

# Diagnostic Challenges and Pitfalls in MR Imaging with Hepatocyte-specific Contrast Agents<sup>1</sup>

## TEACHING POINTS

See last page

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The use of gadolinium-based hepatocyte-specific contrast agents (HSCAs) has increased markedly since their introduction, and hepatocellular phase imaging performed with an HSCA is now a key part of the standard magnetic resonance (MR) imaging work-up for focal liver lesions. An understanding of the mechanisms of action of HSCAs helps ensure their effective use. The optimal delay for hepatocellular phase image acquisition differs between the two currently available HSCAs, gadoxetic acid and gadobenate dimeglumine, and MR imaging protocols must be adjusted accordingly. In addition, familiarity with typical and atypical appearances of benign and malignant focal liver lesions at HSCA-enhanced hepatocellular phase MR imaging, along with knowledge of the processes that are most likely to produce atypical appearances, is required to achieve optimal diagnostic accuracy.

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**Abbreviations:** FNH = focal nodular hyperplasia, GRE = gradient echo, HCC = hepatocellular carcinoma, HSCA = hepatocyte-specific contrast agent, IVC = inferior vena cava, MRP = multidrug resistance protein, OATP = organic anion transporting polypeptide, SPIO = superparamagnetic iron oxide, 3D = three-dimensional, 2D = two-dimensional

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## Introduction

The correct characterization of liver lesions in imaging studies is of major importance, not only to the radiologist and the referring clinician but also to the patient. The relatively recent addition of hepatocyte-specific contrast agents (HSCAs) to the radiologist's armamentarium has had a significant impact on our ability to achieve a confident and correct diagnosis when using MR imaging.

The article describes the mechanism of action of HSCAs, discusses the optimization of MR imaging protocols for hepatocellular phase imaging with an HSCA, describes typical and atypical hepatocellular phase appearances of normal liver and focal hepatic lesions, and surveys the literature about the use of HSCAs for the detection, characterization, and differentiation of focal hepatic lesions. The existing evidence in support of using HSCAs to differentiate between benign and malignant lesions is examined. Particular attention is also given to the potential uncertainties and challenges that arise when using HSCAs.

## HSCAs and Their Mechanisms of Action

Two gadolinium-based HSCAs are commercially available at present: gadoxetic acid, which is marketed under the name Eovist in the United States and Primovist elsewhere worldwide (Bayer Schering Pharma, Berlin, Germany); and gadobenate dimeglumine (MultiHance; Bracco, Milan, Italy). HSCAs combine the properties of extracellular gadolinium chelates, allowing hepatic arterial and portal venous phase imaging, with delayed hepatocyte uptake and partial excretion into the biliary system. This combination of hepatocyte uptake and biliary excretion results in the additional so-called hepatocellular phase of imaging (Fig 1).

An important difference between the two agents is that 50% of the administered dose of gadoxetic acid, but only 5% of the gadobenate dimeglumine dose, is excreted via the hepatobiliary system in a healthy person; the remainder is excreted by the kidneys. Because of its greater hepatic uptake, gadoxetic acid results in more intense hepatocellular phase enhancement than gadobenate dimeglumine (1) and is cleared from the body more rapidly, according to the elimination half-lives stated in the product information sheets (1 hour for gadoxetic acid and 1–2 hours for gadobenate dimeglumine).

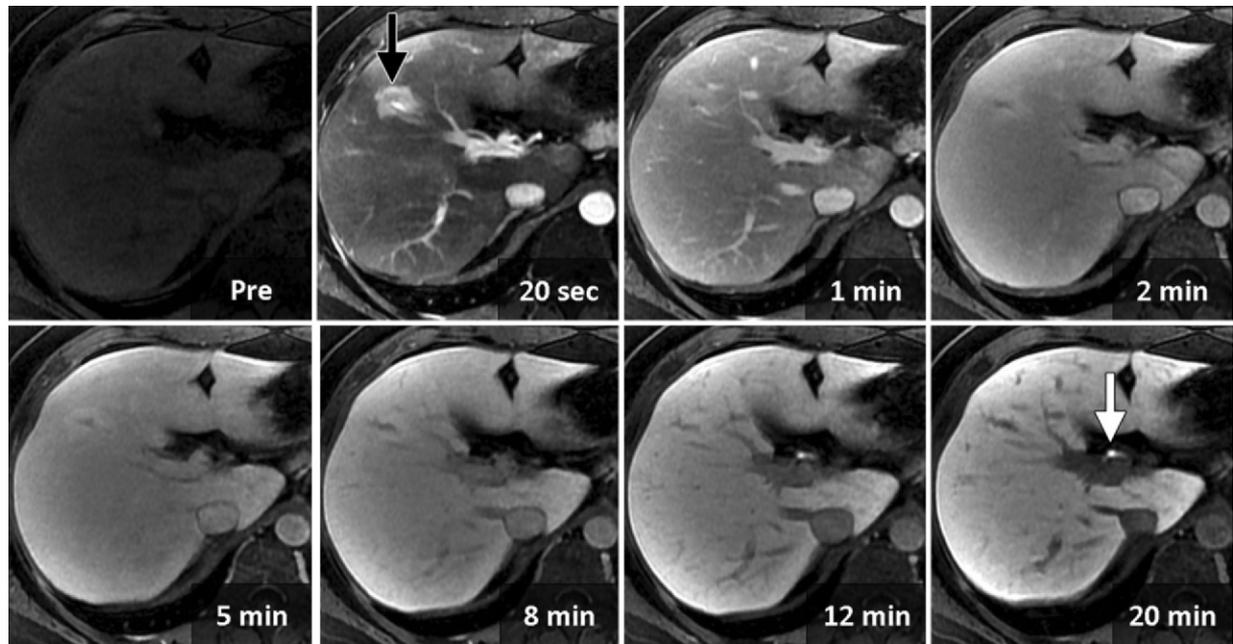
The original pharmacologic model of HSCA activity, derived from rat studies (Fig 2a) (2–4), describes hepatocyte uptake of HSCAs via adenosine triphosphate–dependent organic anion transporting polypeptide 1 (OATP1) and subsequent excretion into bile canaliculi by canalicular multispecific organic anion transporter (cMOAT), also known as multidrug resistance protein 2 (MRP2). Because bilirubin is taken up competitively by OATP1, the extent or magnitude of biliary excretion of HSCAs depends on liver function; thus, hepatocellular phase enhancement of the liver tends to be less intense in patients with hyperbilirubinemia. However, reduced HSCA uptake also has been observed in patients without hyperbilirubinemia, a finding suggesting that other mechanisms play a role in the extent of liver enhancement.

In a recent study of molecular transporter expression in surgically resected human hepatocellular carcinoma (HCC), it was found that the expression of both OATP1B3 (also known as OATP8) and multidrug resistance protein 3 (MRP3, a molecular exporter on the sinusoidal side of the hepatocyte) was significantly correlated with hepatocellular phase enhancement; this finding suggests that these molecules are also involved in gadoxetic acid transport (5). **Indeed, it appears likely that the degree of hepatocellular phase enhancement of individual lesions depends on the expression and activity of a number of different molecular transporters, which in turn depend on the underlying cytogenetic profile (Fig 2b).** This probably explains the heterogeneity among liver lesions with regard to the intensity of their hepatocellular phase enhancement, as described in greater detail in the sections on HSCA-enhanced appearances of benign and malignant focal liver lesions.

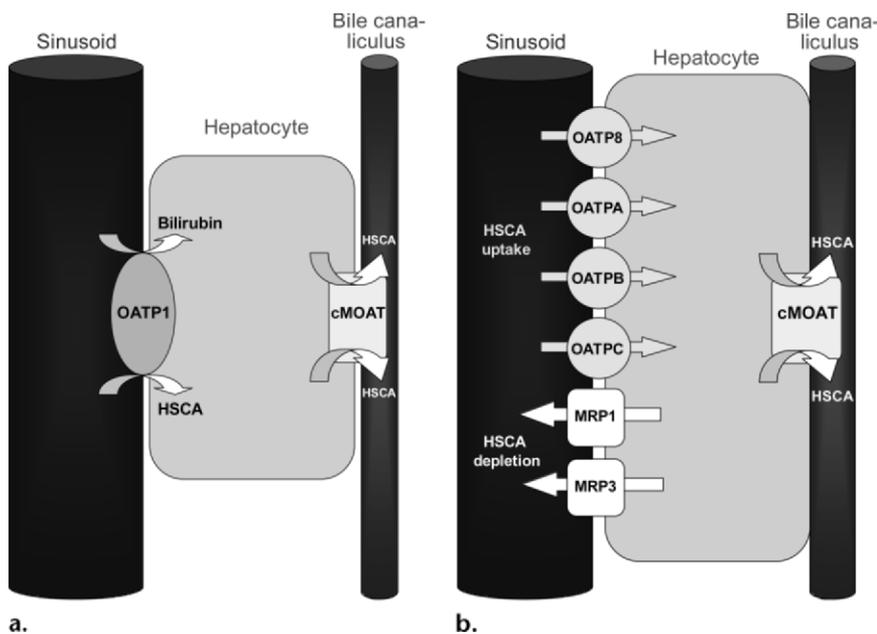
## Optimizing Protocols for Hepatocellular Phase MR Imaging with HSCAs

The optimal time point for imaging the hepatocellular phase differs between the two HSCAs. The product information sheet for gadoxetic acid states that hepatocellular phase imaging can be performed within a broad window of 10–120 minutes but that most of the data in confirmatory studies were obtained at 20 minutes after the injection of the contrast agent. Although at some centers hepatocellular phase imaging is routinely performed as early as 10 minutes after the injection, we typically perform it with a delay of 15–20

Teaching Point



**Figure 1.** Axial T1-weighted fat-saturated MR images obtained with fixed window settings before (*Pre*) and at seven intervals (20 seconds and 1, 2, 5, 8, 12, and 20 minutes) after administration of a gadoteric acid injection show the typical extensive enhancement of liver parenchyma in the hepatocellular phase. Parenchymal enhancement is visible as early as 2 minutes after and reaches a peak 20 minutes after the injection. Note the progressive loss of signal intensity in the portal vein relative to the liver parenchyma: The portal vein and inferior vena cava appear isointense at 5 minutes, mildly hypointense at 8 minutes, and markedly hypointense at 20 minutes after the injection. Enhancement of the common bile duct (white arrow) is seen in the latter part of the hepatocellular phase. A transient hepatic signal intensity difference incidentally depicted on the image obtained with a 20-second delay (black arrow) is due to an arterioportal fistula from a previous percutaneous biopsy.



**Figure 2.** (a) Diagram shows basic membrane transport mechanisms for HSCAs, which undergo competitive uptake into human hepatocytes by OATP1 and are excreted into bile canaliculi by canalicular multispecific organic anion transporter (*cMOAT*). (b) Diagram shows a more complex hypothetical model of HSCA uptake and excretion, which could involve a greater number of transporters than was at first thought. (Source.—Reference 5.)

minutes. For gadobenate dimeglumine, the delay from injection to the hepatocellular phase is longer (1–3 hours) because of a lesser degree of hepatobiliary excretion. Most centers at which gadobenate dimeglumine is used therefore temporarily remove the patient from the MR imaging table to a waiting area, to allow imaging of other patients in the meantime. When gadoxetic acid is used, this is not necessary; instead, the issue has been how to make use of the 10–20-minute interval while waiting for the hepatocellular phase.

Given that T2-weighted fast spin-echo imaging can be performed after portal venous phase imaging without a loss in diagnostic image quality (6) and that gadoxetic acid has no substantial effect on the apparent diffusion coefficients of focal lesions (7), the standard T2-weighted and diffusion-weighted imaging sequences can be performed after the standard three-dimensional (3D) dynamic unenhanced and contrast material-enhanced T1-weighted fat-saturated gradient-echo (GRE) sequences. Thus, a total examination time of 25–30 minutes can be achieved. It remains unclear whether satisfactory MR cholangiopancreatographic images can be obtained after gadoxetic acid injection. Kim et al achieved satisfactory images with both two-dimensional (2D) and 3D MR cholangiopancreatography performed with gadoxetic acid injections (8), but Ringe et al found substantial image degradation on respiratory-triggered 3D MR cholangiopancreatographic images obtained after the administration of gadoxetic acid (9). We therefore currently recommend that MR cholangiopancreatography be performed before gadoxetic acid is administered. A detailed step-by-step outline for the suggested protocol is given in Table 1.

### HSCA-enhanced MR Imaging Appearances

The action of HSCAs is similar to that of conventional extracellular gadolinium chelates during dynamic contrast-enhanced imaging for both normal liver and focal liver lesions. **With gadoxetic acid there are slight differences that the user should be aware of: The hepatic arterial phase may appear less intense than with conventional agents, and hepatocyte uptake starts rapidly, manifesting as parenchymal liver enhancement as early as 90 seconds after injection of the agent (10).** Because of the intense parenchymal enhancement and more rapid clearance from the body, the enhancement

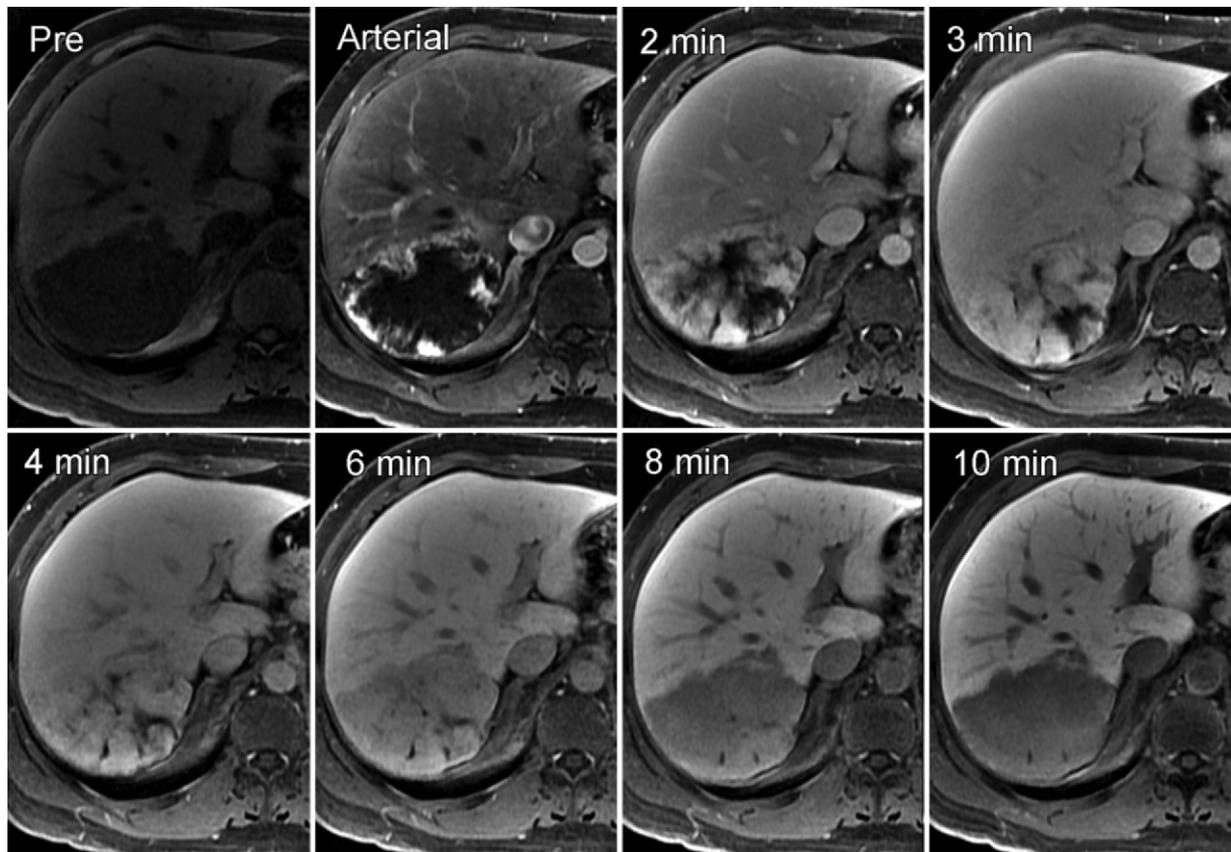
**Table 1**  
Order of Sequences for Gadoxetic Acid-enhanced Hepatic MR Imaging

Sequences applied before the injection of gadoxetic acid
3D T1-weighted in-phase and opposed-phase imaging
2D or 3D T2-weighted fast spin-echo MR cholangiopancreatography
3D unenhanced T1-weighted fat-saturated GRE
Sequences applied after the injection of gadoxetic acid
3D T1-weighted fat-saturated hepatic arterial phase or triple arterial phase GRE
3D T1-weighted fat-saturated portal venous phase GRE
3D T1-weighted fat-saturated late venous phase GRE
Diffusion-weighted imaging
2D T2-weighted fast spin echo (with or without fat saturation)
3D T1-weighted fat-saturated hepatocellular phase GRE (20 minutes after injection)
Optional 2D T1-weighted imaging (without fat saturation)

of vessels relative to that of liver begins to decline within a few minutes of gadoxetic acid injection, and the vessels become hypointense relative to liver by 5–10 minutes after injection.

In the hepatocellular phase, normal liver parenchyma appears uniformly bright on T1-weighted images because of the accumulation of the HSCA. Contrast enhancement also becomes visible within the larger bile ducts, and blood vessels become dark in comparison with liver parenchyma (Fig 1). Focal liver lesions that contain normal hepatocytes connected to functioning bile ducts accumulate HSCA and therefore enhance in the hepatocellular phase. If any part of this axis is disrupted, hepatocellular phase enhancement is impaired or absent. Hence, hepatocellular phase imaging provides unique information about the structure and function of liver lesions by demonstrating the presence (or absence) of functioning hepatocytes.

However, it is difficult to obtain definitive evidence for the HSCA-enhanced appearances of specific liver lesions. Most liver lesions seen at imaging (eg, cysts, cavernous hemangiomas, and focal nodular hyperplasia [FNH] lesions) are benign; these lesions often have characteristic radiologic appearances that are stable over time.



**Figure 3.** Axial T1-weighted fat-saturated MR images obtained before (*Pre*) and at seven intervals after administration of a gadoteric acid injection show a large cavernous hemangioma with marked peripheral enhancement during the hepatic arterial phase (*Arterial*) that becomes less obvious as the liver parenchyma enhances during the hepatocellular phase (*2 min, 3 min, 4 min, 6 min, 8 min*). At the peak of the hepatocellular phase (*10 min*), the lesion appears hypointense relative to normal liver, an expected finding in cavernous hemangiomas. Histologic confirmation was not sought.

Histologic confirmation of imaging and clinical findings is rarely sought in cases of benign lesions, being neither required nor ethically desirable because of the risks associated with biopsy and resection. The calculation of diagnostic performance parameters such as sensitivity, specificity, and accuracy requires measurement of the results of a diagnostic test against those of a reference standard (eg, histologic analysis). When the reference standard is of necessity less than rigorous (eg, diagnosis based on consensus radiologist opinion or interval stability in lesion appearance), the validity of the data is diminished. Diagnosis based on the results of a percutaneous core biopsy, even if they were available for all lesions, would still be problematic because sampling errors occur and the histologic features of lesions may overlap.

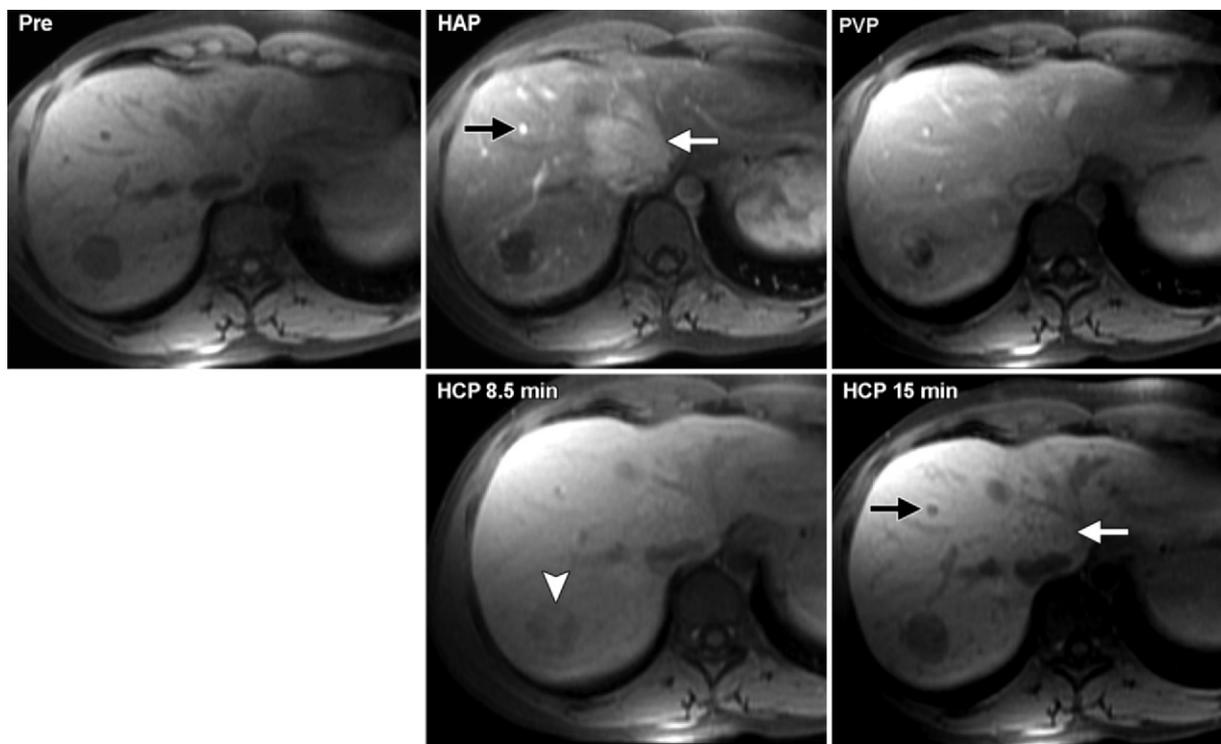
For all these reasons, reliable data about the HSCA-enhanced appearances of focal liver le-

sions are difficult to obtain. However, a body of data does exist, and it is surveyed in the next section. The diagnosis in all cases described in the figures in this article was histologically confirmed, except where otherwise noted.

### Hepatocellular Phase Appearances of Benign Focal Liver Lesions

**Cavernous Hemangioma.**—As is expected in liver lesions that contain no hepatocytes, signal intensity in hemangiomas is typically low in the established 20-minute hepatocellular phase (Figs 3, 4). However, some hemangiomas may show slight central signal hyperintensity in the early hepatocellular phase because of their propensity for persistent centripetal accumulation of extracellular contrast agents beyond the dynamic phase (Fig 4).

**Figure 4.** Axial T1-weighted fat-saturated MR images obtained before (*Pre*) and in the hepatic arterial (*HAP*), portal venous (*PVP*), and hepatocellular (*HCP*) phases after administration of gadoxetic acid show a cavernous hemangioma in hepatic segment VII. On the early hepatocellular phase image (*HCP 8.5 min*), a central hyperintense region (arrow-head) is seen within the lesion. This finding is produced by early extracellular pooling of the contrast agent and has disappeared by the established hepatocellular phase (*HCP 15 min*). A second, smaller hemangioma (black arrows) and a typical central FNH lesion (white arrows) are also present. Histologic analysis was not performed.



Another potential pitfall of using gadoxetic acid at MR imaging of cavernous hemangiomas is that the intense enhancement of normal liver parenchyma because of hepatocellular phase uptake, which begins as early as the portal venous phase, may obscure the characteristic peripheral enhancing “puddles” in these lesions (Figs 3, 4). High-flow hemangiomas may even be mistaken for hypervascular neoplasms: The lesions demonstrate avid arterial enhancement and then, because of rapid progressive hepatic parenchymal enhancement, become hypointense to normal liver as early as 3 minutes after injection, simulating washout. This recently reported phenomenon was described as “pseudo washout” (11). Anecdotally, pseudo washout tends to mimic the level of enhancement within the blood pool (ie, the signal of blood within large vascular structures) and is more gradual than true washout in malignant lesions; hence, the rate of washout may permit differentiation of hemangiomas from ma-

ignant lesions, but this hypothesis requires closer study. Because of these issues, we do not recommend the use of gadoxetic acid for the routine imaging of known or suspected hemangiomas.

**FNH Lesions.**—The conventional MR imaging-based diagnosis of FNH lesions relies on well-documented signal intensity characteristics at both unenhanced and dynamic imaging, as well as architectural features such as scars, septa, and lobulated or microlobulated borders. Despite these helpful features, confident characterization of FNH lesions is sometimes difficult because their features at standard dynamic MR imaging with extracellular gadolinium chelates can overlap with those of hepatic adenomas (Table 2). Hepatocellular phase imaging with HSCAs is often helpful for the diagnosis of these lesions.

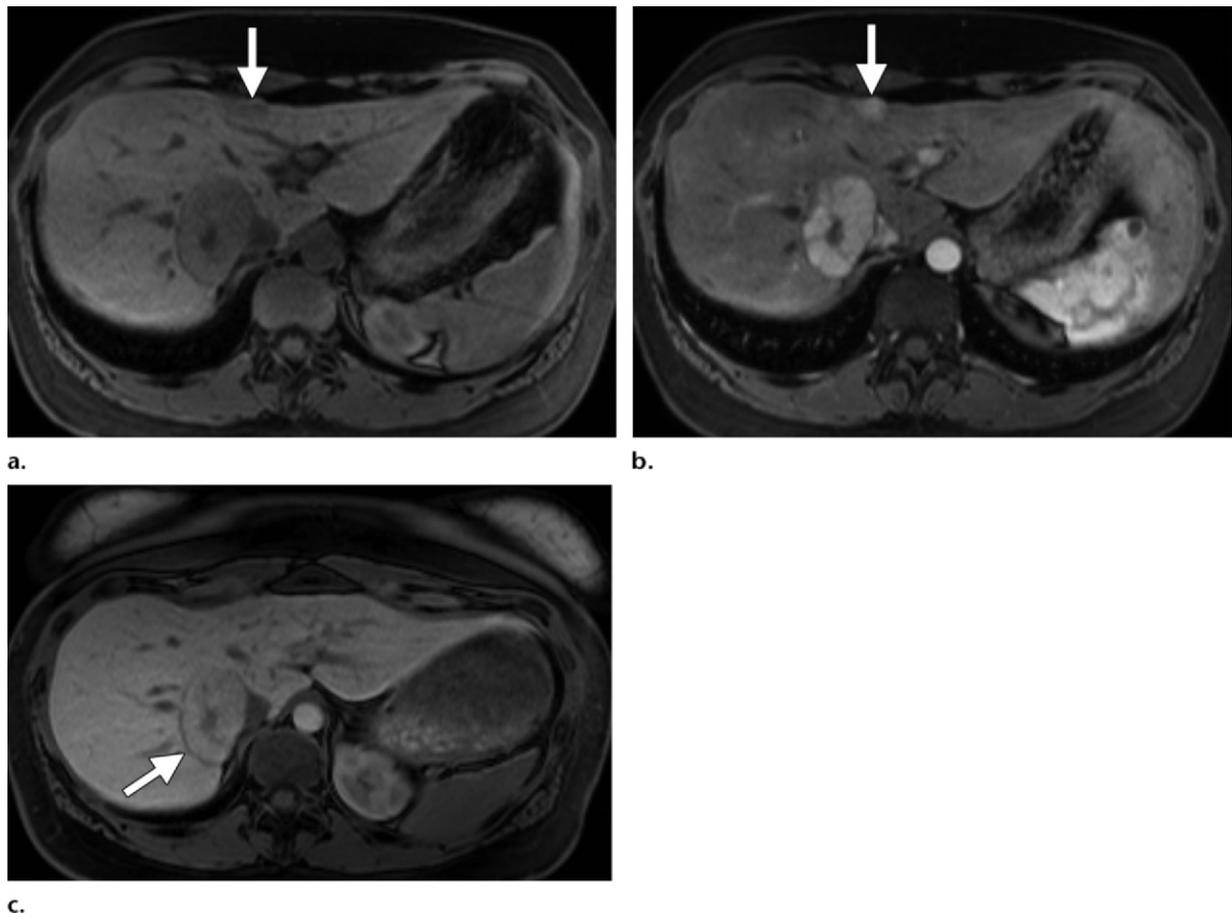
FNH lesions are composed of functioning hepatocytes and bile ducts and are therefore typically isointense (Fig 5) or hyperintense (Figs 6, 7) relative to normal liver parenchyma in the hepatocellular phase. In the largest reported

**Table 2**  
Signal Intensity Patterns in Common Liver Lesions with Standard MR Imaging and Hepatocellular Phase Imaging with HSCAs

Hepatic Lesion	Standard MR Imaging					HCP with HSCAs
	Unenhanced T1	Unenhanced T2	HAP	PVP	LVP	
Focal nodular hyperplasia	→	→	↑	↑ or →	↑ or →	↑ or →
Adenoma	↑ or →	↑ or →	↑	↑ or →	↑ or →	↓
Simple cyst	↓	↑	↓	↓	↓	↓
Cavernous hemangioma	↓	↑	Peripheral nodular ↑	Centripetal filling ↑	Centripetal filling ↑	↓
Hepatocellular carcinoma	↑ or →	↑	↑	↓	↓	↓
Metastasis	↓	↑	↓ or ↑	↓	↓	↓

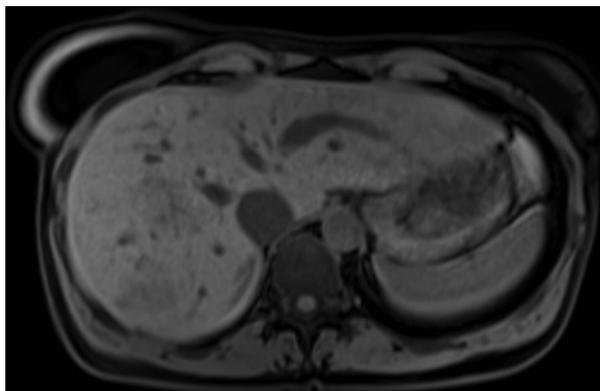
Note.—The table includes only the most common signal intensity patterns. Directional arrows indicate isointensity (→), hypointensity (↓), and hyperintensity (↑) relative to the intensity of normal liver parenchyma. HAP = hepatic arterial phase imaging, HCP = hepatocellular phase imaging, LVP = late venous phase imaging, PVP = portal venous phase imaging, T1 = T1-weighted imaging, T2 = T2-weighted imaging.

**Figure 5.** Axial T1-weighted fat-saturated MR images obtained in a 30-year-old woman before (a) and at two intervals after (b, c) the administration of gadobenate dimeglumine show two FNH lesions that become isointense relative to background liver signal intensity in c, a hepatocellular phase image obtained 2 hours after the contrast agent injection. As expected, both lesions appear hypointense in a, before the injection, and hyperintense relative to background liver signal intensity in b, during the arterial phase. The small anterior lesion (arrow in a and b) is almost undetectable on the hepatocellular phase image in c. The larger lesion demonstrates a low-signal-intensity rimlike feature in the hepatocellular phase (arrow in c). This feature, which is probably due to compressed hepatic parenchyma, is sometimes called a pseudocapsule and is well documented in FNH lesions. The diagnosis was confirmed at histologic analysis.

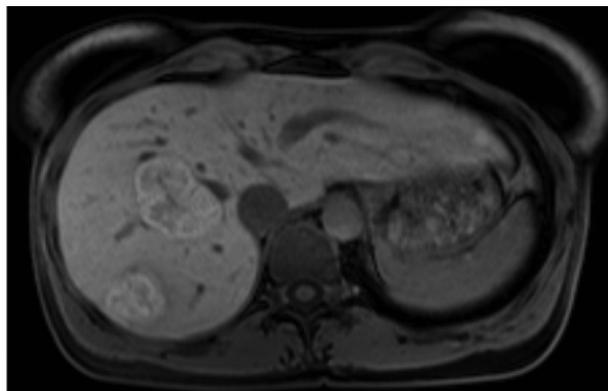


c.

**Figures 6, 7.** (6) Axial T1-weighted fat-saturated MR images obtained in a 48-year-old woman before (a) and during hepatocellular phase enhancement 2 hours after (b) the administration of gadobenate dimeglumine show two FNH lesions. Both lesions demonstrate slightly heterogeneous but definite hyperintensity relative to background liver on the hepatocellular phase image (b), findings that allow a confident diagnosis of FNH. (7) Axial T1-weighted fat-saturated MR image obtained in a 29-year-old woman during hepatocellular phase enhancement 2 hours after administration of a gadobenate dimeglumine injection shows a typical FNH lesion with uniform marked signal hyperintensity (arrow). This is the most common appearance of such lesions in the hepatocellular phase and is highly indicative of FNH. The diagnosis was histologically confirmed.



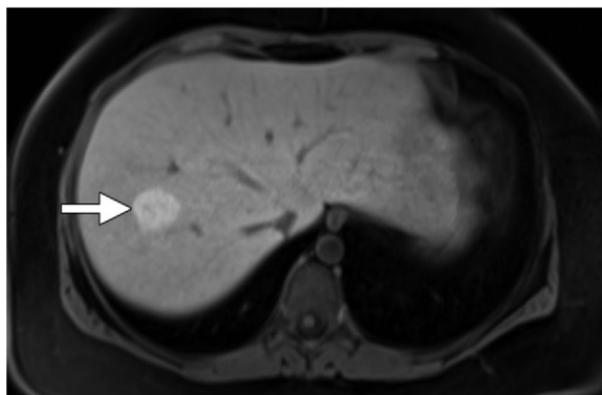
6a.



6b.

study, performed in 73 patients with FNH, 68% of FNH lesions were hyperintense, 28.9% were isointense, and 3.1% were hypointense in the hepatocellular phase; overall, 96.9% of the lesions were either isointense or hyperintense relative to liver parenchyma (12). Hepatocellular phase enhancement was described as homogeneous in 68% of FNH lesions, heterogeneous in 18%, and peripheral in 14%. A hypointense central scar was seen in the hepatocellular phase in 41% of lesions, and most of the lesions that demonstrated a hypointense scar were 3 cm in diameter or larger. Although the central scar in FNH lesions is usually uniformly hypointense in the hepatocellular phase, some enhancement within the scar occasionally is seen (Fig 8), presumably because of extracellular pooling of the contrast agent.

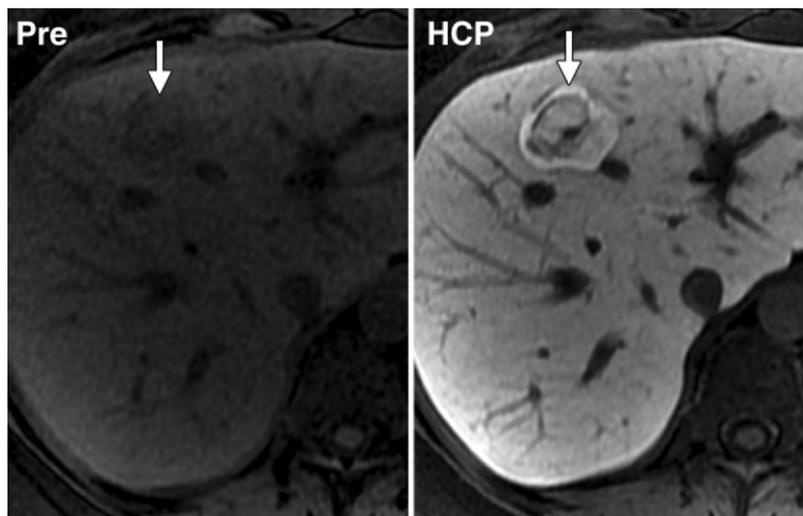
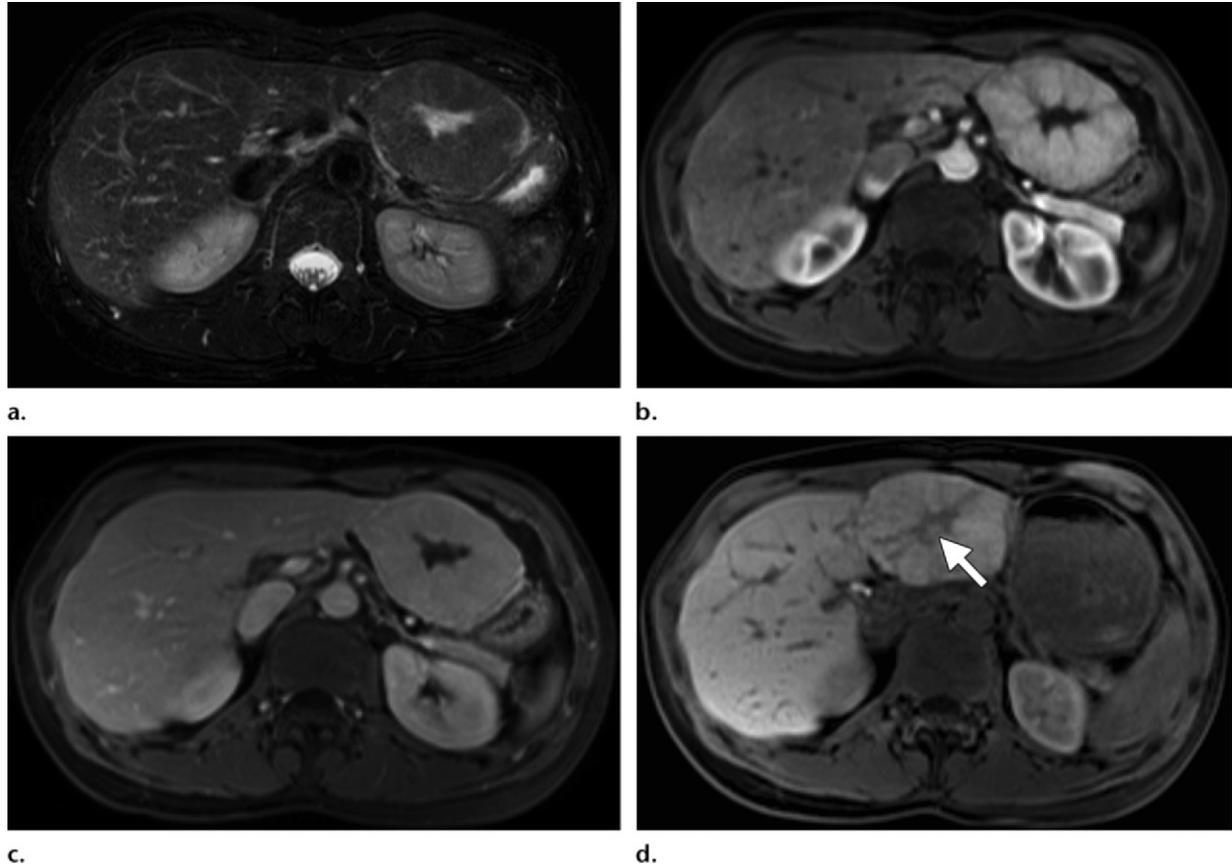
Peripheral enhancement in the hepatocellular phase is an important pattern to recognize in FNH. A peripheral nonenhanced rim in FNH lesions at arterial phase imaging has been well described and is sometimes called a pseudocapsule; it is thought to represent compressed hepatic parenchyma. Peripheral rimlike enhance-



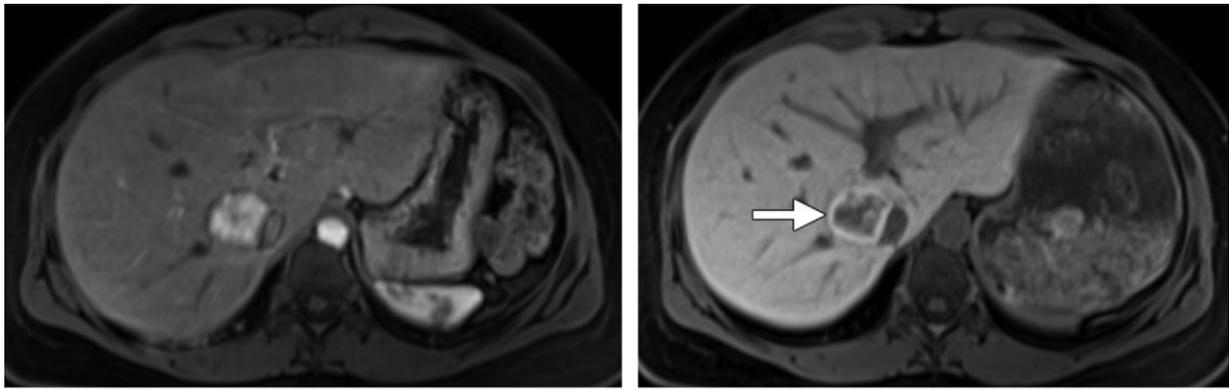
7.

ment of a lesion in the hepatocellular phase often occurs at the same time as hyperintensity or isointensity of the rest of the lesion, allowing accurate characterization of FNH (Fig 9). Only rarely is a hyperintense rim at hepatocellular phase imaging accompanied by relative hypointensity of the rest of the lesion (excluding the expected hypointense central scar); this pattern should be considered atypical for FNH (Fig 10). FNH lesions rarely enhance to a lesser degree than normal hepatic parenchyma (Fig 11); such lesions cannot be reliably diagnosed as FNH on the basis of MR imaging findings alone, and further evaluation is required.

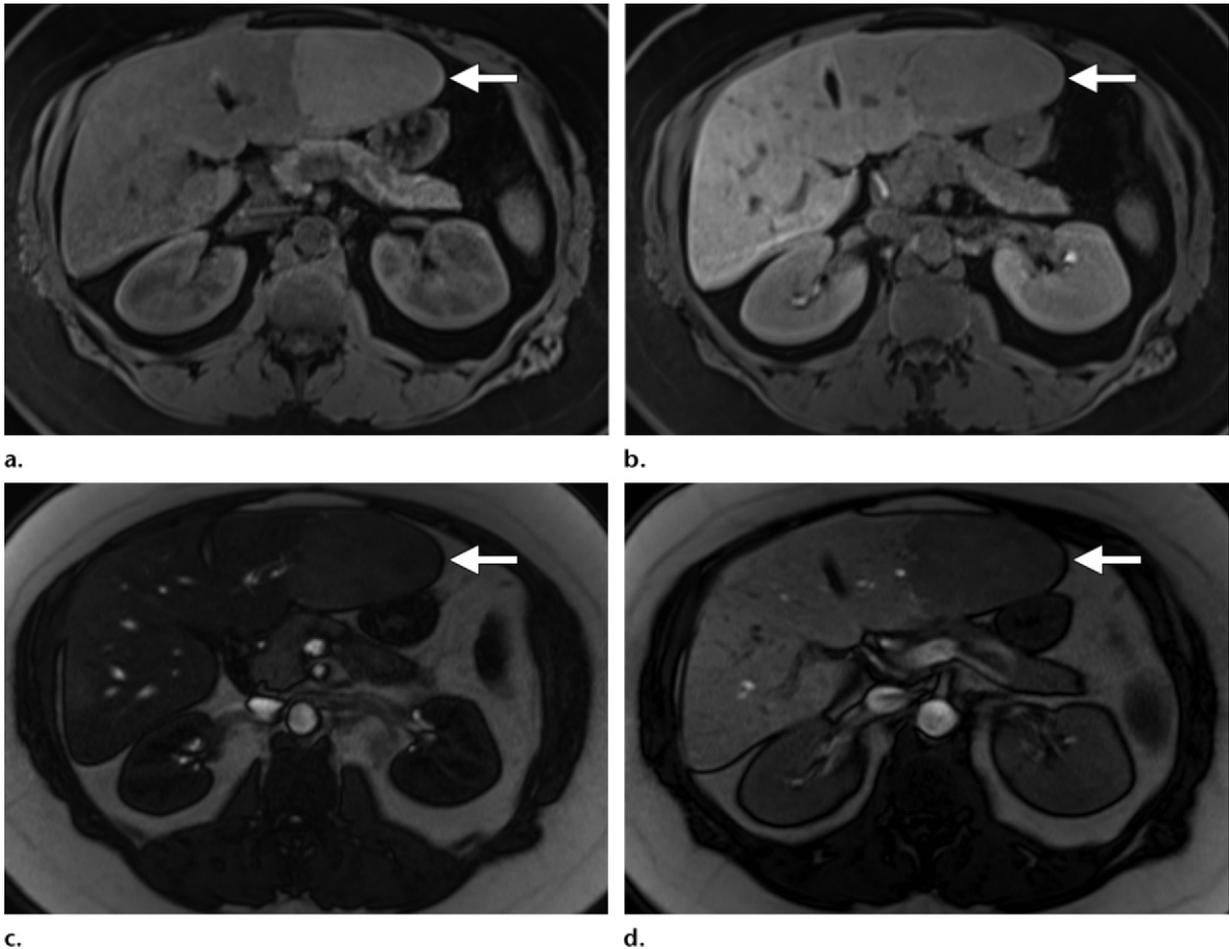
**Figure 8.** Axial T2-weighted fat-saturated (**a**) and T1-weighted fat-saturated arterial (**b**), portal (**c**), and hepatocellular (**d**) phase MR images obtained in a 32-year-old woman 2 hours after administration of a gadobenate dimeglumine injection show a large FNH lesion with a central scar. The scar, a common feature in FNH lesions, has the expected high T2 signal intensity in **a** and low T1 signal intensity in **b** and **c** but is slightly enhanced in **d**, the hepatocellular phase image. This finding of enhancement within the scar is unusual. Note also that the lesion has changed position in the hepatocellular phase, a finding indicative of a mobile pedunculated lesion that should be resected, regardless of its cause. The diagnosis of FNH was confirmed at histologic analysis after resection.



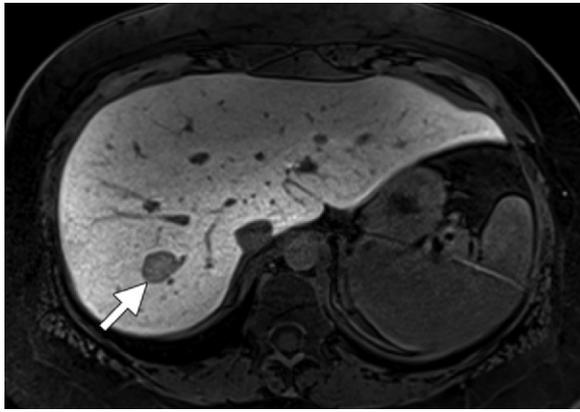
**Figure 9.** Comparison of axial T1-weighted fat-saturated MR images obtained before (*Pre*) and during the hepatocellular phase 20 minutes after (*HCP*) administration of gadoteric acid demonstrates intense uniform enhancement of normal liver parenchyma in the hepatocellular phase. Most of the focal lesion (arrows) enhanced to the same extent as background liver (isointensity), but there is marked peripheral signal hyperintensity. This is the common pattern of peripheral enhancement of FNH lesions in the hepatocellular phase. Histologic analysis was not performed.



**Figure 10.** Axial T1-weighted fat-saturated MR images obtained in a 28-year-old woman during the arterial phase (**a**) and the hepatocellular phase 2 hours after administration of gadobenate dimeglumine (**b**) show an FNH lesion that was subsequently histologically proved. The arterial phase image shows an avidly enhancing lesion with a small central scar. On the hepatocellular phase image, the lesion has a high-signal-intensity rim and a central region of marked signal hypointensity that is much larger than the scar seen on the arterial phase image. Part of the hyperintense rim depicted in **b** is in the same anatomic location as the pseudocapsule seen in **a**.



**Figure 11.** FNH lesion in a 44-year-old woman with severe hepatic steatosis. Axial T1-weighted MR images obtained with (**a**, **b**) and without (**c**, **d**) fat saturation before (**a**, **c**) and 20 minutes after (**b**, **d**) administration of a gadoxetic acid injection show a large hepatic lesion (arrow) that appears hyperintense relative to normal liver parenchyma on unenhanced images and fails to enhance on hepatocellular phase images. The lack of hepatocellular phase enhancement is highly atypical of FNH lesions. This case demonstrates the potentially confusing effect of severe hepatic steatosis: Because the signal from the steatotic liver is suppressed by fat saturation, the lesion appears relatively hyperintense on the fat-saturated unenhanced image and relatively isointense on the fat-saturated hepatocellular phase image. On the images obtained without fat suppression (**c**, **d**), nonenhancement of the lesion relative to the steatotic liver is easier to appreciate. The diagnosis was histologically proved.



**Figure 12.** Histologically proved solitary hepatic adenoma with typical hepatocellular phase features in a 35-year-old woman. Axial T1-weighted fat-saturated MR image obtained during the hepatocellular phase 15 minutes after gadoteric acid injection shows a lesion (arrow) with signal that is markedly hypointense relative to that of normal liver parenchyma; this finding is typical of hepatic adenoma and is helpful for differentiating between a small FNH lesion and hepatic adenoma.

The results of a recent study suggest that venous phase enhancement of the central scar in FNH lesions differs between the two HSCAs. Four patients with FNH lesions with a central scar were retrospectively identified as having undergone MR imaging with both agents at different time points. On images obtained 3 minutes after administration of gadoteric acid, none of the lesions with a central scar demonstrated enhancement within the scar. However, all of the same lesions showed enhancement within the scar on images obtained 3 minutes after administration of gadobenate dimeglumine. Hepatocellular phase appearances were not reported (13). We can suggest a possible explanation for this phenomenon: the rapid clearance of gadoteric acid from the circulation because of the two (hepatic and renal) pathways of its excretion diminishes the concentration of the agent within the extracellular space and reduces the venous phase enhancement of structures with large extracellular spaces, such as the central scar of an FNH lesion.

Why some FNH lesions appear isointense and others appear hyperintense relative to liver parenchyma in the hepatocellular phase is not known. One plausible explanation for isointense FNH lesions is that normal hepatocytes and bile ducts predominate within them, whereas FNH lesions that demonstrate hyperintensity concentrate HSCAs within small malformed bile ductules that fail to communicate with larger bile ducts in the lesions (12).

In the diagnosis of FNH, we believe that the results of hepatocellular phase imaging must be

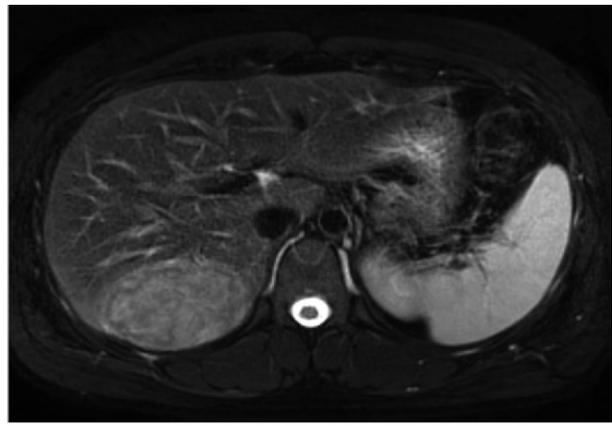
considered within the context of other MR imaging findings and the clinical scenario. To our knowledge, no formal guidelines for the effective use of hepatocellular phase imaging are available. However, in our practice, we give the hepatocellular phase appearances of lesions substantial weight in clinical decision making. Although each diagnostic decision is clearly patient specific, we believe that FNH can be confidently diagnosed if all the findings on both conventional MR images and hepatocellular phase images are characteristic and concordant. In our opinion, lesions with a single minor atypical feature in the hepatocellular phase should be monitored with MR imaging. Lesions with a major atypical feature such as uniform hypointensity in the hepatocellular phase should not be diagnosed as FNH; instead, biopsy, resection, or additional imaging work-up with modalities such as contrast-enhanced ultrasonography should be considered.

**Hepatic Adenoma.**—Hepatic adenoma is an uncommon focal liver lesion. Hepatic adenomatosis, a condition characterized by the presence of numerous adenomas, is probably a separate disease entity that can be associated with metabolic disorders such as glycogen storage disease.

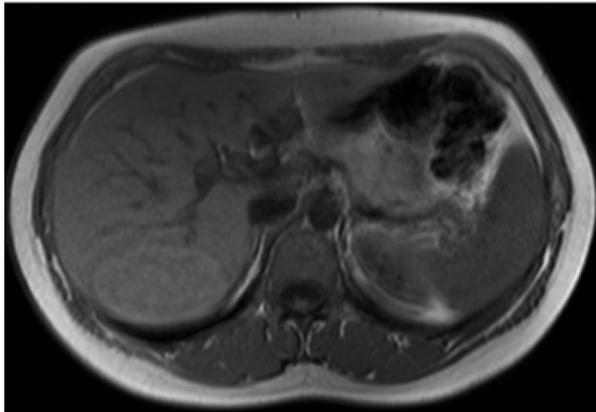
Although hepatic adenoma is uncommon, its differentiation from FNH is clinically important because (a) it may undergo malignant degeneration into HCC and (b) it is much more likely to bleed than FNH, potentially resulting in life-threatening hemoperitoneum. Rapid increase in the size of hepatic adenomas stimulated by increased hormonal levels during pregnancy or exogenous therapy with estrogen or an anabolic steroid is well described in the literature and is associated with an increased risk of rupture. For these reasons, a solitary hepatic adenoma is often resected. However, it may be difficult to recognize a hepatic adenoma because its features at dynamic MR imaging performed with extracellular gadolinium chelates overlap substantially with those of FNH (Table 2) (12).

At hepatocellular phase imaging, hepatic adenomas typically appear hypointense relative to normal liver (Figs 12, 13). In a study of 107 hepatic adenomas in 35 patients, all the lesions (both those occurring singly and those occurring in multiples in hepatic adenomatosis) appeared hypointense in comparison with normal liver in the hepatocellular phase (12). Homogeneous signal hypointensity was seen in 78% of the lesions.

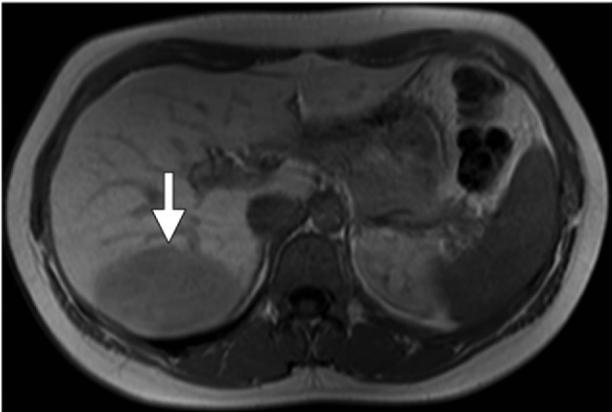
**Figure 13.** Hepatic adenoma in a 31-year-old woman. **(a)** Axial T2-weighted fat-saturated MR image shows a solitary hepatic adenoma with a central region of high signal intensity surrounded by a low-signal-intensity pseudocapsule. **(b, c)** Axial T1-weighted non-fat-saturated images obtained before **(b)** and during the hepatocellular phase 10 minutes after **(c)** gadoxetic acid injection show mild hyperintensity of the lesion relative to background liver in **b** and characteristic marked hypointensity of the lesion (arrow) relative to background liver in **c**. The lesion fails to enhance in the hepatocellular phase, whereas the normal parenchyma is well enhanced. Note that fat suppression was not used for T1-weighted imaging in this case. The diagnosis was proved at subsequent histologic analysis.



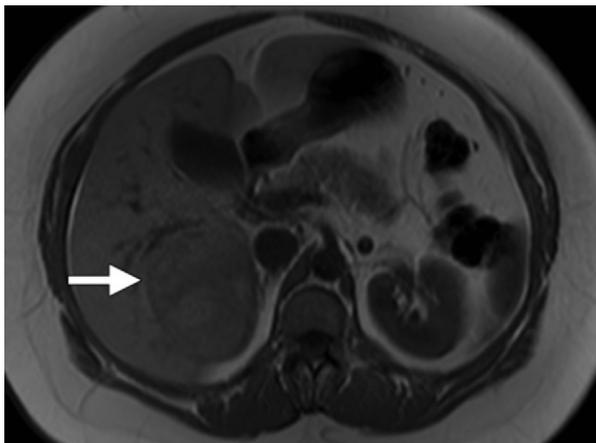
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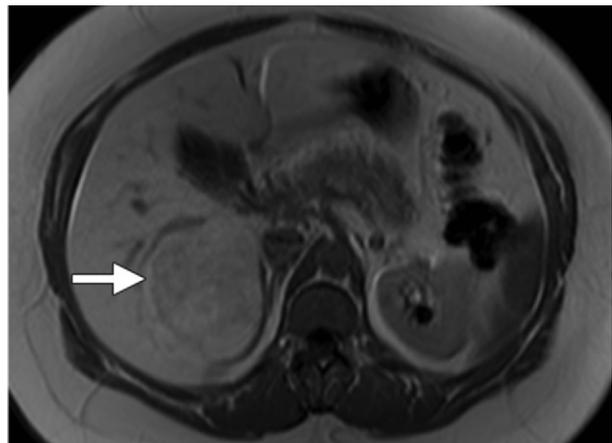
b.



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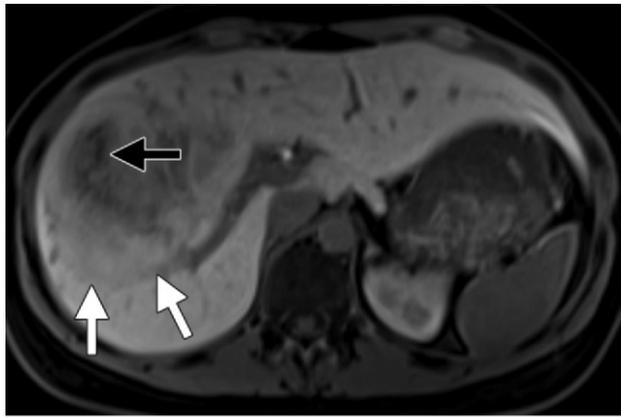


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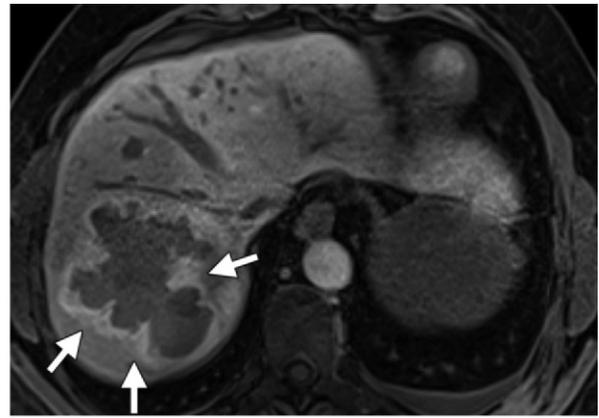
**Figure 14.** Axial T1-weighted MR images obtained in a 42-year-old woman before **(a)** and during the hepatocellular phase 20 minutes after **(b)** gadoxetic acid injection show a hepatic lesion (arrow) with signal that is nearly isointense to that of background liver parenchyma, a highly atypical appearance for hepatic adenomas. The diagnosis of hepatic adenoma was histologically confirmed after surgical resection.

Several explanations have been postulated for the signal hypointensity seen in hepatic adenomas in the hepatocellular phase. One explanation

holds that hepatic adenomas contain functioning hepatocytes but no bile ductules, and bilirubin and HSCAs therefore cannot be excreted. A more plausible explanation is that the expression of OATP1 or similar membrane transporters is reduced in hepatic adenomas.

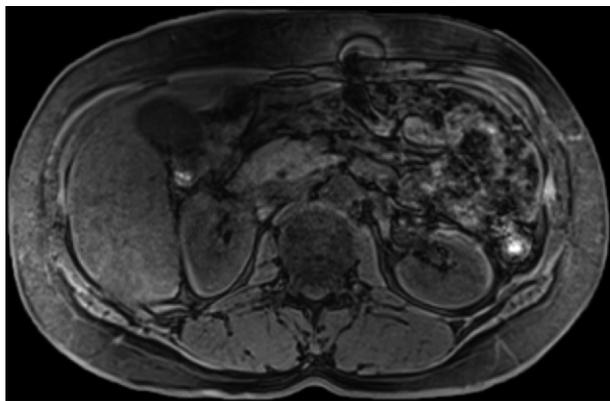


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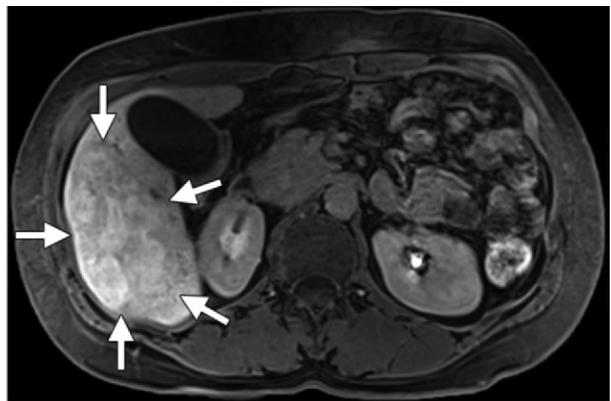


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**Figures 15, 16.** (15) Axial T1-weighted fat-saturated hepatocellular phase image obtained in a 44-year-old woman 90 minutes after administration of a gadobenate dimeglumine injection shows a large, heterogeneously enhancing hepatic adenoma with an atypical appearance. A substantial part of the lesion (white arrows) has signal isointense to that of background liver, an atypical finding, whereas the central part (black arrow) has more characteristically hypointense signal. The diagnosis of hepatic adenoma was histologically confirmed. (16) Atypical appearance of hepatic adenoma. Axial T1-weighted fat-saturated hepatocellular phase MR image obtained in a 36-year-old man 15 minutes after gadoxetic acid injection demonstrates an irregular lesion with the expected low signal intensity at its center but with a thick, lobulated rim of high signal intensity (arrows). The diagnosis of hepatic adenoma was histologically confirmed.



a.



b.

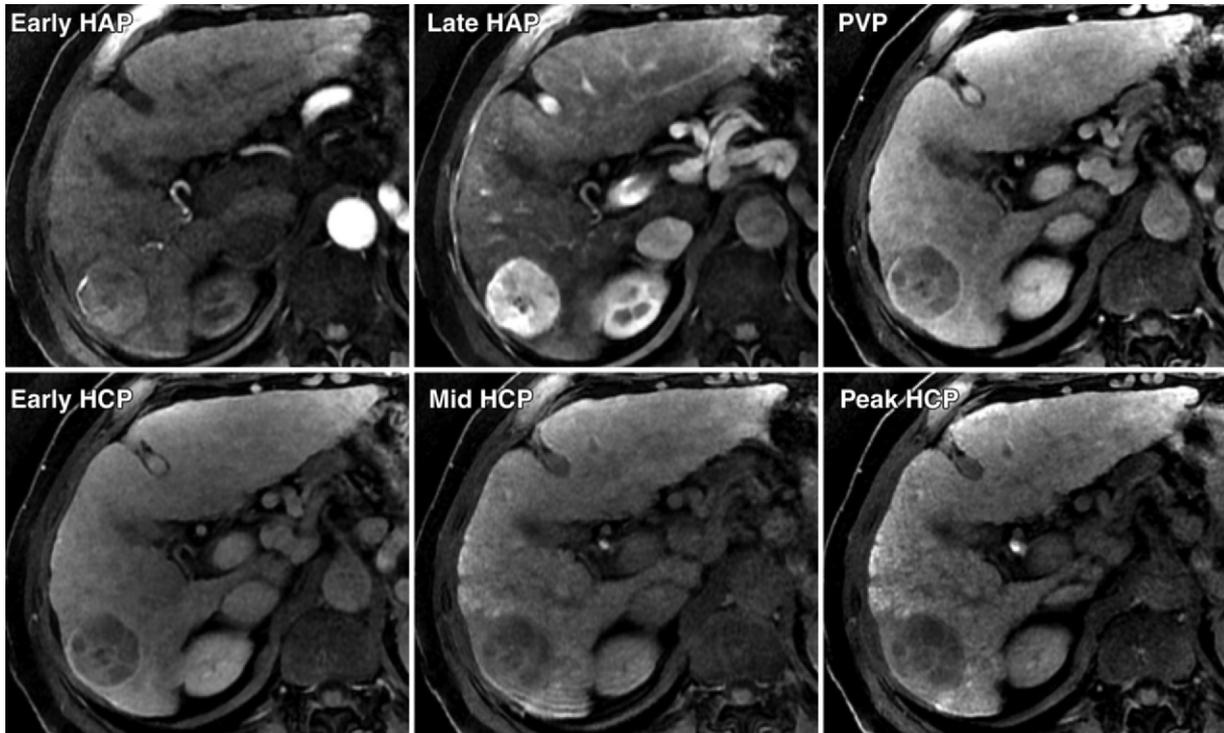
**Figure 17.** Atypical appearance of hepatic adenoma. Axial T1-weighted fat-saturated MR images obtained in a 43-year-old woman before (a) and during the hepatocellular phase 15 minutes after (b) administration of a gadoxetic acid injection show a lesion with heterogeneous internal enhancement (arrows in b). A large part of the lesion displays signal isointense to that of normal liver, but approximately half of the lesion demonstrates higher signal intensity. The finding of lesion hyperintensity relative to background liver signal intensity in the hepatocellular phase is highly atypical. The diagnosis of hepatic adenoma was histologically confirmed.

We found no reports in the literature of atypical appearances of hepatic adenomas in the hepatocellular phase. However, in our own practice we have observed diffuse enhancement in hepatic adenomas that was similar in degree to that in background liver on hepatocellular phase images (Fig 14). We have also observed hepatic adenomas with hepatocellular phase enhancement patterns that overlap somewhat with those of atypical FNH lesions, including heterogeneous enhancement (Fig 15) and rimlike enhancement (Fig 16). We have even seen hepatic adenomas that demonstrated such marked

HSCA uptake that they appeared hyperintense in the hepatocellular phase (Fig 17). The disparate appearances of FNH lesions and hepatic adenomas at hepatocellular phase imaging appear likely to be due to differences in the levels of membrane transporter expression.

The hepatocellular phase imaging features of hepatic adenomas, like those of FNH lesions, must be considered in the context of all the MR imaging findings and the clinical situation. On the basis of our experience to date, cases with

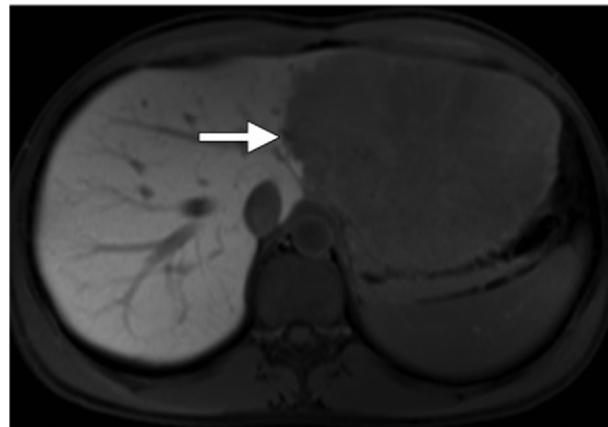
**Figure 18.** Typical appearances of HCC. (a) Axial T1-weighted fat-saturated MR images obtained after gadoxetic acid injection show a round lesion at the periphery of a cirrhotic liver. The lesion shows avid enhancement in the hepatic arterial phase (HAP), washout in the portal venous phase (PVP), and hypointensity in the hepatocellular phase (HCP), features characteristic of HCC. Histologic analysis was not sought, as these appearances conformed to the HCC diagnostic criteria of the American Association for the Study of Liver Diseases (15). (b) Axial T1-weighted fat-saturated MR image obtained in a 32-year-old man during the hepatocellular phase 20 minutes after gadoxetic acid injection shows a typical large fibrolamellar HCC (arrow) with signal that is uniformly hypointense relative to that of background liver in the hepatocellular phase. Histologic confirmation of the diagnosis was obtained after resection.



a.

clinical findings and imaging appearances typical of hepatic adenomas can be diagnosed and managed as such. Depending on lesion size and location, as well as other factors, appropriate management might include follow-up imaging after cessation of exogenous hormone therapy, with biopsy or resection reserved for lesions that do not regress. In our opinion, presumed hepatic adenomas with an atypical hepatocellular phase imaging appearance cannot be confidently diagnosed on the basis of MR imaging findings and may require prompt biopsy or resection instead of follow-up imaging.

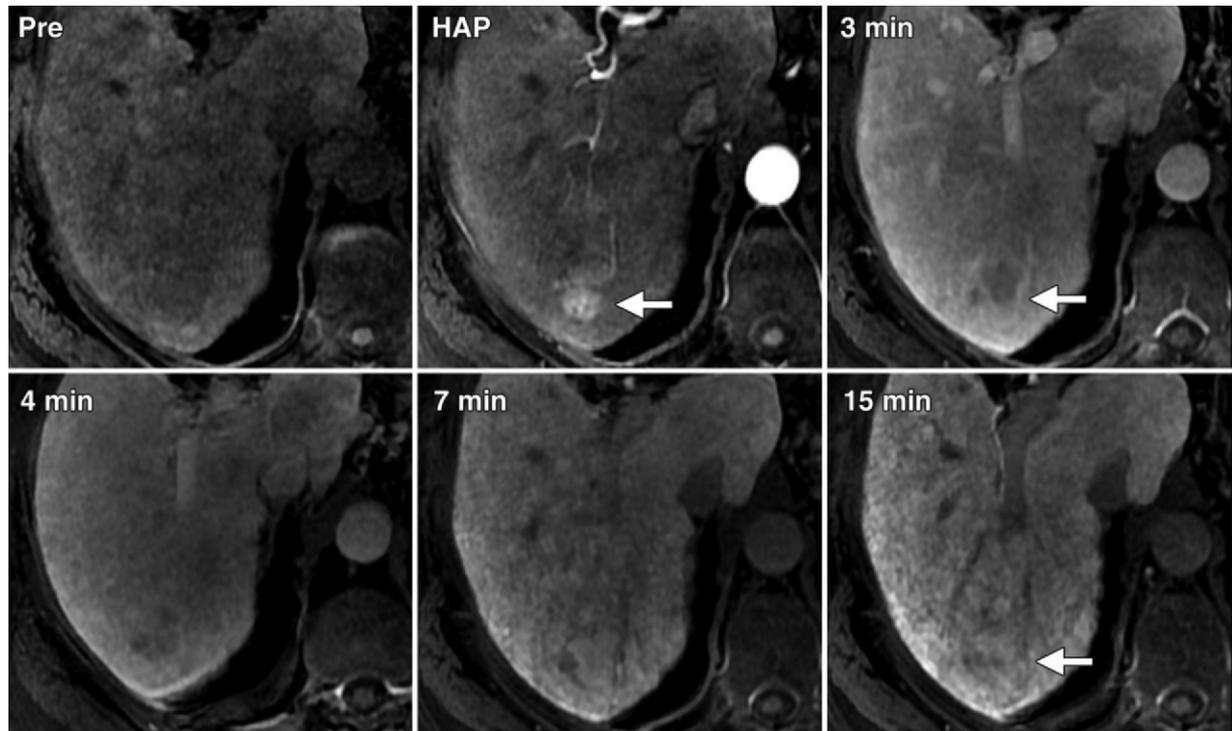
**Evidence for Using HSCAs to Differentiate between FNH and Hepatic Adenoma.**—To our knowledge, the only prospective study of the use of an HSCA for differentiating between FNH lesions and hepatic adenomas was performed with gadobenate dimeglumine. The study investiga-



b.

tors reported a sensitivity of 96.9%, specificity of 100%, positive predictive value of 100%, negative predictive value of 96.4%, and overall accuracy of 98.3% with use of this method for the differentiation of FNH from hepatic adenoma and hepatic adenomatosis (12). Histologic confirmation was available for 46% of lesions (107 of 235) and 62% of patients (67 of 108).

**Figure 19.** Axial T1-weighted fat-saturated MR images obtained before (*Pre*) and at five intervals after gadoxetic acid injection show an HCC with atypical hepatocellular phase appearances. Although the lesion (arrows) demonstrates the characteristic avid enhancement in the hepatic arterial phase (*HAP*) and washout in the late venous phase (*3 min*), it is more difficult to identify in the hepatocellular phase (*15 min*), when it has signal isointense to that of background liver. The diagnosis was histologically confirmed.



Divergence in the level of membrane transporter expression between FNH lesions and hepatic adenomas seems to be an underlying factor aiding their differentiation at hepatocellular phase imaging. In a study of resected liver lesions, hepatic adenomas showed high levels of expression of MRP3 and low levels of OATP2 and OATP8, whereas FNH lesions demonstrated high levels of OATP2 (also known as OATP1B1) and OATP8 and low levels of MRP3 (14). This divergence likely accounts for the difference in HSCA uptake between the two types of lesions.

In our opinion, HSCAs are useful for differentiating FNH lesions from hepatic adenomas, and hepatocellular phase imaging has become a routine part of our MR imaging investigation of these lesions. Hepatocellular phase imaging with an HSCA adds substantial value beyond that of standard MR imaging with extracellular gadolinium chelates because these two disease entities may have similar appearances on images obtained with the latter group of agents.

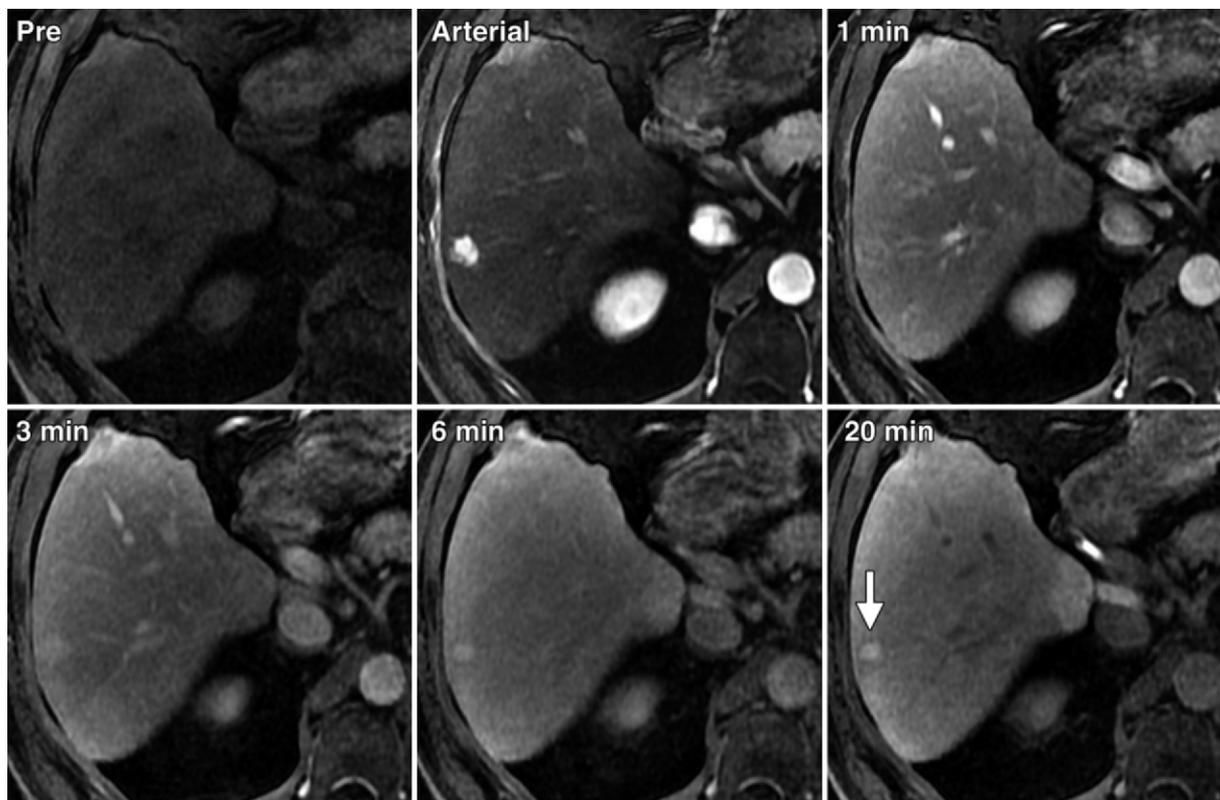
It is noteworthy that MR imaging with HSCAs does not appear to allow reliable differentiation of hepatic adenoma from HCC in patients without cirrhosis.

### Hepatocellular Phase Appearances of Malignant Focal Liver Lesions

**Hepatocellular Carcinoma.**—The appearances of HCCs at HSCA-enhanced MR imaging are described in the current literature, but the descriptions are based on findings in relatively small numbers of patients and tumors. HCC usually has hypointense signal relative to background liver signal intensity in the hepatocellular phase (Fig 18). Expression of the membrane cotransporters necessary for enhancement is probably impaired in HCC, with resultant reduced uptake of the contrast agent producing signal hypointensity in the hepatocellular phase.

A minority of HCCs demonstrate hepatocellular phase uptake, with resultant signal isointensity (Fig 19) or hyperintensity (Fig 20) relative to the background liver signal intensity. In a study of 40 surgically resected HCCs, 80% demonstrated hypointense signal in the hepatocellular phase, whereas 20% showed signal that was isointense or hyperintense relative to background liver signal

Teaching Point



**Figure 20.** Axial T1-weighted fat-saturated MR images obtained before (*Pre*) and at five intervals (hepatic arterial phase and 1, 3, 6, and 20 minutes) after gadoxetic acid injection show a small lesion (arrow) with marked enhancement on the arterial phase image and high signal intensity in comparison to background liver on the hepatocellular phase image (20 min). This hepatocellular phase appearance is atypical of HCC. However, at close inspection of the portal venous phase image (1 min), faint rimlike enhancement of the lesion is seen, a finding suggestive of HCC. Close follow-up was recommended. At follow-up imaging 4 months later, the lesion had grown to a diameter of 4 cm and had classic imaging features of HCC conforming to criteria of the American Association for the Study of Liver Diseases (15). On the basis of these findings at follow-up imaging, a diagnosis of HCC was made without histologic analysis.

intensity (5). The HCCs with either isointense or hyperintense signal showed substantially higher levels of OATP1B3 (also known as OATP8) and MRP3 expression than those with hypointense signal relative to normal liver. In a retrospective study of 22 patients with HCC who had undergone hepatocellular phase imaging with gadoxetic acid, six lesions showed hepatocellular uptake. These lesions were moderately differentiated HCCs, and in comparison with HCCs that remained hypointense, they overexpressed OATP1B3. There was a significant correlation between the level of expression of OATP1B3 and the enhancement ratio within the tumors (16). In another small patient series, HCCs demonstrating signal hyperintensity

in the hepatocellular phase were well differentiated and showed bile staining at histologic examination (17). On the basis of the data published to date, it appears that HCCs with uniform signal hyperintensity in the hepatocellular phase may be well or moderately differentiated but are rarely, if ever, poorly differentiated.

It may be difficult to distinguish HCCs with uniform signal hyperintensity in the hepatocellular phase from benign cirrhosis-associated hepatocellular nodules (eg, dysplastic, regenerative, or hyperplastic nodules). In our experience, most HCCs that appear uniformly hyperintense in the hepatocellular phase are hypervascular and appear hyperintense relative to the background liver in the hepatic arterial phase, whereas most benign cirrhotic nodules that appear hyperin-

tense in the hepatocellular phase are isovascular and appear isointense relative to the background liver in the hepatic arterial phase; thus, inspection of the arterial phase images alongside the hepatocellular phase images usually permits distinction between HCCs and benign nodules. However, some benign lesions that appear hyperintense in the hepatocellular phase are hypervascular and cannot be distinguished from HCC on the basis of an evaluation of their arterial phase enhancement. In hypervascular, hepatocellular phase–hyperintense nodules, we have observed that the presence of a discrete hypointense capsule in the hepatocellular phase or a faint peripheral ring of enhancement in the portal or late venous phase favors a diagnosis of HCC, whereas the absence of these features favors a diagnosis of benign nodule. Because these features have not been scientifically proved to be discriminatory, we recommend close follow-up imaging or biopsy of such lesions. Hypovascular HCCs that are hypointense in the hepatocellular phase also have been described (18). Because it may be difficult to differentiate between hypovascular HCCs and benign nodules in such cases, close follow-up imaging or biopsy is required.

**Evidence for Using HSCAs to Detect HCC.**—With the variability in the hepatocellular phase imaging appearances of HCCs, one might well question whether HSCAs provide added value beyond that of conventional MR imaging techniques for evaluating patients at risk for HCC. Emerging data suggest that HSCAs offer a number of advantages.

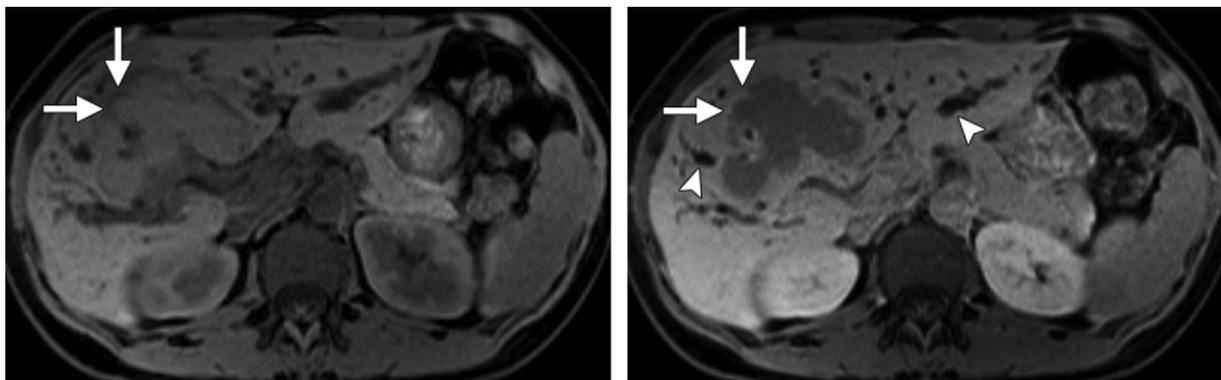
**Hepatocellular phase imaging with an HSCA appears to improve HCC detection beyond levels achievable with conventional MR imaging with extracellular gadolinium chelates.** In a recent publication comparing gadoxetic acid and gadopentetate dimeglumine in the diagnosis of HCC (19), the diagnostic accuracy of both agents was statistically equivalent. Gadoxetic acid allowed visualization of 51 of 59 lesions, whereas only 38 of 59 lesions were identified with gadopentetate dimeglumine. With the use of gadoxetic acid, a significant increase in sensitivity ( $P = .0001$ ) was achieved in the detection of HCCs in this study. In another study, MR imaging with an HSCA was found to be as accurate for HCC detection as dual-contrast MR imaging with the simultaneous use of both a conventional extracellular gadolinium chelate and a superparamagnetic

iron oxide (SPIO) agent (20). In that study, all HCCs were visible with gadoxetic acid (albeit with a low degree of confidence in some cases), whereas three of 56 HCCs were not visible at dual-contrast MR imaging, even retrospectively. In another retrospective study of 84 HCCs in 59 patients who had been imaged with gadoxetic acid, 10.7% of detected HCCs were visible only on hepatocellular phase images (21).

There are admittedly a number of unknowns related to the clinical application of HSCAs for HCC detection. First, there are no large prospective studies to indicate what percentages of HCCs are hypointense, isointense, or hyperintense in the hepatocellular phase. Second, we do not know whether the hepatocellular phase enhancement pattern of HCCs correlates with histologic grade, clinical outcome, or response to therapy. Third, in a patient with cirrhosis, what is the relevance of nodules that are hypointense in the hepatocellular phase but not visible on images obtained in other phases or with other sequences? Such findings in retrospective studies were reported to be associated with HCC; however, the overall frequency with which they are observed and the positive predictive value of these findings for HCC are not known. Prospective studies are needed to answer this question, as well as to establish the relevance of the converse finding: nodules that are hyperintense on hepatocellular phase images but not visible on conventional MR images obtained in patients with cirrhosis.

Despite these unanswered questions and the possibility that HCC may appear enhanced on hepatocellular phase images, we have found HSCAs helpful for the detection and characterization of HCC, and we use them routinely for these purposes.

**Hepatic Metastases.**—Hepatic metastases from extrahepatic malignancies do not contain functioning hepatocytes or bile ducts and therefore do not enhance in the hepatocellular phase. Instead, they typically appear uniformly hypointense in comparison with normal liver. A thin rim of hyperintensity occasionally can be seen at the interface between a metastasis and normal liver parenchyma (Fig 21). This finding is presumed to represent a perileisional biliary reaction, compressed normal hepatic parenchyma, or a combination of the two.



**Figure 21.** Axial T1-weighted fat-saturated MR images obtained before (**a**) and during the hepatocellular phase 20 minutes after (**b**) gadoxetic acid injection show a large hepatic metastasis. The lesion demonstrates signal that is nearly isointense to that of normal liver in **a** and hypointense to that of normal liver in **b**. The thin peripheral rim (arrows) with subtly hyperintense signal in **b** and hypointense signal in **a** is presumably produced by perilesional bile duct reaction, compression of normal hepatic parenchyma, or a combination of the two. The relatively poor hepatic parenchymal enhancement and increased renal enhancement in this case are due to biliary obstruction (arrowheads) with resultant hyperbilirubinemia and a reduced fraction of hepatobiliary excretion of the contrast agent.

Atypical hepatocellular phase appearances of hepatic metastases are rarely seen. In rare cases, the HSCA can concentrate in areas of documented ischemia within either primary (Fig 22) or secondary liver tumors. Another atypical finding is a thick, hyperintense, solid rimlike pattern of enhancement in viable metastases (Fig 23). The mechanisms underlying HSCA uptake in ischemic tumors and viable metastases are poorly understood, and third-space effects may be involved.

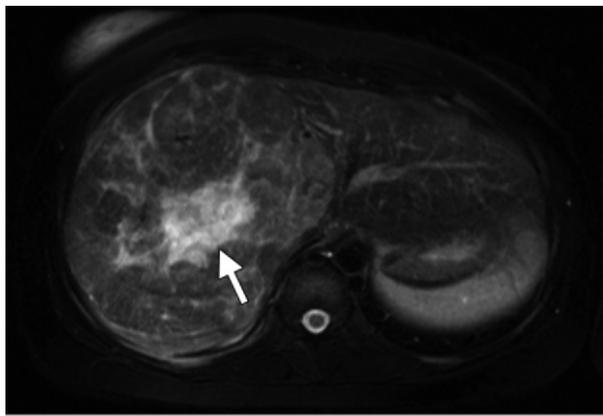
**Evidence for Using HSCAs to Detect Hepatic Metastases.**—Only a few studies have investigated the use of HSCAs for metastasis detection, and none to our knowledge has documented any atypical features. In a study performed in 41 patients with liver metastases by using gadobenate dimeglumine, a significantly increased detection rate was demonstrated with the use of hepatocellular phase imaging, beyond that achieved with either unenhanced MR imaging or conventional dynamic contrast-enhanced MR imaging (22). Hepatocellular phase MR imaging also has been compared with SPIO-enhanced MR imaging. In a small study, the use of gadobenate dimeglumine-enhanced hepatocellular phase MR images (obtained with a delay of 1 hour) was compared with that of SPIO-enhanced MR images for detecting hepatic metastases, and no significant difference was found (23). However, in the same study, the added value of hepatocellular phase imaging for detecting hepatic metastases was demonstrated with significant increases in accu-

racy and in sensitivity beyond the levels achieved with conventional dynamic imaging ( $P < .05$ ) (23). In a different study of 80 liver metastases in 36 patients, in which gadoxetic acid-enhanced MR imaging was compared with ferucarbotran-enhanced MR imaging, no significant difference was found between the two techniques for the detection of liver metastases (24).

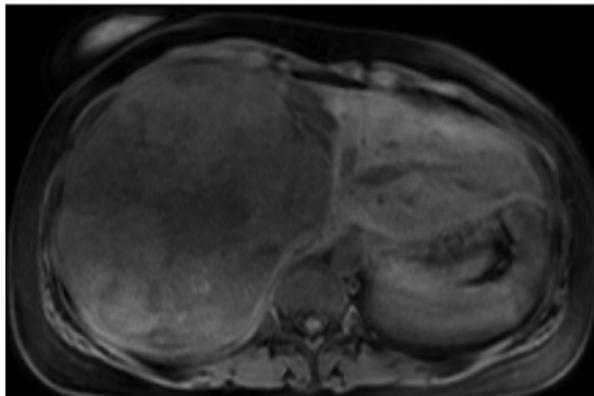
In our clinical practice, we find hepatocellular phase imaging with gadoxetic acid useful for planning of hepatic resections in patients who have liver metastases. Hepatocellular phase imaging helps identify metastases too small to be recognized with other imaging techniques and differentiate true lesions from perfusional pseudolesions. We therefore recommend it for this indication.

### Hepatocellular Phase Appearances of Other Primary Hepatic Lesions

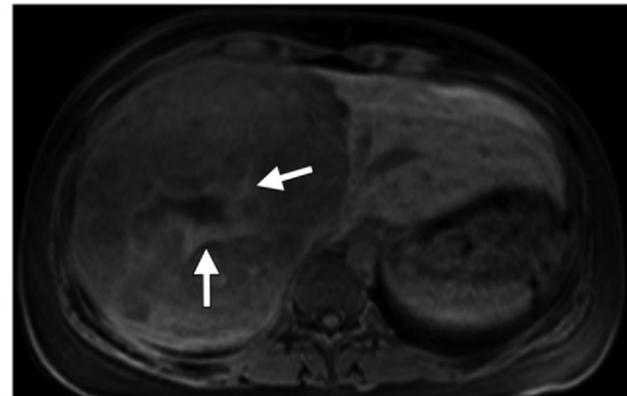
Many rarer primary focal liver lesions exist that are not yet well described in the literature about HSCAs. This group includes malignant lesions such as intrahepatic cholangiocarcinoma and epithelioid hemangioendothelioma, as well as benign lesions such as hepatic angiomyolipoma. Because these lesions do not contain functioning hepatocytes, they should not enhance in the hepatocellular phase; instead, they should appear hypointense in comparison with normal liver signal intensity, just as liver metastases do. We have seen a number of such lesions with typical hepatocellular phase appearances. To date, the only unexpected appearance we have observed is that of an intrahepatic cholangiocarcinoma that demonstrated a thick isointense rim in the hepatocellular phase.



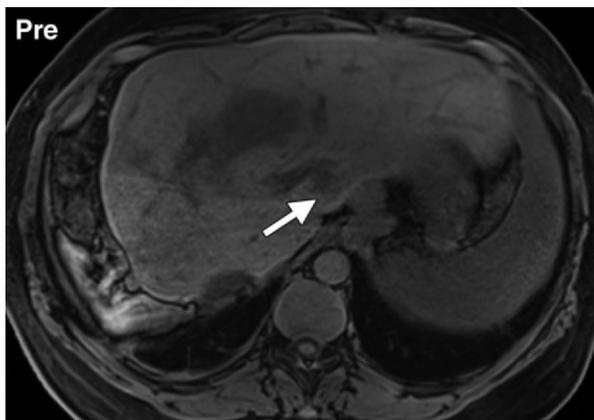
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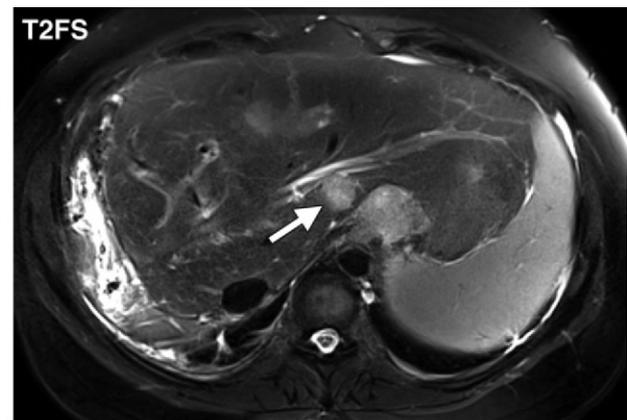
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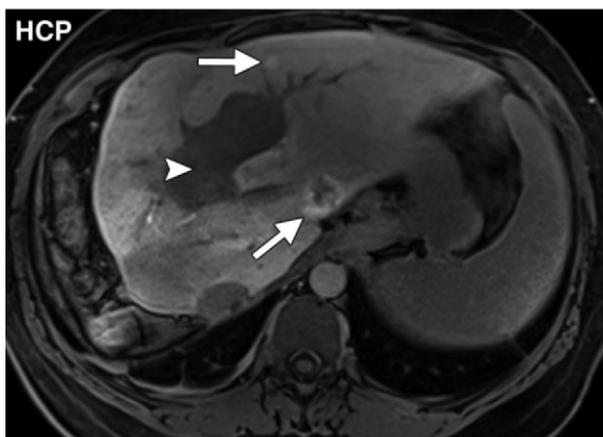
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**Figure 22.** (a) Axial T2-weighted fat-saturated MR image shows a large poorly differentiated HCC with an extensive central region of high signal intensity representing complete necrosis (arrow), findings confirmed at histologic examination after surgical resection. (b) Axial T1-weighted fat-saturated MR image obtained before gadoteric acid injection demonstrates low signal intensity within the necrotic region. (c) Axial T1-weighted fat-saturated hepatocellular phase MR image obtained 20 minutes after gadoteric acid injection shows abnormal enhancement within the necrotic region (arrows).

**Figure 23.** Renal cell carcinoma metastases to liver. (a, b) Axial unenhanced T1-weighted fat-saturated (a) and T2-weighted fat-saturated (b) MR images obtained in a patient with recurrent hepatic disease after a right hemihepatectomy show a metastasis (arrow) in the remnant liver. (c) Axial T1-weighted fat-saturated hepatocellular phase MR image obtained 15 minutes after administration of a gadoteric acid injection shows two hepatic metastases (arrows) with a highly atypical appearance of solid, nearly uniform, hyperintense enhancement. The portal vein is markedly enlarged by intravascular tumor involvement (arrowhead).

## Evidence for Using HSCAs to Distinguish between Benign and Malignant Hepatic Lesions

A recently published retrospective study examined the capability of hepatocellular phase imaging with gadobenate dimeglumine for differentiating benign from high-risk or malignant hypervascular hepatic lesions (25). A total of 550 patients with 910 hypervascular lesions (302 FNH lesions, 82 nodular regenerative hyperplasia lesions, 59 cases of hepatic adenoma or hepatic adenomatosis, 329 HCCs, 12 fibrolamellar HCCs, 21 peripheral cholangiocarcinomas, and 105 metastases) were reviewed. On hepatocellular phase images, 289 of 302 FNH lesions, all of the 82 nodular regenerative hyperplasia lesions, one of 59 hepatic adenomas, 62 of 341 HCCs or fibrolamellar HCCs, and two of 105 metastases were hyperintense or isointense. With iso- or hyperintensity in the hepatocellular phase used as an indicator of lesion benignity, the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value for benign lesion identification were 96.6%, 87.6%, 91.4%, 85.1%, and 97.3%, respectively. Histologic confirmation was available for at least one lesion per patient, except in the cases of FNH. The authors concluded that hepatocellular phase imaging with gadobenate dimeglumine is accurate for distinguishing benign lesions from malignant or high-risk lesions and that biopsy should be considered for hypervascular lesions that appear hypointense in the hepatocellular phase. This study demonstrated the importance of HSCAs for diagnosing different types of lesions with similar appearances at conventional MR imaging.

### Which HSCA Should Be Used?

The choice of HSCA involves consideration of a number of factors, including local preferences, availability, cost implications, and the effect on MR imaging workflow. In a direct comparison, gadoxetic acid was shown to deliver more rapid and more intense hepatocellular phase enhancement than gadobenate dimeglumine (1). In the same study, equivalent relative hepatocellular phase enhancement was found with the use of gadoxetic acid in the overall population and in patients with cirrhotic livers (57% in both groups), whereas relative enhancement with gadobenate dimeglumine both in patients with cirrhosis and in the overall population was inferior to that with gadoxetic acid (27% and 33%, respectively) (1). However, the cost of gadoxetic acid is several times that of gadobenate dimeglumine.

In our opinion, a preference for using gadoxetic acid to obtain optimal hepatocellular phase images is reasonable, except in cases where cavernous hemangiomas are known or suspected to be present. In some cases in our experience, the findings on images obtained with gadoxetic acid were easier to interpret than those on images obtained with gadobenate dimeglumine (Fig 24).

However, there is little evidence in the literature to indicate that one agent offers a clear clinical benefit over the other. The only study that has addressed this issue was a retrospective study of 18 patients with 22 HCCs, in which no significant difference in sensitivity or positive predictive value was found between hepatocellular phase imaging with gadoxetic acid and hepatocellular phase imaging with gadobenate dimeglumine (26).

### Conclusions

Hepatocellular phase imaging with HSCAs is a powerful tool for characterizing benign and malignant focal liver lesions. It is important to be aware that lesions can have atypical appearances at hepatocellular phase imaging and to be able to recognize when appearances diverge from typical enhancement patterns. The mechanisms underlying atypical findings are only beginning to be understood, and further research is required. Although the authors advocate routine hepatocellular phase imaging with HSCAs for the significant additional information it can contribute toward decision making, **findings at hepatocellular phase imaging cannot be used in isolation but should be assessed in light of the clinical context, findings at conventional MR imaging, and appearances with other imaging modalities.**

Teaching Point

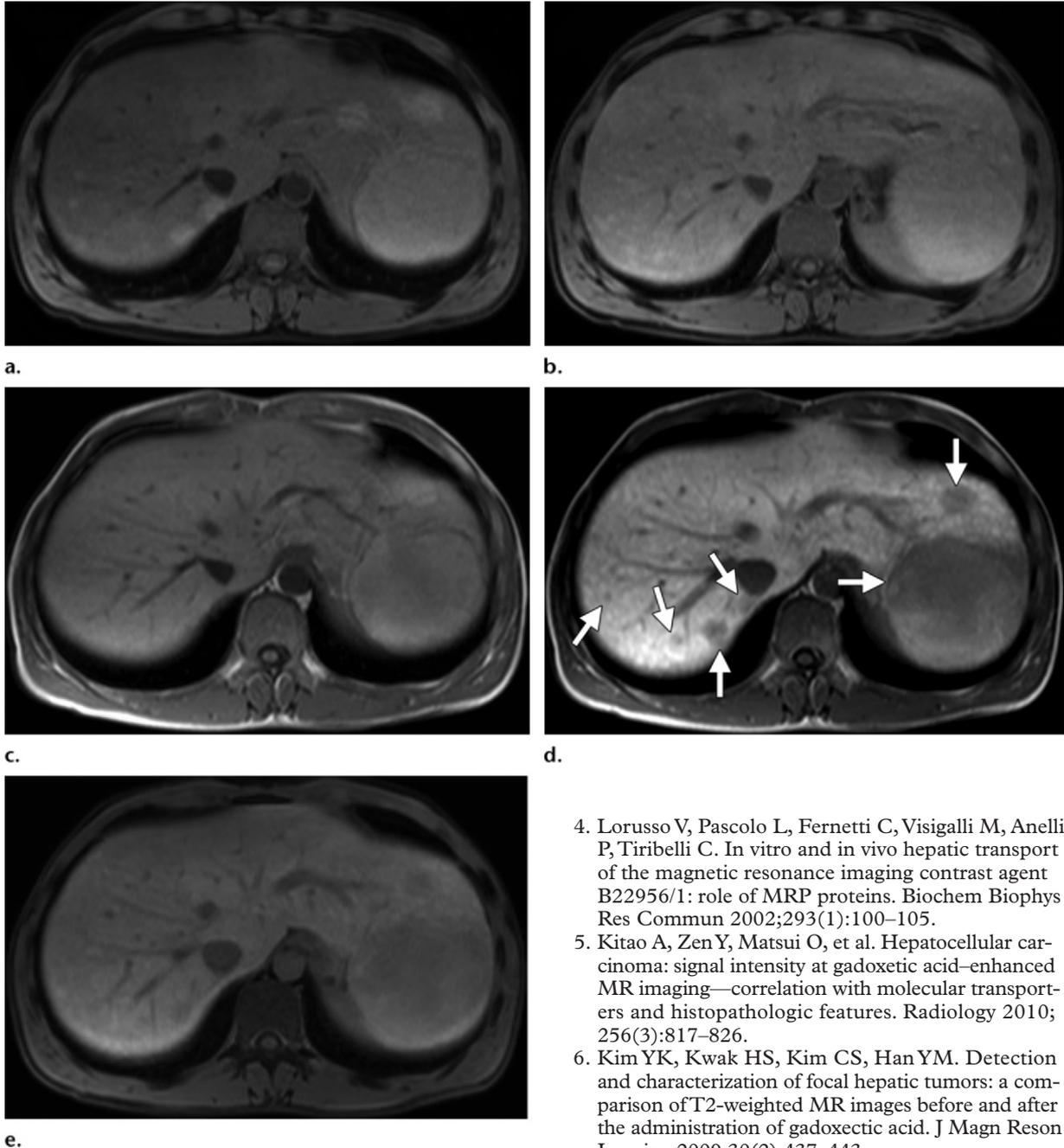
### Disclosures of Potential Conflicts of Interest.—

**C.B.S.:** *Related financial activities:* consultant for Bayer Pharmaceuticals; institution received grant from Bayer. *Other financial activities:* adviser for GE Healthcare, GENZYME, and ISIS; consultant for Bayer, Merck, and VICAL pharmaceutical companies; course developer for ICPME. **D.L.S.:** *Related financial activities:* none. *Other financial activities:* speaker for various corporate entities, royalties from sales of CD-ROM for teaching radiologic anatomy to medical students at University of Melbourne, Royal Melbourne Hospital.

### References

1. Filippone A, Blakeborough A, Breuer J, et al. Enhancement of liver parenchyma after injection of hepatocyte-specific MRI contrast media: a comparison of gadoxetic acid and gadobenate dimeglumine. *J Magn Reson Imaging* 2010;31(2):356–364.
2. Ringe KI, Husarik DB, Sirlin CB, Merkle EM. Gadoxetate disodium-enhanced MRI of the liver. I. Protocol optimization and lesion appearance in the noncirrhotic liver. *AJR Am J Roentgenol* 2010;195(1):13–28.

**Figure 24.** MR imaging examinations performed with gadoxetic acid and gadobenate dimeglumine in a 32-year-old man with hepatic steatosis. (**a, b**) Axial T1-weighted fat-saturated images obtained before (**a**) and 90 minutes after (**b**) the administration of a gadobenate dimeglumine injection show multiple hepatic lesions. In **b**, the hepatocellular phase image, the lesions are essentially isointense to normal liver. (**c–e**) Axial T1-weighted images obtained without (**c, d**) and with (**e**) fat saturation 10 days later, before (**c**) and 20 minutes after (**d, e**) administration of a gadoxetic acid injection. Several small lesions that were not visible in **b**, the hepatocellular phase image obtained with gadobenate dimeglumine, are clearly depicted in **d**, the hepatocellular phase image obtained with gadoxetic acid and without fat saturation. The presence of hepatic steatosis can be confusing: Because the steatotic liver has relatively low signal intensity on T1-weighted fat-saturated images, it is more difficult to appreciate the relative absence of lesion enhancement in **e** than in **d**. The hepatic adenomas were histologically proved. Arrows = lesions.



3. van Montfoort JE, Stieger B, Meijer DK, Weinmann HJ, Meier PJ, Fattinger KE. Hepatic uptake of the magnetic resonance imaging contrast agent gadoxetate by the organic anion transporting polypeptide OATP1. *J Pharmacol Exp Ther* 1999;290(1):153–157.

4. Lorusso V, Pascolo L, Ferneti C, Visigalli M, Anelli P, Tiribelli C. In vitro and in vivo hepatic transport of the magnetic resonance imaging contrast agent B22956/1: role of MRP proteins. *Biochem Biophys Res Commun* 2002;293(1):100–105.
5. Kitao A, Zen Y, Matsui O, et al. Hepatocellular carcinoma: signal intensity at gadoxetic acid-enhanced MR imaging—correlation with molecular transporters and histopathologic features. *Radiology* 2010; 256(3):817–826.
6. Kim YK, Kwak HS, Kim CS, Han YM. Detection and characterization of focal hepatic tumors: a comparison of T2-weighted MR images before and after the administration of gadoxetic acid. *J Magn Reson Imaging* 2009;30(2):437–443.
7. Choi JS, Kim MJ, Choi JY, Park MS, Lim JS, Kim KW. Diffusion-weighted MR imaging of liver on 3.0-Tesla system: effect of intravenous administration of gadoxetic acid disodium. *Eur Radiol* 2010;20(5):1052–1060.

8. Kim KA, Kim MJ, Park MS, et al. Optimal T2-weighted MR cholangiopancreatographic images can be obtained after administration of gadoxetic acid. *Radiology* 2010;256(2):475–484.
9. Ringe KI, Gupta RT, Brady CM, et al. Respiratory-triggered three-dimensional T2-weighted MR cholangiography after injection of gadoxetate disodium: is it still reliable? *Radiology* 2010;255(2):451–458.
10. Vogl TJ, Kümmel S, Hammerstingl R, et al. Liver tumors: comparison of MR imaging with Gd-EOB-DTPA and Gd-DTPA. *Radiology* 1996;200(1):59–67.
11. Doo KW, Lee CH, Choi JW, Lee J, Kim KA, Park CM. “Pseudo washout” sign in high-flow hepatic hemangioma on gadoxetic acid contrast-enhanced MRI mimicking hypervascular tumor. *AJR Am J Roentgenol* 2009;193(6):W490–W496.
12. Grazioli L, Morana G, Kirchin MA, Schneider G. Accurate differentiation of focal nodular hyperplasia from hepatic adenoma at gadobenate dimeglumine-enhanced MR imaging: prospective study. *Radiology* 2005;236(1):166–177.
13. Karam AR, Shankar S, Surapaneni P, Kim YH, Hussain S. Focal nodular hyperplasia: central scar enhancement pattern using gadoxetate disodium. *J Magn Reson Imaging* 2010;32(2):341–344.
14. Vander Borgh S, Libbrecht L, Blokzijl H, et al. Diagnostic and pathogenetic implications of the expression of hepatic transporters in focal lesions occurring in normal liver. *J Pathol* 2005;207(4):471–482.
15. Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology* 2011;53(3):1020–1022.
16. Narita M, Hatano E, Arizono S, et al. Expression of OATP1B3 determines uptake of Gd-EOB-DTPA in hepatocellular carcinoma. *J Gastroenterol* 2009;44(7):793–798.
17. Lee SA, Lee CH, Jung WY, et al. Paradoxical high signal intensity of hepatocellular carcinoma in the hepatobiliary phase of Gd-EOB-DTPA enhanced MRI: initial experience. *Magn Reson Imaging* 2011;29(1):83–90.
18. Golfieri R, Renzulli M, Lucidi V, Corcioni B, Trevisani F, Bolondi L. Contribution of the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI to dynamic MRI in the detection of hypovascular small ( $\leq 2$  cm) HCC in cirrhosis. *Eur Radiol* 2011;21(6):1233–1242.
19. Park G, Kim YK, Kim CS, Yu HC, Hwang SB. Diagnostic efficacy of gadoxetic acid-enhanced MRI in the detection of hepatocellular carcinomas: comparison with gadopentetate dimeglumine. *Br J Radiol* 2010;83(996):1010–1016.
20. Kim YK, Kim CS, Han YM, Park G. Detection of small hepatocellular carcinoma: can gadoxetic acid-enhanced magnetic resonance imaging replace combining gadopentetate dimeglumine-enhanced and superparamagnetic iron oxide-enhanced magnetic resonance imaging? *Invest Radiol* 2010;45(11):740–746.
21. Ahn SS, Kim MJ, Lim JS, Hong HS, Chung YE, Choi JY. Added value of gadoxetic acid-enhanced hepatobiliary phase MR imaging in the diagnosis of hepatocellular carcinoma. *Radiology* 2010;255(2):459–466.
22. Choi JY, Choi JS, Kim MJ, et al. Detection of hepatic hypovascular metastases: 3D gradient echo MRI using a hepatobiliary contrast agent. *J Magn Reson Imaging* 2010;31(3):571–578.
23. Kim YK, Lee JM, Kim CS, Chung GH, Kim CY, Kim IH. Detection of liver metastases: gadobenate dimeglumine-enhanced three-dimensional dynamic phases and one-hour delayed phase MR imaging versus superparamagnetic iron oxide-enhanced MR imaging. *Eur Radiol* 2005;15(2):220–228.
24. Kim YK, Lee YH, Kwak HS, Kim CS, Han YM. Detection of liver metastases: gadoxetic acid-enhanced three-dimensional MR imaging versus ferucarbotran-enhanced MR imaging. *Eur J Radiol* 2010;73(1):131–136.
25. Morana G, Grazioli L, Kirchin MA, et al. Solid hypervascular liver lesions: accurate identification of true benign lesions on enhanced dynamic and hepatobiliary phase magnetic resonance imaging after gadobenate dimeglumine administration. *Invest Radiol* 2011;46(4):225–239.
26. Park Y, Kim SH, Kim SH, et al. Gadoxetic acid (Gd-EOB-DTPA)-enhanced MRI versus gadobenate dimeglumine (Gd-BOPTA)-enhanced MRI for preoperatively detecting hepatocellular carcinoma: an initial experience. *Korean J Radiol* 2010;11(4):433–440.

## Diagnostic Challenges and Pitfalls in MR Imaging with Hepatocyte-specific Contrast Agents

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### Page 1548 (Figure on page 1549)

Indeed, it appears likely that the degree of hepatocellular phase enhancement of individual lesions depends on the expression and activity of a number of different molecular transporters, which in turn depend on the underlying cytogenetic profile (Fig 2b).

### Page 1550

With gadoxetic acid there are slight differences that the user should be aware of: The hepatic arterial phase may appear less intense than with conventional agents, and hepatocyte uptake starts rapidly, manifesting as parenchymal liver enhancement as early as 90 seconds after injection of the agent (10).

### Page 1561 (Figure 19 on page 1561. Figure 20 on page 1562)

A minority of HCCs demonstrate hepatocellular phase uptake, with resultant signal isointensity (Fig 19) or hyperintensity (Fig 20) relative to the background liver signal intensity.

### Page 1563

Hepatocellular phase imaging with an HSCA appears to improve HCC detection beyond levels achievable with conventional MR imaging with extracellular gadolinium chelates.

### Page 1566

Findings at hepatocellular phase imaging cannot be used in isolation but should be assessed in light of the clinical context, findings at conventional MR imaging, and appearances with other imaging modalities.