minutes before being placed on the imaging table.

**Patient removed from imager between dynamic imaging and delayed imaging.

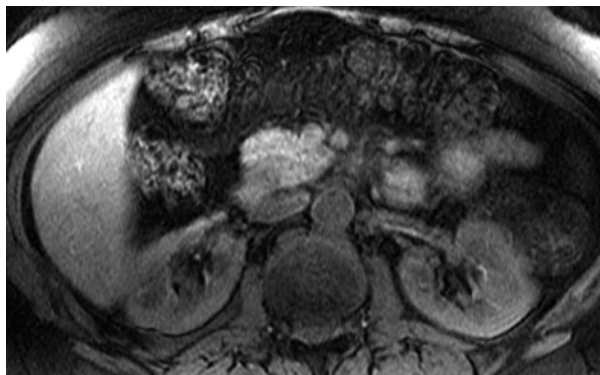
definition can be inconsistent. Some investigators have suggested using Gd-BOPTA at half of the manufacturer's recommended dose to exploit its higher T1 relaxivity. Although this suggestion may be satisfactory for dynamic liver imaging, we recommend using the full dose for any examination in which the hepatobiliary phase may be relevant, given the small percentage of hepatobiliary excretion of this agent.

Because the hepatobiliary phase of enhancement is relatively prolonged with all hepatobiliary-specific agents, the following three features are seen: (a) imaging in this phase does not have to be precisely timed (as it does in rapid dynamic imaging with extracellular fluid agents); (b) liver imaging can be accomplished by using high-spatial-resolution sequences in separate breath holds; and (c) imaging can be performed for a longer time if needed, for example, to study bile leak or contrast agent washout. These three features, combined with advances in MR imaging hardware and software, such as the development of phased-array body coils and T1-weighted three-dimensional

gradient-echo sequences, allow high-resolution images of the liver to be obtained. It should be noted that much of the research to date involving hepatobiliary-specific agents has been performed by using older machines with older software. Newer technologies should lead to continual improvement in the imaging performance of these agents.

The timing of hepatobiliary phase imaging varies with the three hepatobiliary-specific agents, as outlined in Tables 3 and 4. In particular, the hepatobiliary phase of Gd-BOPTA is relatively late, which may raise logistical issues. We overcome this issue by imaging another patient in between the dynamic and hepatobiliary phases of imaging one patient with Gd-BOPTA.

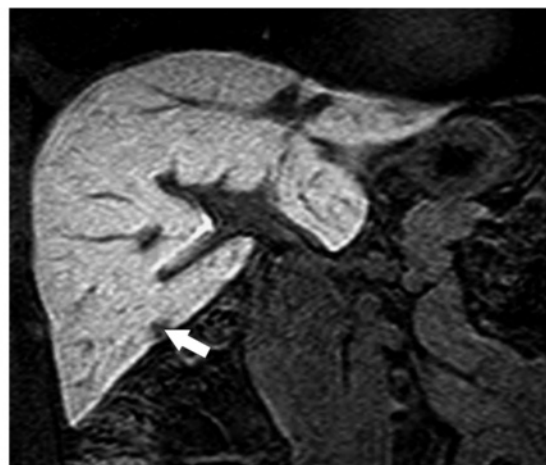
Generally, hepatobiliary-specific agents are more expensive than nonspecific extracellular fluid agents. However, in our experience, this expense is often offset by the additional information obtained, which may negate the need for other imaging studies, follow-up, biopsy, or even surgery. Other pitfalls of liver MR imaging with hepatobiliary-specific agents will be discussed later in relevant sections of this article.



a.



b.



c.

Figure 2. Colorectal carcinoma metastasis to the liver of a 49-year-old man. Metastatic liver lesions are unable to retain Gd-EOB-DTPA because they are devoid of hepatocytes. (a) Axial nonenhanced T1-weighted fat-suppressed MR image shows no obvious liver lesion. (b, c) Axial (b) and coronal (c) T1-weighted fat-suppressed MR images obtained 20 minutes after Gd-EOB-DTPA injection show that the small metastasis (arrow) in segment VI stands out from the enhancing background liver as a well-defined hypointense area, thereby allowing accurate staging.

Combination Agents

Gd-BOPTA and Gd-EOB-DTPA are sometimes described as “combination agents” because of their dual capability for imaging in the dynamic and delayed hepatocyte-specific phases of enhancement. These two agents potentially allow comprehensive noninvasive imaging assessment of the liver parenchyma, intrahepatic lesions, hepatic vessels, and the biliary tree in one examination.

Uses of Hepatobiliary-specific Contrast Agents in the Liver

For clarity, we have divided the discussion of lesion detection and characterization with hepatobiliary-specific agents into two groups: normal liver and cirrhotic liver.

Lesion Detection in Normal Liver

A major role of liver MR imaging in cancer patients is to identify curable (ie, resectable) metastatic disease. This particularly applies to colorectal cancer, in which resection of hepatic metastases has been shown to improve survival compared with other treatment methods (12,13). Liver resection is also sometimes considered for limited

metastatic disease from other primary malignancies (eg, carcinoma of the breast). Because partial hepatectomy entails considerable risk to the patient, sensitive and specific lesion detection and accurate localization are essential for suitable patient selection and for surgical planning. Hepatobiliary-specific agents exploit the fact that the metastases are nonhepatocellular and so appear hypointense compared with liver in the delayed phase, regardless of whether the metastases are hypo- or hypervascular on dynamic images (Fig 2).

Dynamic contrast-enhanced MR imaging with extracellular fluid agents is well established as being (a) more sensitive than contrast-enhanced CT and as sensitive as fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET) in depicting liver metastases from colorectal cancer and (b) more specific in lesion characterization in this setting (14,15). Hepatobiliary-specific agents show promise in increasing the sensitivity of MR imaging for depiction of colorectal metastases in the liver even further. The results of several studies have shown

Table 5
Sensitivity for Detection of Hepatic Colorectal Metastases at Liver MR Imaging with Hepatobiliary-specific Contrast Agents

Hepatic Colorectal Metastases	ECF Contrast Agents	Mn-DPDP	Gd-BOPTA	Gd-EOB-DTPA
All metastases	90%–95% (19)	81%–90% (18,20,21)	81%–96% (22,23)	NA*
Metastases <1 cm	83%	100%	NA	NA*

Note.—ECF = extracellular fluid, NA = not available.

*Published data from most studies to date include all liver lesions; sensitivity is as much as 87% for detection of all lesions; improved detection of lesions measuring less than 1 cm is consistently reported (24,25).

that contrast-enhanced MR imaging with a hepatobiliary-specific agent depicts more colorectal metastatic lesions in the liver than contrast-enhanced MR imaging with an extracellular fluid agent does and also adds diagnostic information and confidence (16,17) (Table 5) (18–25) (Figs 3, 4). This may be particularly useful after neoadjuvant chemotherapy, which often renders known metastases difficult to depict at contrast-enhanced CT and at MR imaging, presumably because of changes in tumor vascularity and steatosis in the background liver.

In a study in which MR imaging with Mn-DPDP was compared with whole-body FDG PET, investigators found equivalence in the diagnosis of metastatic disease on a per-patient basis, but more liver metastases were depicted with MR imaging, especially those measuring less than 1 cm in diameter. However, FDG PET remains better at depicting extrahepatic disease (18).

Pitfalls of Lesion Detection with Hepatobiliary-specific Agents

Of note, the relative merit of hepatobiliary-specific agents versus reticuloendothelial contrast agents for detection of metastases is controversial. In some studies, investigators have shown equivalent accuracy (20), while others have suggested that reticuloendothelial agents are more sensitive

(22). However, hepatobiliary-specific agents are considerably more appealing for the practical reasons of (a) ease of use (reticuloendothelial-specific agents are administered by slow infusion during a period of 30 minutes), (b) work-flow benefits, and (c) a more favorable adverse-reaction profile compared with reticuloendothelial-specific agents. In addition, hepatobiliary-specific agents allow lesion depiction and characterization in a single examination.

In the published literature, many studies of lesion detection with hepatobiliary-specific agents focus on colorectal cancer metastases. Data with regard to the detection of other metastases are currently limited.

Lesion Characterization in Normal Liver

Accurate characterization of focal liver lesions is important because of the high rate of occurrence of benign lesions in the general population. The gadolinium-based hepatobiliary-specific agents (Gd-BOPTA and Gd-EOB-DTPA) have been shown to be equivalent to nonspecific extracellular fluid agents for lesion characterization at dynamic imaging (11,26). All hepatobiliary-specific agents are taken up by functioning hepatocytes in the delayed phase, which provides further information that allows improved diagnostic confidence and accuracy in some situations. Table 6 (26–28) summarizes the MR imaging appearance of several common liver lesions.

Figure 3. Colorectal carcinoma metastases to the liver of a 54-year-old man. **(a)** Axial contrast-enhanced CT image fails to demonstrate metastases. **(b)** Axial T1-weighted fat-suppressed hepatobiliary phase MR image obtained 10 minutes after Mn-DPDP injection shows multiple small hypointense lesions (arrows) that are conspicuous against the background of enhancing liver in the caudate lobe and segment IV, thereby allowing accurate depiction and localization of liver metastases prior to liver resection.

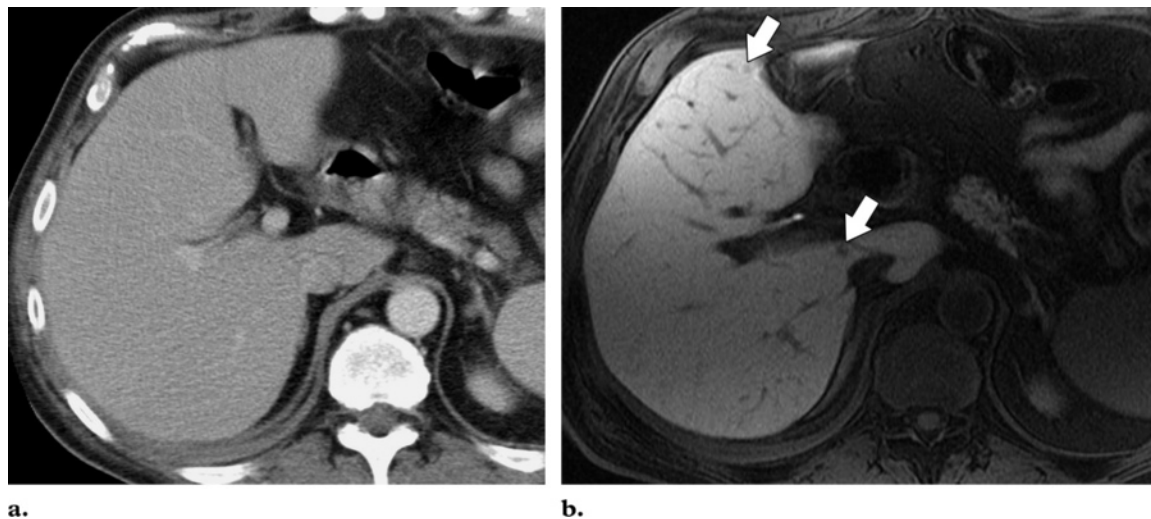


Figure 4. A 58-year-old man with a history of pancreatic endocrine neoplasm and a Whipple procedure in whom the results of a staging contrast-enhanced CT examination were suggestive of a possible new liver metastasis in segment VI. MR imaging with Gd-EOB-DTPA was performed for further characterization of the lesion. **(a)** Axial T2-weighted MR image shows a hyperintense 1-cm lesion (arrow) in segment VI. **(b)** Axial contrast-enhanced arterial phase MR image shows marked enhancement of the lesion (arrow). **(c)** Axial contrast-enhanced hepatobiliary phase MR image shows no Gd-EOB-DTPA retention in the lesion (arrow), allowing confirmation of this lesion as non-hepatocellular and hence presumably metastatic. At follow-up imaging, the lesion had enlarged, and new lesions had appeared, findings that confirmed metastatic disease.

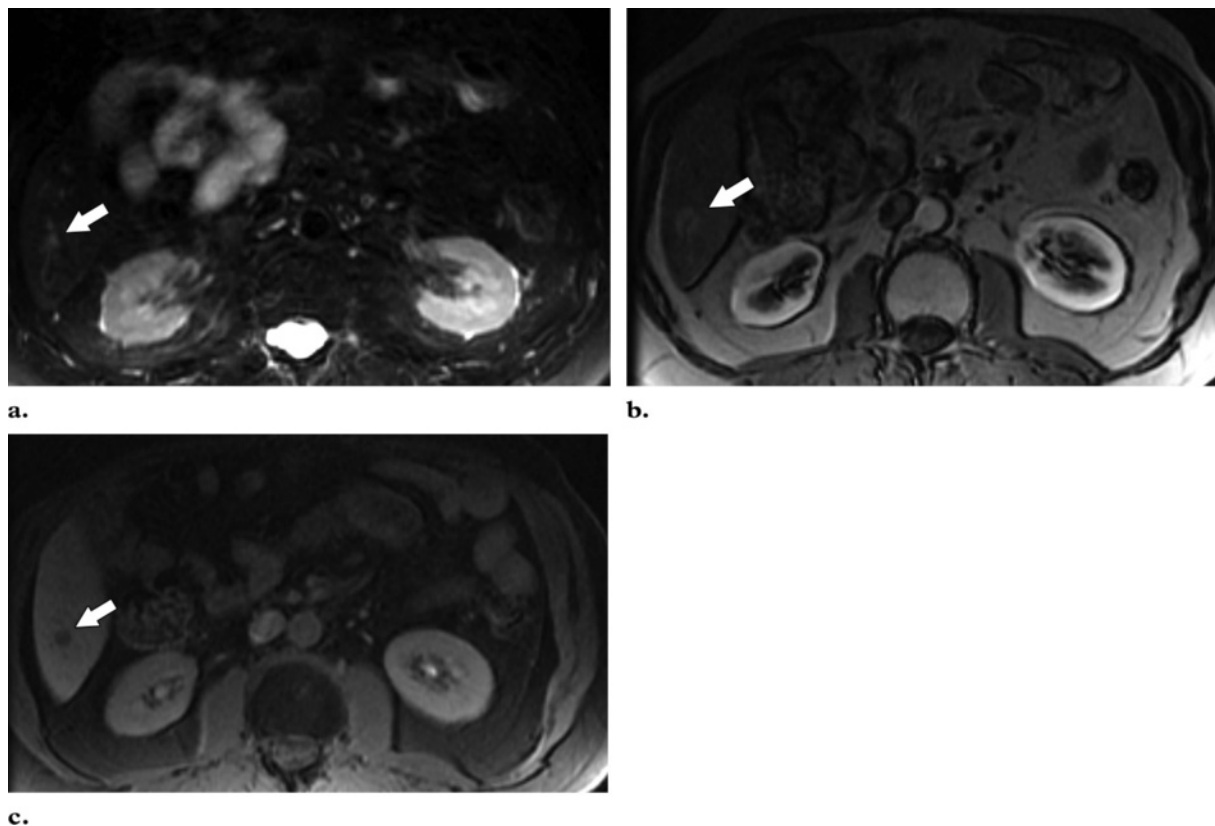


Table 6
Typical Appearance of Common Liver Lesions at Contrast-enhanced MR Imaging

Lesion	T1-weighted Imaging	T2-weighted Imaging	Dynamic Imaging	Delayed Phase*	Other Comments
Metastasis	Usually hypointense	Variable degree of hyperintensity	Usually hypovascular and hence hypointense; hyperintense in arterial phase if hypervascular	No enhancement	...
Cavernous hemangioma	Homogeneously hypointense	Homogeneously hyperintense; increasing hyperintensity with increasing echo time	Usually characteristic peripheral nodular enhancement with centripetal progression	No enhancement	Large lesions may have nonenhancing central scar
Hepatic adenoma	Usually heterogeneous with areas of hyperintensity (caused by lipid, hemorrhage)	Usually hyperintense	Hypervascular but often not as vividly enhancing as focal nodular hyperplasia	No enhancement with Gd-BOPTA (28), may enhance with Mn-DPDP and Gd-EOB-DTPA	Usually no central scar
Focal nodular hyperplasia	Iso- to hypointense	Iso- to hyperintense	Hypervascular, iso- to hyperintense to liver in portal venous phase	Enhances, becoming iso- or hyperintense to normal liver	Central scar in 80%, scar usually hyperintense on T2-weighted images, with delayed enhancement
Hepatic cyst	Hypointense	Hyperintense	No enhancement	No enhancement	...
Fibrolamellar HCC	Homogeneously hypointense	Heterogeneously hyperintense	Heterogeneous enhancement in arterial and portal venous phases, becoming more homogeneous with time	Enhances, with variable homogeneity	Commonly has hypointense nonenhancing central scar on T1- and T2-weighted images

Source.—References 26–28.

Note.—HCC = hepatocellular carcinoma.

*After administration of hepatobiliary-specific contrast agent.

Hepatobiliary-specific agents are particularly useful in determining whether a lesion is of hepatocellular origin (eg, focal nodular hyperplasia, adenoma) or not (eg, cyst, hemangioma, metastasis). Of the benign hepatocellular lesions, enough evidence exists in the literature to support the belief that focal nodular hyperplasia may be defini-

tively diagnosed by using hepatobiliary-specific contrast agents (26,28–30). Confident diagnosis of focal nodular hyperplasia at imaging allows conservative management (31). On the other hand, hepatic adenoma occurs in a similar patient population and shares some features with focal nodular hyperplasia at dynamic imaging but may require surgical treatment or close monitoring in some situations because of the known risk of

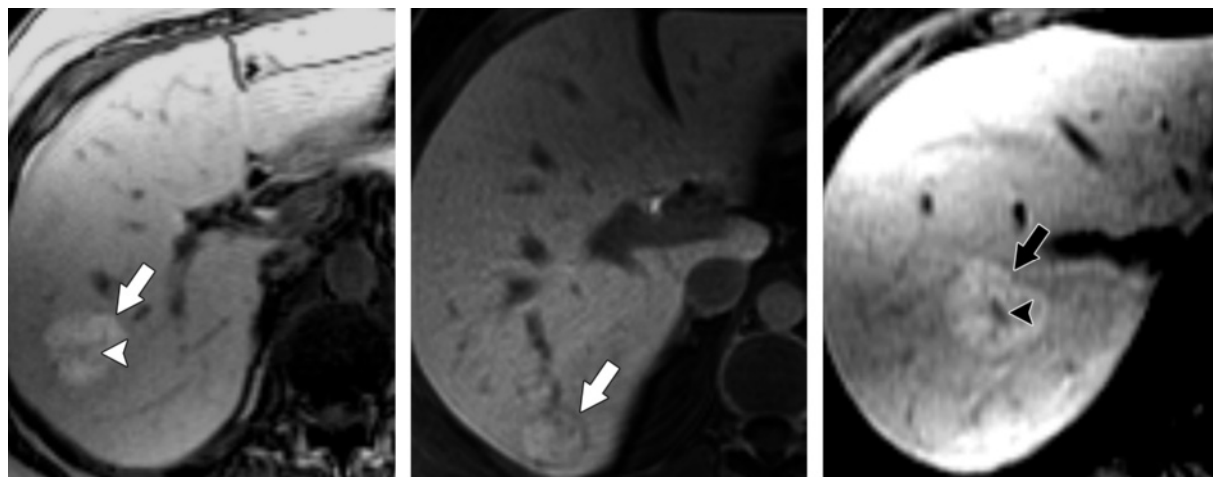


Figure 5. Axial hepatobiliary phase MR images of focal nodular hyperplasia that were obtained in three different patients after administration of the three different hepatocyte-specific contrast agents. Images were obtained 20 minutes after the start of Mn-DPDP injection (**a**), 60 minutes after the start of Gd-BOPTA injection (**b**), and 20 minutes after the start of Gd-EOB-DTPA injection (**c**). In each image, note that each focal nodular hyperplasia lesion (arrow) retains the hepatobiliary-specific contrast agent more than the normal liver parenchyma does and appears hyperintense compared with the background liver. A central scar (arrowhead in **a** and **c**) is seen in two of the lesions.

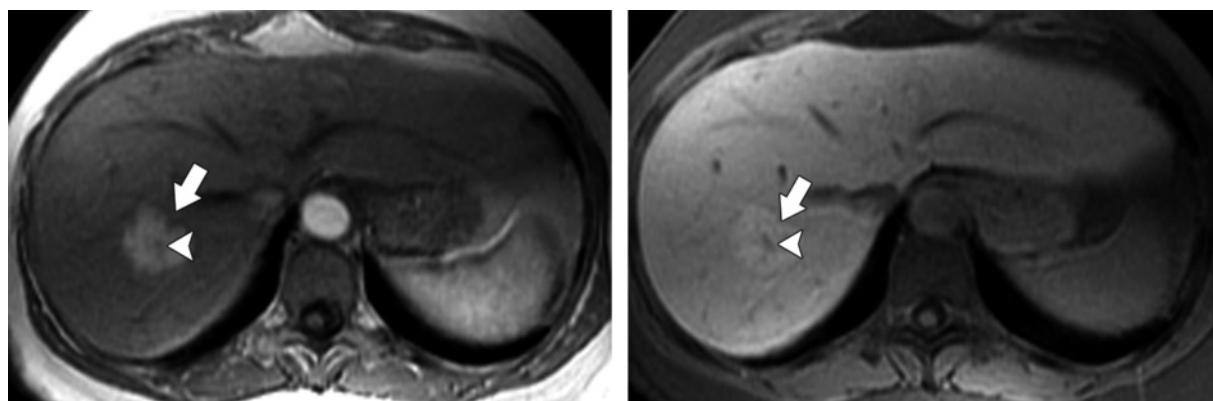


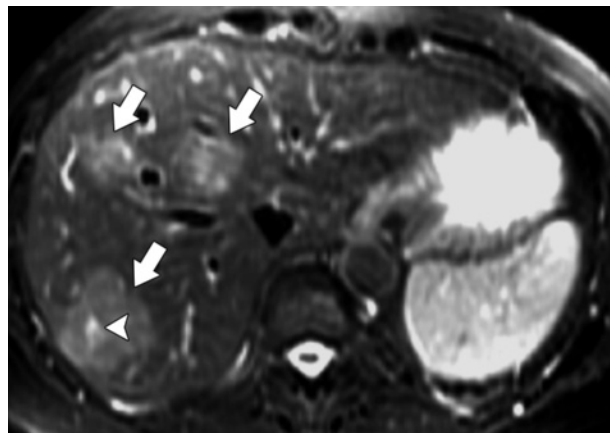
Figure 6. Incidental liver mass discovered at a chest CT examination of a 38-year-old man. Liver MR imaging with Gd-EOB-DTPA was performed for lesion characterization. (**a**) Axial contrast-enhanced T1-weighted arterial phase MR image shows that the lesion (arrow) in segment VII of the liver demonstrates homogeneous enhancement and a faint nonenhancing central scar (arrowhead). (**b**) Axial T1-weighted fat-suppressed MR image obtained 20 minutes after Gd-EOB-DTPA administration shows that the lesion (arrow) retains the contrast agent and appears hyperintense compared with background liver enhancement and also demonstrates a nonenhancing central scar (arrowhead). At subsequent biopsy, the diagnosis of focal nodular hyperplasia was confirmed.

spontaneous rupture and hemorrhage (31). Differentiating focal nodular hyperplasia and hepatic adenoma at conventional contrast-enhanced MR imaging can be particularly difficult if “typical” features are not seen. This scenario is reasonably common; for example, the classic T2 hyperintense scar is absent in 20% of focal nodular hyperplasia lesions (27), particularly when they are small (5), and intratumoral fat or hemorrhage is not seen in 30%–40% of hepatic adenomas (32).

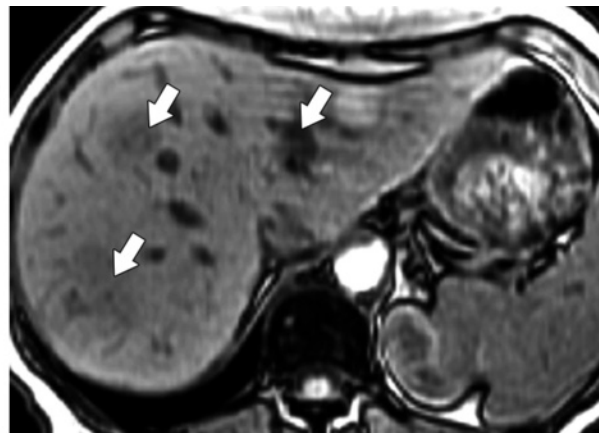
Histologically, focal nodular hyperplasia consists of functional hepatocytes associated with abnormal blind-ending biliary ductules, which

do not communicate with larger bile ducts (27). Hence, biliary excretion is slow compared with that of normal liver (5). In addition, the density of hepatocytes is increased in focal nodular hyperplasia compared with that of normal liver (33). At imaging with hepatobiliary-specific agents in the delayed phase, focal nodular hyperplasia becomes hyperintense because of retained contrast agent and the high density of hepatocytes (5,26,33,34) (Figs 5–7).

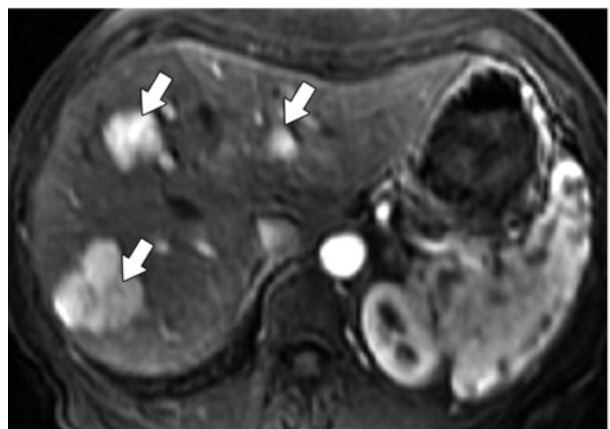
Figure 7. Multiple focal nodular hyperplasia lesions in a 45-year-old woman with a recent diagnosis of breast cancer. A staging contrast-enhanced CT examination of the abdomen had demonstrated multiple enhancing liver lesions. **(a)** Axial fast spin-echo T2-weighted fat-suppressed MR image demonstrates that the lesions (arrows) are hyperintense compared with background liver. A hyperintense central scar (arrowhead) is seen in the segment VII lesion. **(b)** Axial nonenhanced T1-weighted MR image shows that the lesions (arrows) are iso- to hypointense to the liver. **(c)** Axial arterial phase MR image obtained after Gd-BOPTA injection shows homogeneous enhancement of all of the lesions (arrows). **(d)** Axial contrast-enhanced portal venous phase MR image demonstrates that the lesions (arrows) become almost isointense to the liver, with enhancement of the central scar (arrowhead). **(e)** Axial T1-weighted fat-suppressed MR image obtained 60 minutes after Gd-BOPTA injection shows that all of the lesions (arrows) retain the contrast agent to a greater degree than the surrounding liver does. These features were considered diagnostic of focal nodular hyperplasia, and therefore a liver biopsy was not performed. Follow-up imaging at 1 year demonstrated stability of the lesions, further confirming their benign nature.



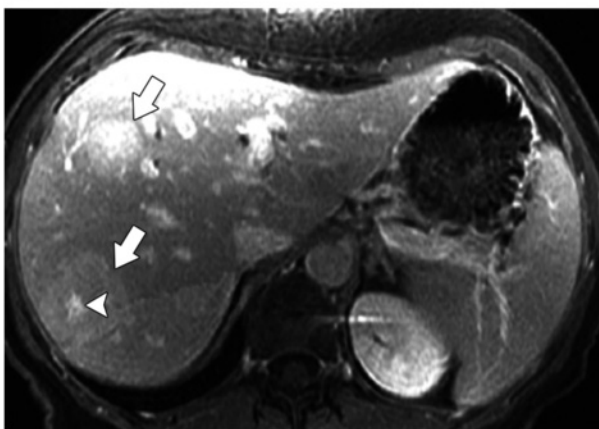
a.



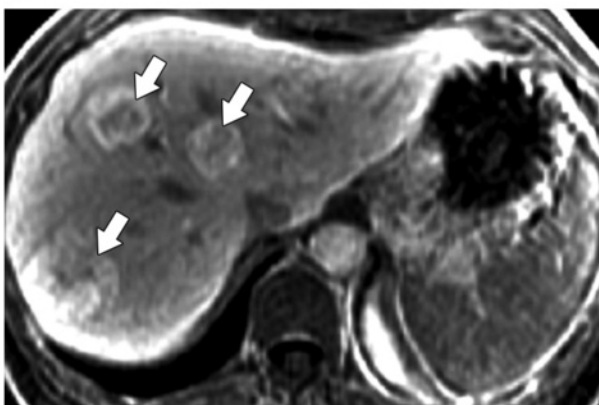
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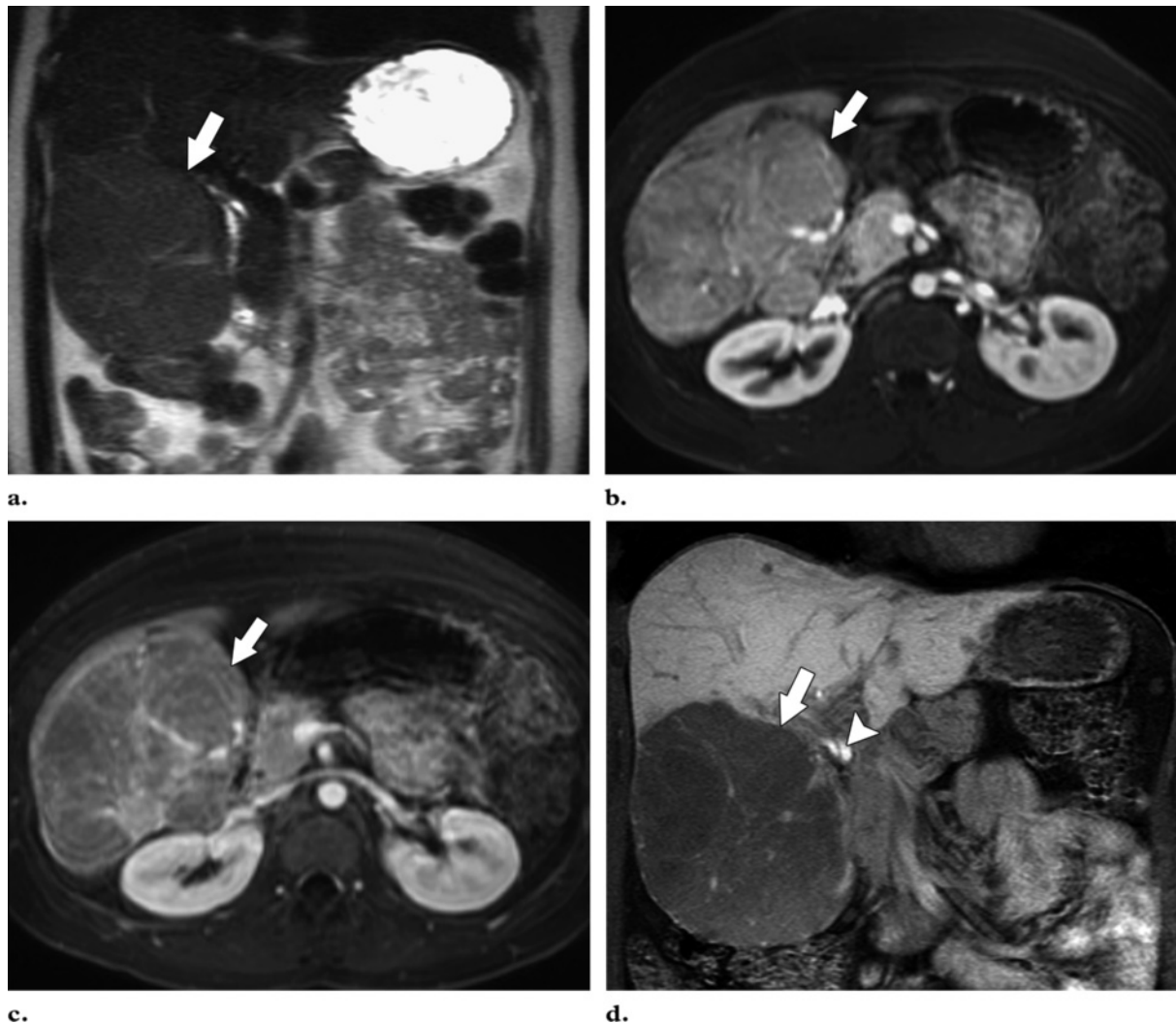


d.



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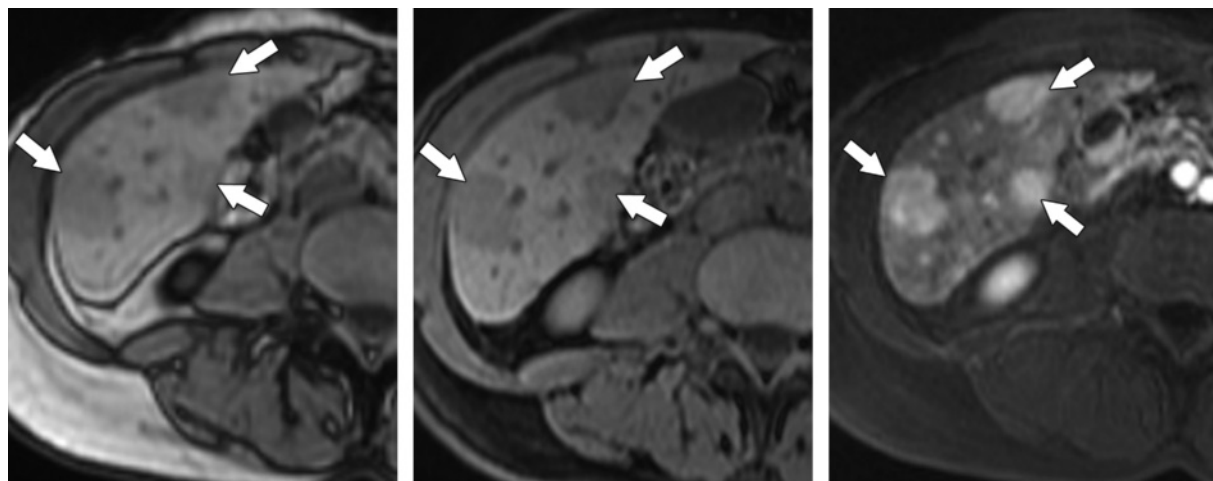
Figure 8. A 32-year-old woman with a long history of oral contraceptive use who presented with right upper abdominal pain. US examination of the abdomen had disclosed a large solid mass in the liver. Liver MR imaging without and with Gd-BOPTA was performed for lesion characterization. **(a)** Coronal T2-weighted steady-state fast spin-echo MR image demonstrates a large well-defined mass (arrow), slightly hyperintense to the liver. **(b)** Axial contrast-enhanced T1-weighted fat-suppressed arterial phase MR image show that the lesion (arrow) displays heterogeneous enhancement. **(c)** Axial contrast-enhanced T1-weighted fat-suppressed portal venous phase MR image shows subsequent contrast agent washout (arrow) from the lesion. **(d)** Coronal contrast-enhanced fat-suppressed hepatobiliary phase MR image obtained 1 hour after Gd-BOPTA injection demonstrates that the mass (arrow) shows no contrast agent retention. These imaging features excluded a diagnosis of focal nodular hyperplasia, and therefore hepatocellular adenoma was considered the most likely pathologic condition. Surgical resection was performed, and findings confirmed the diagnosis of benign adenoma. Incidentally, note excretion of Gd-BOPTA into the biliary tree (arrowhead in **d**).



In hepatic adenoma, hepatocytes are present in a cordlike arrangement separated by sinusoids with a lack of biliary ductules (27). The exact handling of hepatobiliary-specific agents by hepatocytes in an adenoma is poorly understood, but normal excretion into the biliary system certainly is not possible, and hence bile metabolism is substantially altered in the cells of the tumor. At

delayed phase imaging, investigators have shown that hepatic adenomas do not enhance with Gd-BOPTA (28) (Figs 8, 9), but variable enhancement may occur with Mn-DPDP (33,34) and Gd-EOB-DTPA (35).

Figure 9. A 37-year-old woman presenting with mild nonspecific abdominal pain who had abnormal results of liver function tests. A US examination performed at another institution disclosed multiple solid liver lesions. Liver MR imaging without and with Gd-BOPTA was performed for lesion characterization. **(a)** Axial nonenhanced T1-weighted MR image shows three subtly hypointense lesions (arrows) in segments V and VI of the liver. **(b)** Corresponding axial nonenhanced T1-weighted fat-saturated MR image shows that the lesions (arrows) are more hypointense. **(c)** Axial arterial phase MR image shows that the lesions (arrows) demonstrate strong homogeneous enhancement. **(d)** Coronal T1-weighted fat-saturated MR image obtained 60 minutes after contrast agent injection shows no retention of Gd-BOPTA in the liver lesions (arrows), which appear hypointense relative to normal liver. This finding indicates a lack of functioning hepatic parenchyma and/or an absence of normal biliary ductules. The presence of fat, as demonstrated by hypointensity on the T1-weighted fat-saturated image, the lack of a central scar, the marked homogeneous arterial enhancement, and the lack of Gd-BOPTA retention in the hepatobiliary phase of imaging favored a diagnosis of multiple adenomas. The findings from biopsy of the lesion in segment VI confirmed this benign diagnosis.



a.

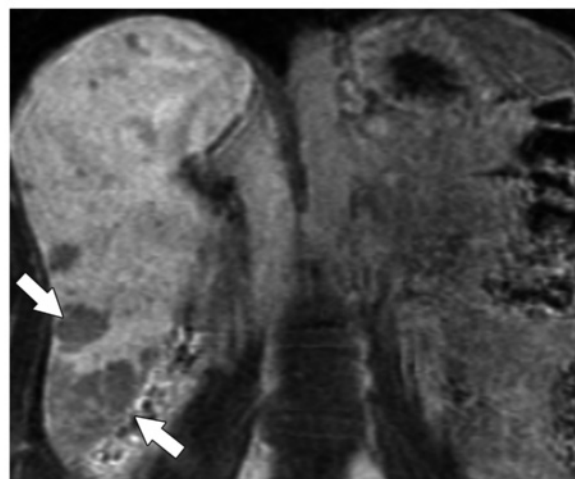
b.

c.

Hence, all hepatobiliary-specific contrast agents can be used to diagnose focal nodular hyperplasia with a high degree of confidence. In addition, Gd-BOPTA may be particularly useful in discriminating hepatic adenoma from focal nodular hyperplasia because the former does not appear to take up this agent in the hepatobiliary phase.

Lesion Detection and Characterization in Cirrhotic Liver

The rate of occurrence of hepatocellular carcinoma is increasing in the United States, largely because of the increasing rate of occurrence of hepatitis C. Screening for hepatocellular carcinoma with liver MR imaging is increasingly being considered for at-risk subjects because early detection and treatment of hepatocellular carcinoma have been shown to improve survival (36).



d.

The reported sensitivity of dynamic contrast-enhanced MR imaging with an extracellular fluid agent for detection of hepatocellular carcinoma (regardless of lesion size) ranges from 70% to 100%, with a systematic review by Colli et al (37) indicating a pooled estimate of 81%

Table 7
Sensitivity for Detection of HCC at Liver MR Imaging with Hepatobiliary-specific Contrast Agents

HCC Group	Extracellular Fluid Agents	Mn-DPDP	Gd-BOPTA	Gd-EOB-DTPA
All HCCs	70%–100%; pooled estimate, 81% (37)	81% (38)	80%–85% (39)	NA*
HCCs <1 cm	4%–33%	NA	29%–43%	NA*

Note.—HCC = hepatocellular carcinoma, NA = not available.

*Published data from most studies to date include all liver lesions; sensitivity is as much as 87% for detection of all lesions; improved detection of lesions measuring less than 1 cm is consistently reported (24,25).

Table 8
Typical Appearance of Cirrhotic Nodules at MR Imaging with Hepatobiliary-specific Contrast Agents

Type of Cirrhotic Nodule	T1-weighted Imaging	T2-weighted Imaging	Dynamic Imaging	Delayed Phase*
Regenerative nodule	Iso- to hyperintense	Iso- to hypointense	Enhances in portal venous phase, becoming iso- or hyperintense	Iso- to hyperintense
Dysplastic nodule				
Well differentiated	Variable, often hyperintense	Iso- to hypointense	Enhances in portal venous phase, becoming iso- or hyperintense	Enhances
Poorly differentiated	Variable	Mildly hyperintense	May enhance in arterial phase	May or may not enhance
HCC				
Well differentiated	Variable	Hyperintense	May enhance in arterial phase	May or may not enhance
Moderately to poorly differentiated	Variable, usually heterogeneous	Hyperintense	80%–90% enhance in arterial phase	No enhancement

Source.—References 36, 40, and 41.

Note.—Appearance is described relative to surrounding liver.

*After administration of hepatobiliary-specific contrast agent.

(Table 7) (24,25,37–39). However, detection of small lesions (<1 cm) remains a challenge, along with discriminating various cirrhosis-associated nodules, such as benign regenerative nodules and premalignant dysplastic nodules, from hepatocellular carcinoma. Not only is there considerable overlap among these nodules at histologic analysis and at imaging (Table 8) (36,40,41),

but lesion detection and characterization are often compounded further by the inhomogeneous appearance of the cirrhotic liver caused by fibrosis and hemodynamic alterations (40) (Fig 10).

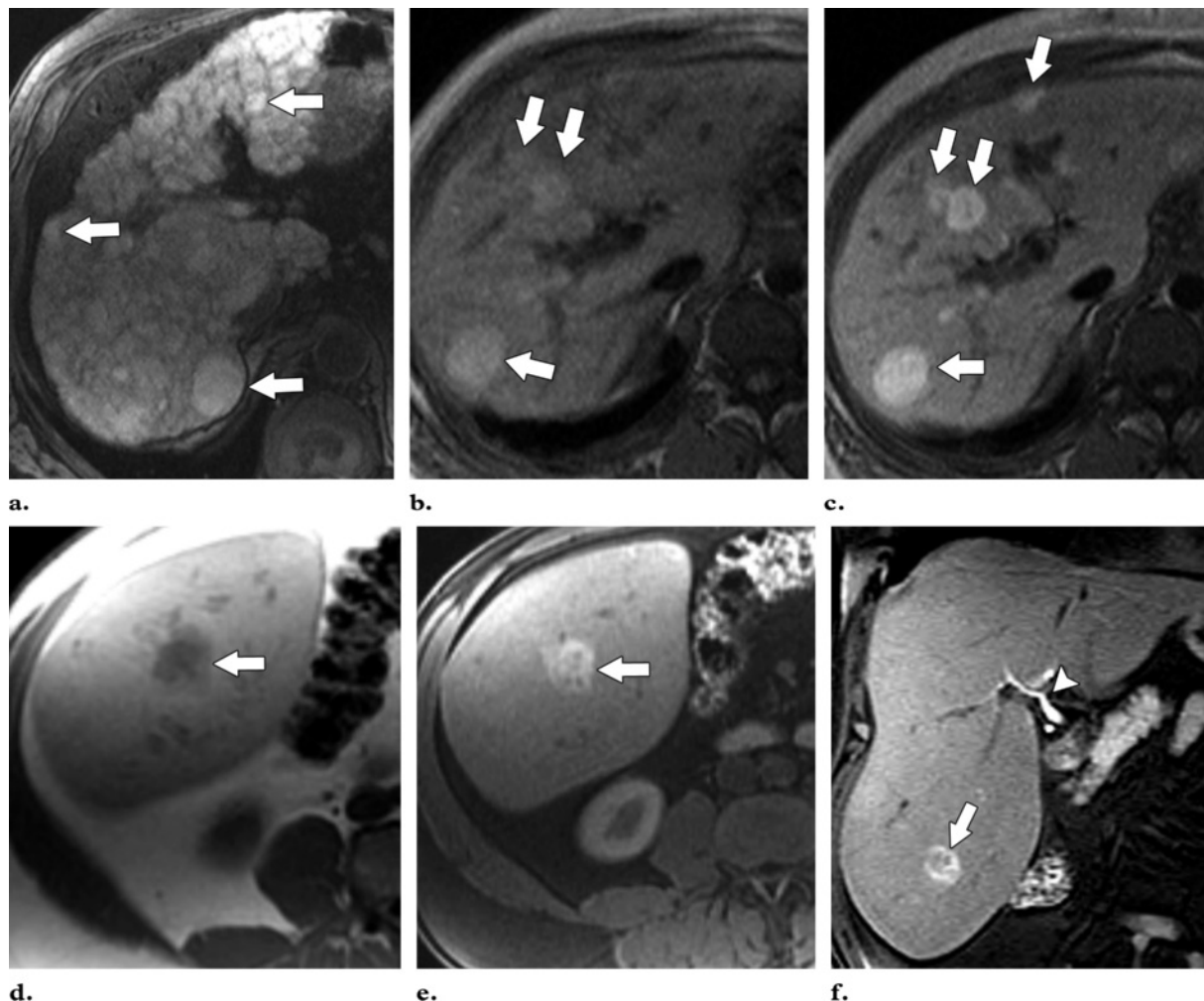


Figure 10. Hepatocellular lesions in three different patients who underwent liver MR imaging with Mn-DPDP. **(a)** Known cirrhosis in a 55-year-old man. Axial contrast-enhanced T1-weighted fat-suppressed hepatobiliary phase MR image demonstrates innumerable hyperintense regenerative nodules (arrows) in the cirrhotic liver. **(b, c)** Chronic liver disease in a 62-year-old woman. **(b)** Axial nonenhanced T1-weighted MR image shows several well-defined hyperintense nodules (arrows) in the liver. **(c)** Subsequent axial T1-weighted MR image obtained 4 hours after Mn-DPDP injection shows that the nodules (arrows) demonstrate marked accumulation of Mn-DPDP, with increased hyperintensity relative to the adjacent liver. The dominant nodule in segment VII was dysplastic at biopsy. Stability of the lesion was documented at follow-up imaging. Retention of Mn-DPDP is typical of functioning hepatic tissue, a feature shared by regenerative nodules, dysplastic nodules, and well-differentiated hepatocellular carcinoma. Therefore differentiation among these different entities relies on the dynamic contrast-enhanced imaging features and/or biopsy. **(d–f)** Liver lesion found at a recent US examination of the upper portion of the abdomen of a 57-year-old noncirrhotic patient. **(d)** Axial nonenhanced T1-weighted MR image demonstrates a 3-cm hypointense lesion (arrow) in the right lobe of the liver. Axial **(e)** and coronal **(f)** T1-weighted fat-suppressed images acquired 30 minutes after Mn-DPDP injection show that the lesion (arrow) demonstrates heterogeneous uptake of Mn-DPDP. Surgical resection of the right lobe of the liver yielded well-differentiated hepatocellular carcinoma. Note concomitant excretion of Mn-DPDP in the biliary tree (arrowhead in **f**).

The use of hepatobiliary-specific agents in this setting is controversial. In some studies, investigators have suggested that these hepatobiliary-specific agents may have a role in detecting small

hepatocellular carcinomas (Table 7), but the overall sensitivity for lesion detection is not greater than that of extracellular fluid agents, for the same reasons described previously. In addition, when hepatocyte function is impaired, the uptake of hepatobiliary-specific agents in the de-

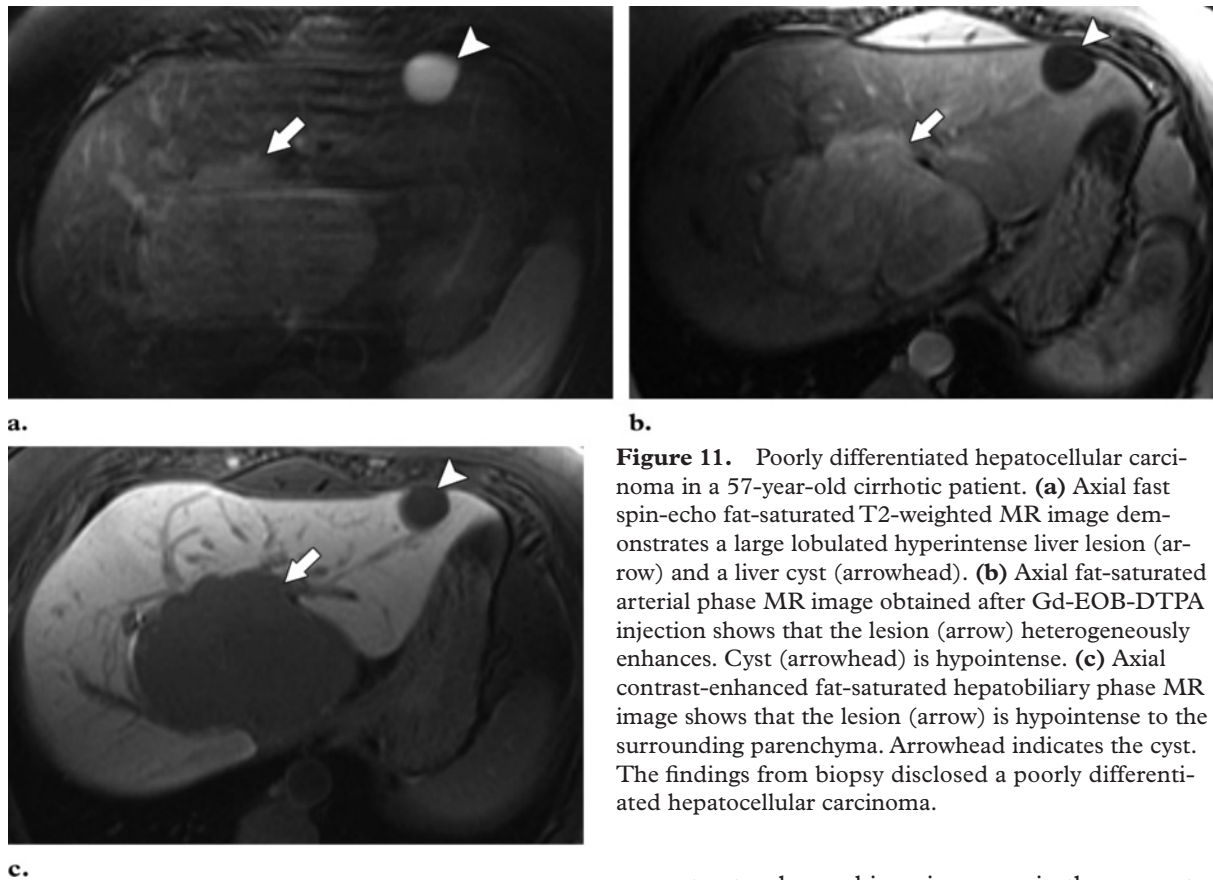


Figure 11. Poorly differentiated hepatocellular carcinoma in a 57-year-old cirrhotic patient. **(a)** Axial fast spin-echo fat-saturated T2-weighted MR image demonstrates a large lobulated hyperintense liver lesion (arrow) and a liver cyst (arrowhead). **(b)** Axial fat-saturated arterial phase MR image obtained after Gd-EOB-DTPA injection shows that the lesion (arrow) heterogeneously enhances. Cyst (arrowhead) is hypointense. **(c)** Axial contrast-enhanced fat-saturated hepatobiliary phase MR image shows that the lesion (arrow) is hypointense to the surrounding parenchyma. Arrowhead indicates the cyst. The findings from biopsy disclosed a poorly differentiated hepatocellular carcinoma.

layered phase may be compromised, which results in decreased distinction between the liver and the lesion (33,39).

Moreover, the appearance of hepatocellular carcinoma at delayed imaging with hepatobiliary-specific agents is dependent on the degree of tumor differentiation. Hepatocytes in well-differentiated hepatocellular carcinoma may retain enough hepatocellular function to take up hepatobiliary-specific agents, may appear iso- or hyperintense to liver at delayed imaging, and hence may be overlooked at this phase of imaging or appear similar to a regenerative or dysplastic nodule (Fig 10c). Moderately to poorly differentiated hepatocellular carcinomas do not take up or excrete hepatobiliary-specific agents and appear relatively hypointense to the liver at delayed imaging (Fig 11). **It is important to note that it is not possible to distinguish benign from well-differentiated malignant hepatocellular lesions with hepatobiliary-specific agents (26,33).**

Because of these issues, standard T1- and T2-weighted sequences, together with dynamic

contrast-enhanced imaging, remain the current mainstay for hepatocellular carcinoma detection. Hepatobiliary-specific agents are best reserved for use in problematic cases. For example, hepatobiliary-specific agent uptake may help determine the degree of differentiation of hepatocellular carcinoma; that is, if a known hepatocellular carcinoma enhances in the delayed phase, it is probably well differentiated.

Preoperative Assessment of Hepatic Vascular Anatomy

Accurate preoperative assessment of the anatomic structures of the liver is becoming increasingly important because of refinements in hepatobiliary surgery and the complexity of liver anatomy. Preoperative knowledge of the hepatic vascular and biliary anatomy, in particular any anatomic variants, is desirable in a wide range of surgical procedures, including tumor resection, partial hepatectomy for living donor transplantation, intraarterial chemotherapy infusion pump placement, and biliary surgery (42).

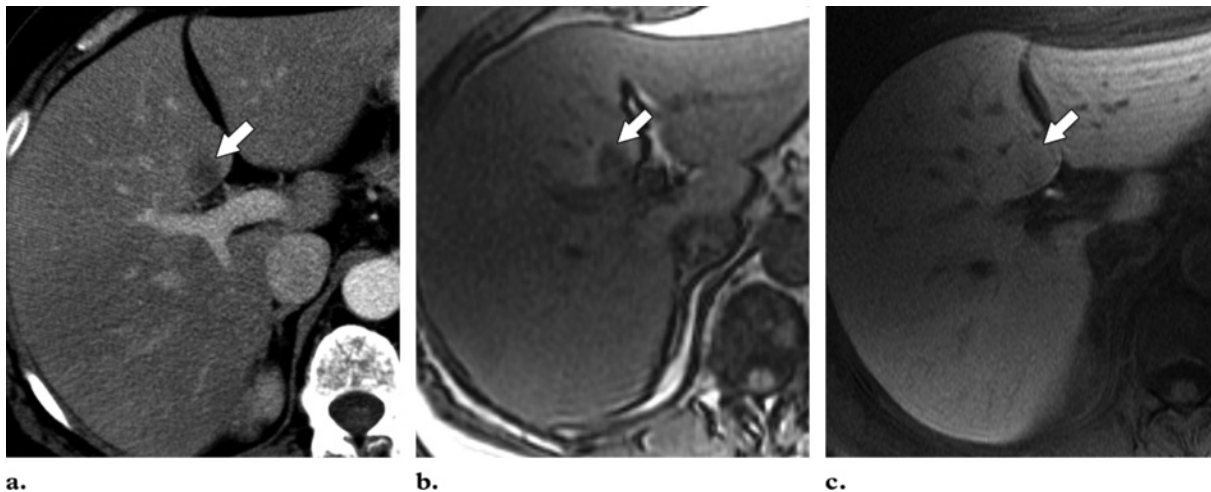


Figure 12. Liver lesion in a 67-year-old woman with colorectal cancer. **(a)** Axial contrast-enhanced CT image demonstrates an ill-defined area of hypoattenuation (arrow) in segment IV of the liver, which raises the possibility of liver metastasis. **(b)** Axial nonenhanced T1-weighted out-of-phase MR image shows the lesion (arrow) to be hypointense, which is suggestive of steatosis. **(c)** Axial hepatobiliary phase MR image obtained after Gd-EOB-DTPA injection demonstrates homogeneous signal intensity of the liver, with no focal lesion identified (arrow). This finding rules out metastatic disease and confirms that the lesion is due to focal fat deposition.

All hepatobiliary-specific agents may be used for contrast-enhanced cholangiography, which will be described later. In addition, the dynamic capabilities of Gd-BOPTA and Gd-EOB-DTPA allow noninvasive vascular assessment of the liver. These agents potentially allow a comprehensive noninvasive imaging assessment of liver parenchyma, intrahepatic lesions, hepatic vessels, and the biliary tree.

After dynamic imaging, hepatic arterial, hepatic venous, and portal venous anatomic structures are evaluated. Variants in any of these systems are particularly important in liver transplant surgery, where anomalous anatomic variants in the donor or recipient may alter the surgical approach or require additional surgical steps (43).

In hepatic tumor resection, knowledge of vascular anatomic structures helps to clarify the relationship of the tumor to the major vessels, helps to plan the surgical approach, and ensures that the remnant liver is not devascularized (44). Hepatic arterial anatomic structures may determine patient suitability for and influence the placement of intraarterial chemotherapy pumps in patients with liver metastases (42).

Problem Solving

Hepatobiliary-specific agents can be useful in patients who are suspected of having a pseudo-

lesion; the agents can help to characterize the pseudolesion, such as focal fat, focal fatty sparing, or perfusion abnormality. In these cases, the pseudolesion usually shows contrast agent uptake in the delayed phase and appears isointense compared with the remainder of the liver, which confirms the presence of functional hepatocytes (Fig 12).

Uses of Hepatobiliary-specific Contrast Agents for Imaging the Biliary Tree

Hepatobiliary-specific agents are all excreted into the biliary tree, causing T1 shortening of bile, and so can be used for contrast-enhanced T1-weighted MR cholangiography (Fig 13). This can be combined with conventional T2-weighted MR cholangiopancreatography to add valuable information. Potential uses of contrast-enhanced MR cholangiography include preoperative anatomic assessment, postoperative assessment, functional assessment, and problem solving.

Preoperative Anatomic Assessment

Preoperative anatomic assessment of the biliary tree is valuable in preventing inadvertent complications in procedures as common as laparoscopic cholecystectomy and also in complex biliary surgical procedures, such as biliary-enteric anastomosis and liver transplantation. Although conventional T2-weighted MR cholangiopancreatography is widely used, it may be insufficient to

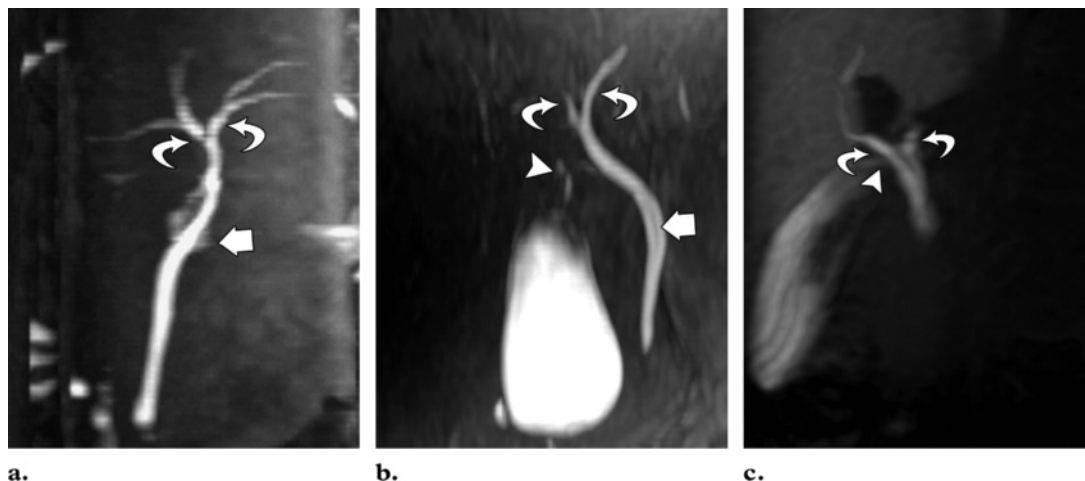


Figure 13. Contrast-enhanced MR cholangiographic images obtained from three different patients with the three different hepatobiliary-specific contrast agents. Coronal T1-weighted images obtained after injection of Mn-DPDP (**a**), Gd-BOPTA (**b**), and Gd-EOB-DTPA (**c**) show contrast agent excretion into the biliary tree, with resultant T1 shortening of the bile. Note that the strong excretion of Mn-DPDP and Gd-EOB-DTPA allows superior-quality contrast-enhanced MR cholangiographic images and more confident depiction of the bile duct bifurcation and the intrahepatic ducts compared with the contrast-enhanced MR cholangiographic image following Gd-BOPTA injection, in which there is incomplete depiction of the bile duct bifurcation and intrahepatic ducts. The common bile duct (straight arrow in **a** and **b**) and the right and left hepatic ducts (curved arrows) are well depicted. Note the cystic duct (arrowhead in **b** and **c**).

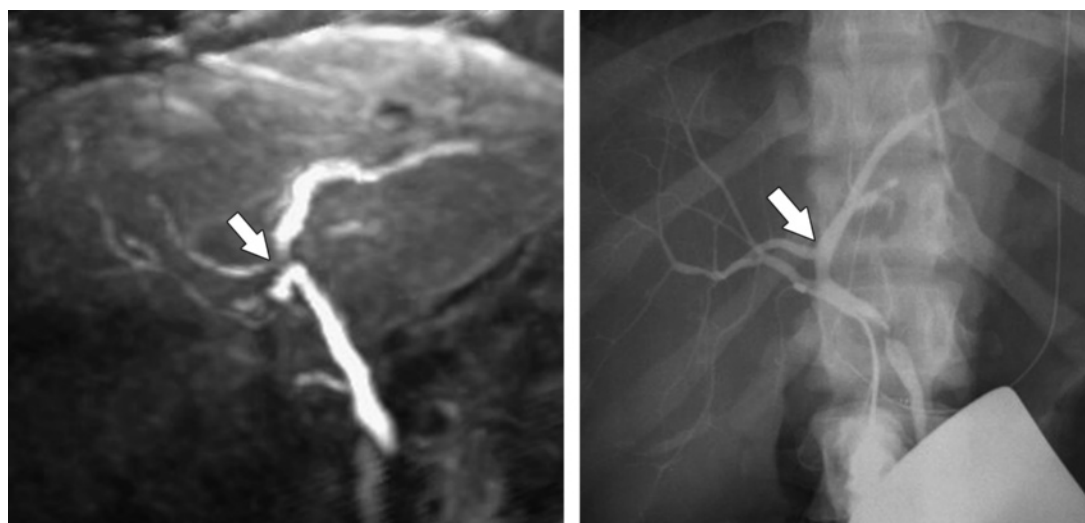


Figure 14. Definition of biliary anatomic structures in a 49-year-old living liver donor candidate prior to hepatectomy. (**a**) Volume maximum intensity projection display in a coronal plane of T1-weighted fat-suppressed three-dimensional data obtained 20 minutes after Mn-DPDP injection shows the right anterior hepatic duct draining into the left hepatic duct (arrow). (**b**) Intraoperative cholangiographic image subsequently helped confirm this finding (arrow). Preoperative knowledge of this anatomic variant allowed accurate surgical planning.

identify intrahepatic ducts and anatomic variants (43). Contrast-enhanced MR cholangiography with Mn-DPDP has been shown to be accurate for use in identifying anatomic variants of the

intrahepatic biliary tree (43) (Fig 14). In addition, contrast-enhanced MR cholangiography has the potential to provide higher-resolution

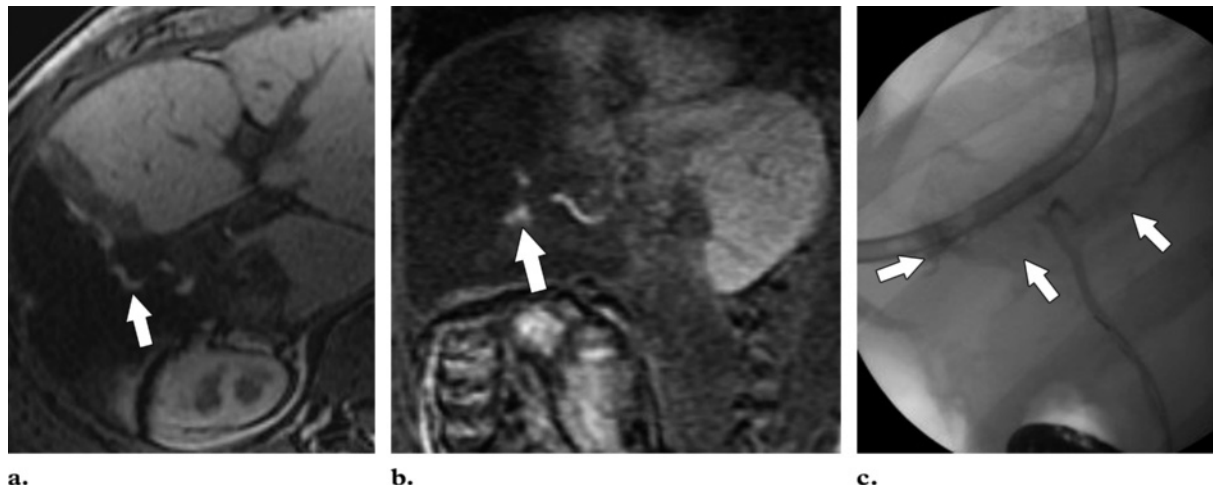


Figure 15. A 55-year-old man who was suspected of having a bile leak 3 days after right hemihepatectomy. Axial (**a**) and coronal (**b**) T1-weighted fat-suppressed MR images obtained 30 minutes after Mn-DPDP injection demonstrate areas of high T1 signal intensity (arrow) in the right hepatectomy bed that match the signal intensity of the excreted Mn-DPDP in the bile duct, a finding that supports the clinical suspicion of a bile leak. (**c**) Endoscopic retrograde cholangiopancreatographic image, which was obtained after MR imaging, helped confirm the leak (arrows) and enabled placement of a plastic stent to treat it.

images than those of conventional T2-weighted MR cholangiopancreatography because an inherently higher-resolution sequence is used (three-dimensional gradient echo vs T2-weighted fast spin echo) (45) and because T1-weighted sequences, which are generally shorter than T2-weighted sequences, allow better cooperation with breath-hold requirements.

Preoperative recognition of bile duct anatomic variants reduces the risk of bile leak, a major cause of morbidity in living donor liver transplantation and in tumor resection, particularly when surgery involves the left lobe of the liver. Inadvertent ligation or transection of aberrant bile ducts may also occur in laparoscopic cholecystectomy if the anatomic variant is not recognized.

Postoperative Assessment

MR imaging provides a noninvasive means of assessing the biliary tree after surgery, when complications such as bile leak or inadvertent biliary duct ligation or stricture are suspected. Although conventional T2-weighted MR cholangiopancreatography provides considerable anatomic information, contrast-enhanced MR cholangio-

pancreatography adds functional information with regard to biliary excretion and may be particularly useful in identifying the site of the bile leak, which is not usually possible at conventional T2-weighted MR cholangiopancreatography (46). In addition, fluid collections, ascites, and fluid-containing structures that can obscure findings at conventional T2-weighted MR cholangiopancreatography are inherently less conspicuous with the T1-weighted sequences used in contrast-enhanced MR cholangiography, which may help depiction of the biliary tree (Figs 15, 16).

Functional Assessment

Established noninvasive methods of imaging the biliary tree currently include ultrasonography (US), CT cholangiography, T2-weighted MR cholangiopancreatography, and cholescintigraphy. Of these, only scintigraphy provides functional information about the flow of bile, with sensitivities of more than 95% for the diagnosis of acute cholecystitis and complete extrahepatic biliary obstruction (47). However, cholescintigraphy does not have adequate resolution to demonstrate the cause of obstruction or ductal abnormalities such as strictures, and partial obstruction may be missed (45).

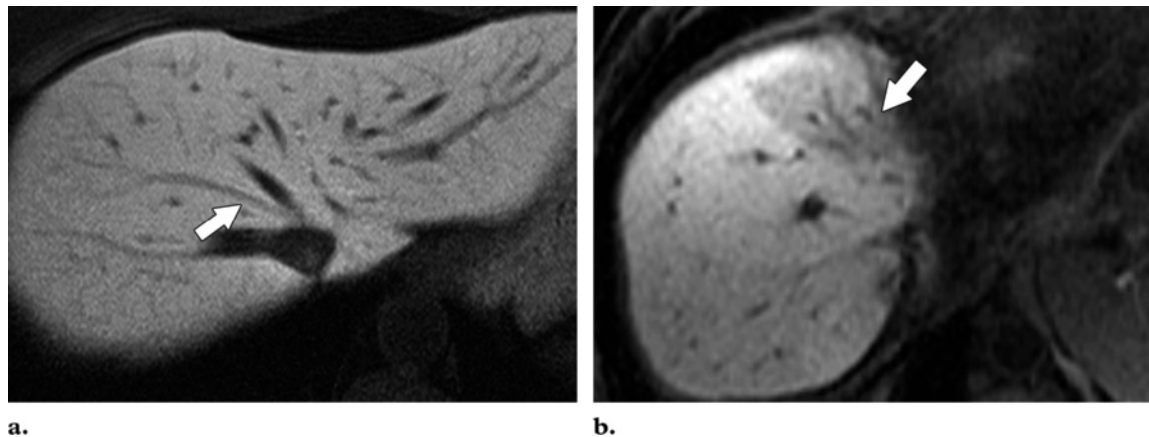


Figure 16. Assessment of liver parenchymal viability and/or injury after adult-adult right lobe liver transplantation. **(a)** Axial T1-weighted fat-suppressed MR image obtained 15 minutes after Mn-DPDP injection in a 58-year-old living donor shows a venous tributary (arrow) draining a part of segments VIII and V into the middle hepatic vein. The transection plane for the right lobe graft intersects this accessory vein. **(b)** Postoperative axial contrast-enhanced T1-weighted fat-suppressed MR image obtained after Mn-DPDP injection in the transplant recipient shows mild volume loss and poor contrast agent uptake in the corresponding liver segment (arrow), consistent with a parenchymal injury secondary to venous congestion in the affected area.

In the normal liver, Mn-DPDP, Gd-BOPTA, and Gd-EOB-DTPA begin appearing in the bile at 10 minutes, 20 minutes, and 10 minutes, respectively, after the start of contrast agent injection (45,48). By referring to these reference values for biliary excretion, an indication of excretory function may be obtained during clinical examination. Delayed imaging may be required in cases of obstruction.

Scintigraphically, acute cholecystitis is diagnosed by nonfilling of the gallbladder at 4 hours, or at 90 minutes with pharmacologic stimuli (morphine or cholecystokinin) (47). Similar criteria have been applied to contrast-enhanced MR cholangiography with good results in one small study (45). Research concerning the diagnosis of chronic cholecystitis with hepatobiliary-specific agents is extremely limited, but there is potential for the use of contrast-enhanced MR cholangiography, by using findings such as *(a)* delayed gallbladder filling and/or emptying and *(b)* decreased gallbladder response to intravenous administration of cholecystokinin (45). Contrast-enhanced MR cholangiography may help to rule out obstruction in a dilated unobstructed biliary tree (eg, caused by previous obstruction) (45).

Problem Solving

A flow artifact is sometimes encountered on T2-weighted MR cholangiopancreatographic images, particularly in the common bile duct. The flow artifact is usually absent on contrast-enhanced MR cholangiographic images, which can help to exclude pathologic conditions.

Pitfalls of Contrast-enhanced MR Cholangiography

Of note, hepatobiliary-specific agents do cause some T2 shortening. Hence, if T2-weighted MR cholangiopancreatography is being performed during a study in which a hepatobiliary-specific agent is administered, the T2-weighted MR cholangiopancreatography should be performed before the hepatobiliary-specific contrast agent appears in the biliary tree.

Adding contrast-enhanced MR cholangiography to an imaging protocol obviously adds to imaging time and expense and exposes the patient to the inherent risks associated with intravenous contrast agents. In addition, excretion of hepatobiliary-specific agents may be impaired in patients with obstructive jaundice and hepatic

dysfunction, and repeated delayed imaging may be required until the contrast agent appears in the biliary tree. In cases of high-grade obstruction or hepatic dysfunction, no excretion may occur.

Depiction of gallstones in the gallbladder may be decreased if gallbladder filling is poor because on contrast-enhanced MR cholangiographic images, gallstones appear as filling defects in the contrast agent-filled gallbladder. **Hence, contrast-enhanced MR cholangiography should not replace T2-weighted MR cholangiopancreatography but can be considered a useful adjunct.**

Future Uses of Hepatobiliary-specific Contrast Agents

Noninvasive Grading of Cirrhosis

Presently, liver biopsy remains the reference standard for the diagnosis and grading of liver fibrosis and cirrhosis. Development of a noninvasive method of assessment for liver fibrosis is desirable, given the morbidity and potential mortality associated with liver biopsy.

Although much research has been done with regard to the potential roles of diffusion-weighted MR imaging and MR spectroscopy in the assessment of fatty liver disease, quantifying fibrosis has not been possible. However, the results of recent animal studies suggest that MR imaging with Gd-EOB-DTPA may have a role in this area. Tsuda and colleagues (49) have shown delayed peak liver enhancement and slowed washout of Gd-EOB-DTPA in rats with nonalcoholic steatosis (which is characterized by steatosis, lobular inflammation, and perisinusoidal fibrosis and is progressive, ultimately leading to cirrhosis), compared with rats with simple fatty liver (which is reversible). In addition, correlation has been demonstrated between the degree of fibrosis and the delay in maximum enhancement and washout (50).

Functional Assessment of the Liver

By using a similar rationale of quantifying liver enhancement, it may be possible in the future to assess hepatic functional reserve by quantifying hepatic signal intensity changes in the hepatobiliary phase of enhancement. This has potential applications in noninvasively predicting residual

liver function in patients undergoing partial hepatectomy for tumor resection or to provide a living donor liver transplant graft. Likewise in the transplant graft recipient, this approach might be able to be used to diagnose early liver failure and other liver parenchymal manifestations of post-transplantation complications.

Conclusions

In summary, hepatobiliary-specific contrast agents are an interesting group of compounds that form part of the armamentarium for MR imaging of the liver. Although experience with these agents may be limited in some centers, the agents show considerable promise for the investigation of many complex liver pathologic conditions. We believe that the most appropriate use of these agents is in (a) detection of hepatic metastases; (b) differentiation of nonhepatocellular lesions from well-differentiated hepatocellular lesions; (c) diagnosis of focal nodular hyperplasia with a high degree of confidence, and discrimination of hepatic adenoma from focal nodular hyperplasia (with the use of Gd-BOPTA); and (d) contrast-enhanced MR cholangiography for anatomic and functional assessment of the biliary tree.

Dynamic contrast-enhanced cross-sectional imaging remains the mainstay in diagnosing hepatocellular carcinoma. Hepatocyte-specific phase imaging with hepatobiliary-specific agents may provide information on the degree of differentiation of hepatocellular carcinoma. Other uses of hepatobiliary-specific agents in the cirrhotic liver may evolve with further research.

In some situations (eg, living donor liver transplant graft assessment), hepatobiliary-specific agents offer the assessment of liver parenchyma, intrahepatic lesions, hepatic vasculature, and the biliary tree in a single noninvasive examination. Future uses of these agents may include functional assessment of the liver.

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Hepatobiliary-specific MR Contrast Agents: Role in Imaging the Liver and Biliary Tree

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RadioGraphics 2009; 29:1725–1748 • Published online 10.1148/rg.296095515 • Content Codes: **GI** **MR**

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These hepatobiliary-specific agents are taken up to varying degrees by functioning hepatocytes and are excreted in the bile.

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The predominant use of all three hepatobiliary-specific agents is for imaging the liver in the delayed or hepatobiliary phase.

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Hepatobiliary-specific agents are particularly useful in determining whether a lesion is of hepatocellular origin (eg, focal nodular hyperplasia, adenoma) or not (eg, cyst, hemangioma, metastasis).

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It is important to note that it is not possible to distinguish benign from well-differentiated malignant hepatocellular lesions with hepatobiliary-specific agents (26,33).

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Hence, contrast-enhanced MR cholangiography should not replace T2-weighted MR cholangiopancreatography but can be considered a useful adjunct.