Gastrointestinal Imaging

Hyperintense Liver Masses at Hepatobiliary Phase Gadoxetic Acid–enhanced MRI: Imaging Appearances and Clinical Importance

Gadoxetic acid, a hepatobiliary-specific contrast medium used for MRI, is becoming increasingly important in the detection and characterization of hepatic mass lesions. This medium is taken up by functioning hepatocytes, and the liver parenchyma is strongly enhanced in the hepatobiliary phase (HBP), during which hepatic mass lesions without functioning hepatocytes commonly show hypointensity. However, some hepatic mass lesions show hyperintensity in the HBP. Focal nodular hyperplasia (FNH) and FNH-like lesions show hyperintensity in the HBP owing to the uptake of gadoxetic acid by hyperplastic normal hepatocytes. The tumor cells of some types of hepatocellular adenoma (eg, β-catenin–activated type, inflammatory type) and hepatocellular carcinoma (eg, green hepatoma) can show uptake of gadoxetic acid. Retention of gadoxetic acid in the extracellular space can cause hyperintensity of fibrotic tumors or hemangiomas during the HBP owing to the extracellular contrast agent characteristics of gadoxetic acid. During the HBP, peritumoral retention is observed in some tumors, such as hepatocellular carcinomas, gastrointestinal stromal tumors, and neuroendocrine tumors. Gadoxetic acid is excreted into the bile; therefore, biliary tract enhancement can be observed in the cystic components of intraductal papillary neoplasms of the bile duct. Intratumoral bile ducts can be observed in malignant lymphomas. Knowledge of these specific mechanisms, which can cause hyperintensity during the HBP depending on the pathologic or molecular background, is important not only for precise imaging-based diagnoses but also for understanding the pathogenesis of hepatic mass lesions.

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SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

■ List the spectrum of hepatic mass lesions that can show hyperintensity during the HBP of gadoxetic acid–enhanced MRI.

■ Describe the pathologic and molecular features, clinical significance, and usefulness of the differential diagnoses of hyperintense hepatic masses seen at gadoxetic acid–enhanced MRI.

■ Discuss the clinical usefulness of gadoxetic acid–enhanced MRI for improved image interpretation and patient care.

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B-HCA is the most common HCA subtype that takes up gadoxetic acid. According to previous reports, more than 80% of B-HCA lesions show isointensity or hyperintensity during the HBP.

Approximately 10%-15% of HCCs are hyperintense during the hepatic biliary phase (HBP), and the distinct pathologic and biologic characteristics of hyperintense HCCs have been reported.

Liver lesions that have expanded extracellular volume, such as fibrosis and necrosis, possibly demonstrate gadoxetic acid retention in the extracellular space during the HBP owing to the properties of gadoxetic acid that are similar to those of conventional extracellular contrast material.

Histopathologically, peritumoral retention corresponds to peritumoral hyperplasia, which is defined as a rim of hyperplastic hepatocytes surrounding the tumor.

Introduction

Gadoxetic acid (gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid [Eovist or Primovist; Bayer Healthcare, Berlin, Germany]) is a hepatobiliary-specific contrast medium used for MRI (1, 2). This agent is becoming increasingly important for detecting and characterizing lesions in patients known or suspected to have hepatic mass lesions (3, 4). During the hepatobiliary phase (HBP), hepatic mass lesions without functioning hepatocytes commonly show hypointensity relative to the background liver tissue. Compared with conventional extracellular contrast material–enhanced CT or MRI, gadoxetic acid–enhanced MRI has been proven to have higher sensitivity in the detection of hepatic mass lesions because of this feature (5, 6).

However, hepatic mass lesions can show hyperintensity partially or entirely during the HBP owing to the following mechanisms (Table 1): (a) uptake by hyperplastic hepatocytes, (b) uptake by tumor cells, (c) retention in extracellular space, (d) peritumoral retention, and (e) biliary enhancement in the tumor. Understanding these mechanisms as they relate to the HBP findings and pathologic and/or molecular background is useful for image interpretation and understanding the pathogenesis of hepatic mass lesions.

In this article, we review the hepatic mass lesions that can demonstrate hyperintensity during the HBP of gadoxetic acid–enhanced MRI. This review article is especially focused on (a) the spectrum of imaging findings of hepatic mass lesions that may show hyperintensity during the HBP, (b) the pathologic and molecular features that cause hyperintensity during the HBP, (c) the clinical significance of hyperintensity during the HBP, and (d) the usefulness of the differential diagnoses of hepatic mass lesions.

Kinetic Features of Gadoxetic Acid

Gadoxetic acid has the properties of a conventional nonspecific extracellular contrast agent during the vascular phases after it is administered and thus enables dynamic imaging for evaluation of vascularity. During the HBP, approximately 20 minutes after this agent is intravenously injected, it also has the properties of a hepatocyte-specific agent and thus enables assessment of hepatocellular uptake (17). After intravenous injection, gadoxetic acid distributes into the vascular and extravascular spaces during the arterial, portal, and transitional dynamic phases.

Tumor vascularity can be evaluated in the arterial phase. During the arterial and portal venous phases, there is limited distribution of contrast material in true extracellular spaces. After these phases, the entry of gadoxetic acid into the liver cells causes intense parenchymal enhancement, beginning within 1 or 2 minutes after it is administered. Therefore, there are no true extracellular phases (equivalent to delayed phase with conventional extracellular contrast agent) in gadoxetic acid–enhanced MRI (17).

The period 2–5 minutes after the injection (ie, transitional phase) represents a transition from extracellular-dominant (ie, portal venous phase) to intracellular-dominant (ie, HBP) enhancement (18). Consequently, in the HBP, the liver parenchyma is strongly enhanced. The liver parenchyma and hepatic mass lesions expressing transporters of gadoxetic acid can show uptake early in the transitional phase. This early uptake progresses until it reaches a peak during the HBP. The product information sheet for gadoxetic acid from the manufacturer states that although the HBP can occur within 10–120 minutes after the contrast agent injection, in confirmatory studies most of the data were obtained within 20 minutes after the injection (19). After gadoxetic acid is taken up by hepatocytes, it is excreted from these cells into the biliary canaliculi (20). Thus, unlike the extravascular spaces with traditional gadolinium-based contrast agents, the extravascular spaces with gadoxetic acid comprise extracellular space, hepatocellular space, and bile ducts.

During the HBP, normal liver parenchyma appears uniformly bright on T1-weighted MR images because of the accumulation of gadoxetic acid. In addition, contrast enhancement becomes visible in the larger bile ducts, and blood vessels become dark compared with the liver parenchyma (19).
MRP2 expressed on the canalicular side are export transporters of gadoxetic acid (22) (Fig 1). For hepatic mass lesions, a significant correlation between the signal intensity of these lesions during the HBP and their OATP1B3 expression has been reported (23,24). On the other hand, the influence of MRPs on HBP findings is considered to be minimal (4). Because mass lesions without functioning hepatocytes commonly exhibit low or no OATP1B3 expression, they are hypointense relative to the background liver tissue during the HBP. Gadoxetic acid–enhanced MRI has been proven to have higher sensitivity in the detection of hepatic mass lesions because of these features. Additional molecular-genetic analyses of HCCs have revealed that HCC with hyperintensity during the HBP (ie, OATP1B3-overexpressed HCC) shows β-catenin and hepatocyte nuclear factor 4α activation (25,26). A similar molecular mechanism of OATP1B3 expression can be expected in other hepatocellular nodules (4).

### Gadoxetic Acid–enhanced MRI Findings in LI-RADS

The Liver Imaging Reporting and Data System (LI-RADS) standardizes interpretation of the imaging features of hepatic lesions in patients.
who are at risk for HCC (18). This system was developed by a committee that is supported by the American College of Radiology and that comprises diagnostic radiologists with expertise in liver imaging. This committee receives valuable input from hepatobiliary surgeons, hepatologists, hepatopathologists, and interventional radiologists (27).

Nonperipheral washout, nonrim arterial phase hyperenhancement, and capsule enhancement are major features of HCC. Nonperipheral washout should be assessed in the later phases—during the portal venous phase of gadoxetic acid–enhanced MRI or during the portal venous phase or delayed phase of conventional extracellular contrast material–enhanced CT or MRI (28). This means that the transitional phase in gadoxetic acid–enhanced MRI cannot be used to evaluate nonperipheral washout. In gadoxetic acid–enhanced MRI, the transitional phase represents transition from the extracellular-dominant phase to the intracellular-dominant phase. With use of other contrast agents, the transitional phase is fundamentally different from the conventional delayed phase, during which enhancement reflects the extracellular distribution of contrast material. In the LI-RADS, the transitional phase rather than the delayed phase is used for gadoxetic acid–enhanced MRI. For this reason, the transitional phase of gadoxetic acid–enhanced MRI is not appropriate for evaluating the presence of washout (18).

Advantages and Disadvantages of Using Gadoxetic Acid

Table 2 summarizes the advantages and disadvantages of using gadoxetic acid as an imaging contrast agent. The primary advantage is improved detection of hepatic masses, especially small lesions (5,6). Another advantage of using gadoxetic acid is that it facilitates diagnosis of borderline hepatic nodules such as dysplastic nodules and early-manifesting HCCs. Early HCCs and approximately one-third of high-grade dysplastic nodules appear as nonhypervascular nodules that demonstrate hypointensity during the HBP (4). Gadoxetic acid can also help to characterize hepatic mass lesions.

The arterial and venous phase enhancement seen with gadoxetic acid has been described as weak compared with that seen with conventional extracellular contrast agents (29). In addition, transient dyspnea (30) and transient severe motion (31) related to gadoxetic acid uptake during the arterial phase have been reported previously. Gadoxetic acid causes imaging artifacts during the arterial phase. In addition, uptake in the liver parenchyma reflects liver function (32) and fibrosis (33), and, thus, the uptake of gadoxetic acid decreases as liver function or fibrosis worsens. These disadvantages of gadoxetic acid can decrease diagnostic accuracy and overall sensitivity in the detection of hepatic lesions.

Gadoxetic Acid Uptake by Hyperplastic Hepatocytes

Focal Nodular Hyperplasia

FNH is the second most common benign tumor after hemangioma, with a prevalence of 0.9% (4). FNH typically occurs as a solitary lesion in young females. It is usually discovered incidentally in individuals, more commonly women, in their 3rd to 5th decade of life. FNH typically consists of two components: hyperplastic hepatocytes and a central scar. Hyperplastic hepatocytes are considered to be a proliferative response of hepatocytes secondary to an underlying perfusion disorder (34). The central scar is not a true scar; rather, it represents a congeries of blood vessels and bile ducts.

At MRI, findings of FNH typically include areas of peripheral hyperplastic hepatocytes and central scars (Fig 2). The hyperplastic area is slightly hypointense to hyperintense on T1-weighted MR images and isointense to slightly hyperintense on T2-weighted MR images, with intense homogeneous enhancement during the arterial phase (35). In FNH, the presence of fat, which demonstrates signal loss on out-of-phase gradient-echo MR images compared with the signal intensity seen on in-phase images, is extremely rare (36). The majority of hyperplastic areas are isointense or hyperintense relative to the surrounding liver tissue during the HBP. This finding enables differential diagnosis (37).
because most hypervascular liver masses show hypointensity during the HBP.

Hyperplastic hepatocytes represent a nonneoplastic condition that involves normal functioning hepatocytes and abnormal bile ducts that do not communicate with the normal surrounding biliary system. These characteristics account for the uptake of gadoxetic acid in functioning hepatocytes in FNH and the isointensity or hyperintensity during the HBP (38). On the other hand, the central scar is usually hyperintense at T2-weighted MRI (35) and hypointense during the HBP because it contains no or few functioning hepatocytes (24). Therefore, the imaging findings of FNH during the HBP include ring or doughnut-like enhancement (4,39).

FNH has various imaging appearances, depending on the proportions of peripheral hyperplastic areas and central scars (Figs 3, 4). In addition, in FNH, especially that involving lesions smaller than 3 cm, macroscopic central scars are often absent (40). Thus, it is not rare for small FNH lesions to show uniform iso- or hyperintensity during the HBP. Mohajer et al (41) reported that almost 40% of FNH lesions showed uniform iso- or hyperintensity and almost 60% of FNH lesions showed ring or doughnut-like enhancement during the HBP.

There is an equal or stronger expression of OATP1B3 in FNH compared with that in the background liver tissue, and this expression correlates with the isointensity or hyperintensity seen during the HBP (24). In contrast, no somatic mutations in the β-catenin, TP53, APC, or HNF1α gene have been identified at genetic analysis of FNH (4). The researchers in one study (42) found that FNH showed activation of the Wnt/β-catenin pathway without any mutations in the gene that encodes β-catenin. Such a molecular mechanism might explain the equal or stronger

Figure 2. Typical MRI findings of FNH in a 19-year-old woman. (a) Axial T2-weighted MR image shows an isointense hyperplastic area (arrow) and a hyperintense central scar (arrowhead). (b) Axial T1-weighted MR image shows a slightly hyperintense hyperplastic lesion (arrow) and a hypointense central scar (arrowhead). (c) Axial arterial phase T1-weighted MR image shows enhancement of the hyperplastic area (arrow) and nonenhancement of the central scar (arrowhead). (d) On the axial HBP MR image, the hyperplastic area (arrow) is hyperintense and the central scar (arrowhead) is hypointense.
OATP1B3 expression and hyperintensity of FNH during the HBP.

The differential diagnosis of incidental hypervascular liver masses includes HCC, hemangioma, and HCA (37). Differentiating HCC from FNH is important for selecting the appropriate treatment and avoiding unnecessary interventions. Typical FNH occurs in the noncirrhotic liver. In contrast, HCC commonly occurs in persons with chronic liver disease. An enhancing capsule, nonperipheral washout, and threshold growth are typical of HCC (43). A hypointense rim during the HBP, like the appearance of a capsule at gadoxetic acid–enhanced MRI, could improve detection of the tumor capsule and the subsequent diagnosis (44).

HCC demonstrating hyperintensity during the HBP, as compared with hyperintense FNH, is not common (10%–15% of cases) (45,46). However, in the LI-RADS, HBP hyperintensity is not included as a feature of benignity. Thus, the diagnosis must be based on primary features (43). HCC occasionally contains fat, and fat in a mass is one of the ancillary features favoring a diagnosis of HCC in the LI-RADS (47).

Fibrolamellar HCC is an uncommon type of HCC that affects young adults. It frequently appears as a large well-demarcated lobulated liver mass that may contain a scar and calcifications. A fibrolamellar HCC scar demonstrates hypointensity at T2-weighted MRI (17). In addition, fibrolamellar HCC is hypointense, as compared with the background liver parenchyma, during the HBP (17,48).

Hemangiomas show well-known peripheral nodular enhancement with centripetal progression at dynamic CT and MRI performed with extracellular contrast agents. It has been reported that lesion isointensity or hyperintensity during the HBP is accurate for distinguishing FNH from HCA (37). However, McInnes et al (49) reported...
that the previously reported high accuracy of HBP findings might be overestimated.

**FNH-like Lesions**

An FNH-like lesion is a benign lesion that manifests in cirrhotic livers, cases of alcoholic liver cirrhosis especially (50). FNH-like lesions are observed in 3.4% of cirrhotic livers (7). They are considered to result from acquired hyperplastic responses to cirrhosis-related vascular alterations (17). In noncirrhotic livers, FNH-like lesions have been reported to be histopathologically indistinguishable from FNH (7). Therefore, the imaging findings of FNH-like lesions are similar to those of FNH. In the cirrhotic liver, an FNH-like lesion, similar to FNH, is considered to be benign. However, studies have revealed that some FNH-like nodules—specifically, serum amyloid A–positive hepatocellular neoplasms—have the histopathologic features of inflammatory HCA (I-HCA) and that some have neoplastic features that are similar to those of HCA (51). Further investigation of these findings is needed.

At MRI, FNH-like lesions are isointense or mildly hyperintense on T1-weighted images and mildly hyperintense on T2-weighted images, with arterial phase hyperenhancement. If a central scar is present, it is hyperintense on T2-weighted MR images. Like FNH, FNH-like lesions are usually iso- to hyperintense during the HBP (Fig 5). In addition, similar to FNH, FNH-like nodules show equal or stronger OATP1B3 expression compared with the background liver tissue (24).

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**Figure 4.** Small FNH with a large central scar in a 65-year-old man. (a) Axial T2-weighted MR image shows a large hyperintense central scar with a small mildly hyperintense peripheral hyperplastic area (arrow). (b) Axial T1-weighted MR image shows the lesion (arrow) with slight hypointensity. (c) Axial arterial phase T1-weighted MR image shows the lesion (arrow) with intense peripheral enhancement and the central scar with mild enhancement. (d) Axial HBP MR image shows a hyperplastic area (arrow) with peripheral hyperintensity and a large hypointense central scar.
The majority of cirrhosis-related nodules exhibit regenerative changes without cellular atypia; these nodules are termed regenerative nodules. Regenerative nodules typically are isointense to hyperintense on T1-weighted MR images and isointense to hypointense on T2-weighted MR images. On dynamic MR images, regenerative nodules show enhancement similar to that of the adjacent liver, and during the HBP, they are isointense. Lipid-containing and steatotic nodules display a loss of signal on out-of-phase gradient-echo MR images compared with their signal intensity on in-phase MR images. Iron-containing and siderotic nodules appear markedly hypointense on T2- and T2*-weighted MR images.

Dysplastic nodules also are usually detected in cirrhotic and chronically damaged livers. High-grade dysplastic nodules with clonal features are categorized as premalignant lesions and frequently progress to HCCs. The imaging findings of dysplastic nodules at T1- and T2-weighted MRI are similar to those of regenerative nodules. Also, dysplastic nodules show no definite enhancement during the arterial dominant phase, but they are commonly isointense or hypointense relative to the surrounding liver tissue during the HBP. However, one-third of high-grade dysplastic nodules can appear as hypointense nodules with decreased OATP1B3 expression.

An important differential diagnosis of FNH-like lesion is HCC because both of these tumors occur in cirrhotic livers. Hyperintensity during the HBP is characteristic of FNH-like lesions. In addition, the presence of a central scar favors the presence of an FNH-like lesion. An enhancing capsule, nonperipheral washout, and threshold growth are typical of HCC. Other ancillary imaging features, such as nodule-in-nodule architecture, fat in a mass, corona enhancement, and restricted diffusion, also favor a diagnosis of HCC. However, while most FNH-like lesions exhibit hyperintensity during the HBP, these lesions may show portal venous phase washout and hypointensity during the HBP, mimicking HCC. In equivocal cases, close follow-up or biopsy should be considered.

**Figure 5.** FNH-like lesion in a 57-year-old man with hepatitis B–related cirrhosis. (a) Axial T1-weighted MR image shows a lesion (arrow) with slight hyperintensity. (b) Axial arterial phase T1-weighted MR image shows enhancement of the lesion (arrow). (c) Axial HBP MR image shows the lesion (arrow) with hyperintensity.

**Nodular Regenerative Hyperplasia**
NRH commonly manifests in normal liver parenchyma. The prevalence of NRH has been reported as 2.6% in autopsy series, and this entity is considered to be a response of hepatocytes secondary to the underlying portal blood flow. NRH is characterized by diffuse hyperplastic nodules, commonly 1–3 mm in size, and hepatocytes in the absence of fibrosis. It is often associated with underlying systemic diseases, including lymphoproliferative and myeloproliferative disorders, autoimmune diseases, drug exposure, and Budd-Chiari syndrome. Although NRH is a distinct entity from cirrhosis-related regenerative nodules, it also has been associated with portal hypertension.
Because NRH is supplied by portal blood flow, it is hypointense during the arterial dominant phase, shows mild to moderate enhancement during the portal venous phase, and is isointense during the delayed phase (4). NRH may manifest as hypo-, iso-, or hyperintense regions on T1- and T2-weighted MR images (52). In the HBP, NRH shows hyperintensity, with relative hypointensity in the central region of the lesion; this finding is seen as ring or doughnut-like enhancement. The hyperintense portion corresponds to hyperplastic hepatocytes that express OATP1B3, and the central hypointense portion corresponds to the portal tracts (4).

Gadoxetic Acid Uptake by Tumor Cells

Hepatocellular Adenoma

HCA is a rare benign tumor of the liver. Most HCAs occur in young women. The incidence of these tumors is three to four of 100,000 persons in Europe and the United States (9). Oral contraceptive use; androgenic steroid use; and other conditions such as familial diabetes mellitus, galactosemia, and glycogen storage disease type 1 are known risk factors of HCA (52). In addition, persons with HCA are at risk for hemorrhage and malignant transformation (52). Surgical resection is recommended for patients who have an HCA tumor 5 cm or larger or hemorrhage (53).

The imaging findings of HCA at MRI have been well described (4,35). On T1-weighted MR images, HCA can demonstrate areas of high signal intensity. Fat is the main element responsible for the hyperintensity of adenoma seen on T1-weighted MR images. Areas of internal subacute hemorrhage are markedly hyperintense on T1-weighted MR images. Chemical shift MRI can be performed to confirm the fat content, with a decrease in tumor signal intensity seen on opposed-phase MR images (36). HCA has a heterogeneous appearance, with areas of hypointensity or hyperintensity at T2-weighted MRI; demonstrates a blush of enhancement during the arterial phase; and becomes nearly isointense during the later phases of dynamic gadolinium-based contrast material–enhanced MRI.

HCAs have been classified into four distinct subtypes by using the Bordeaux group system, which is based on genotype and phenotype classifications: β-catenin activated HCA (B-HCA), I-HCA, hepatocyte nuclear factor 1α–mutated HCA (H-HCA), and unclassified HCA (U-HCA) (Table 3). The imaging features of these subtypes, including the findings seen during HBP gadoxetic acid–enhanced MRI, have been reported by using this classification (56–63). HCA usually shows hypointensity during the HBP, and this finding facilitates the differentiation of HCA from FNH (38,41,49,64,65). However, study groups (56–63) have reported that some HCAs, especially the B-HCA and I-HCA subtypes, can take up gadoxetic acid. B-HCA accounts for 15%–18% of all HCAs. Compared with the other HCA subtypes, B-HCA occurs more frequently in men (4). Owing to β-catenin gene mutation, B-HCA has the highest risk for malignant transformation. In addition, B-HCA is the most common HCA subtype that takes up gadoxetic acid. According to previous reports (59,63,66), more than 80% of B-HCA lesions show isointensity or hyperintensity during the HBP (Fig 6). It also has been reported that glutamine synthetase and OATP1B3, which are downstream targets of the Wnt/β-catenin pathway, are diffusely positive in immunohistochemical studies of B-HCA (4,67). Such preserved or increased OATP1B3 expression has been shown to correlate with the hyperintensity seen during the HBP (63,68). Otherwise, no discriminant characteristics of the lesion pattern of B-HCA have been found.

I-HCA is the most common subtype of HCA, accounting for 40%–55% of these tumors. I-HCA most commonly occurs in young women and sometimes occurs in men. Obesity and

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Note.—NA = not applicable.

*Data are the percentages of the given HCA subtype that take up gadoxetic acid.
alcohol intake are risk factors for I-HCA (4). This HCA subtype has the highest risk for hemorrhage (53). The neoplastic hepatocytes show strong and diffuse expression of the acute phase inflammatory reactants serum amyloid A and C-reactive protein (53).

I-HCA is the second most common HCA subtype that takes up gadoxetic acid. According to previous reports (56,59,62), 26%–33% of I-HCA lesions are isointense or hyperintense during the HBP. In addition, it has been reported that approximately 20% of I-HCAs show β-catenin activation (55). Thus, I-HCAs with β-catenin activation might show expression of OATP1B3 and hyperintensity during the HBP. Moreover, marked hyperintensity at T2-weighted MRI due to sinusoidal dilatation has been found to be typical of I-HCA, with a sensitivity of 85.2% and a specificity of 87.5% (Fig 7) (57). The signal intensity pattern of I-HCA at T2-weighted MRI includes global sinusoidal dilatation and the atoll sign (69,70), which refers to a characteristic hyperintense rimlike band at the periphery of the lesion (70).

H-HCA constitutes 25%–50% of all HCAs, occurs predominantly in women who use oral contraceptives, and often involves multiple nodules (4). Liver-type fatty acid–binding protein, whose expression is controlled by hepatocyte nuclear factor 1α, is lost in H-HCA tumor cells and is used immunohistochemically to identify H-HCA (53). H-HCA is the least aggressive HCA subtype; individuals with tumors smaller than 5 cm have minimal risk of complications (53). H-HCA usually does not show uptake of gadoxetic acid (59,60). The typical imaging finding of H-HCA is a homogeneous or heterogeneous intratumoral fatty component that shows signal loss during the opposed phase of T1-weighted MRI (59,69,70).

U-HCA constitutes approximately 10% of HCAs. A lesion is assigned to this subtype by...
default, when it is negative for all of the features known for the other subtypes, including their immunohistochemical markers (53). U-HCA usually does not show uptake of gadoxetic acid (59). We have found no other specific MRI characteristics of U-HCA. Relatively recently, an additional subgroup of U-HCAs has been described: Sonic hedgehog HCA is characterized by activation of the sonic hedgehog pathway (71). This subgroup is associated with histologically detected hemorrhage and overexpression of argininosuccinate synthase 1 (71,72). Given the clinical importance of hemorrhage, further studies of U-HCAs are required.

It has been reported that distinct imaging characteristics of HCA versus FNH during the HBP of gadoxetic acid-enhanced MRI, with HCA being hypointense and FNH being iso- or hyperintense, have high diagnostic accuracy in the differentiation of these two lesion types (38,41,49,64,65). However, study investigators have reported that this diagnostic accuracy may be overestimated, especially for B-HCA and I-HCA (49,61). Agarwal et al (56) reported that I-HCA can mimic FNH during the HBP. In addition, the entity previously termed telangiectatic focal nodular hyperplasia is now thought to represent I-HCA (55). Given that the classification of HCA subtypes requires immunohistochemical testing that has only recently been part of routine pathologic assessment, further imaging studies with consideration of the more recent classifications of HCAs are needed. The imaging features of benign lesions seen during the HBP are summarized in Table 4.

**Hepatocellular Carcinoma**

HCC is the fifth most common neoplasm in the world and the most common primary malignant hepatic tumor (73). The prevalence of HCC is 6.2 cases in 100,000 persons in the United States (10). Underlying chronic hepatitis or cirrhosis that is related to hepatitis B virus, hepatitis C virus, alcoholism, or nonalcoholic steatohepatitis is a risk factor. Accurate detection of HCC is one of the...
most important components in the management of patients with such chronic liver disease.

Gadoxetic acid–enhanced MRI has become an important imaging modality for diagnosing HCC, with high accuracy due to the high lesion-to-liver contrast achieved with this modality (74,75). HCCs show arterial phase nonrim hyperenhancement and washout during the portal phase. As described earlier, imaging artifact during the arterial phase caused by transient dyspnea (30) or transient severe motion (31) can affect the sensitivity and specificity of gadoxetic acid–enhanced MRI in the detection of HCC. HCCs without functioning hepatocytes usually are hypointense relative to the background liver tissue during the HBP. In addition, it has been reported that a peritumoral area of decreased uptake during the HBP of gadoxetic acid–enhanced MRI is predictive of microscopic vascular invasion by HCC (76).

Approximately 10%–15% of HCCs are hyperintense during the HBP, and the distinct pathologic and biologic characteristics of hyperintense HCCs have been reported (45,46). In hyperintense HCCs, expression of OATP1B3 (an uptake transporter) is preserved, whereas hypointense HCCs show lower or no OATP1B3 expression. Histopathologically, a pseudoglandular proliferation pattern with bile plugs, also called green hepatoma, is commonly observed in hyperintense HCCs (Fig 8). Moreover, hyperintense HCCs exhibit less malignant behavior compared with hypointense HCCs. Hyperintense HCCs seen during the HBP have had significantly lower recurrence rates than have hypointense HCCs seen during this phase (77,78).

The molecular mechanisms that explain the differences between hyperintense and hypointense HCCs have been demonstrated in relatively recent studies (25,26). It has been reported that activation of β-catenin and hepatocyte nuclear factor 4α correlates with hyperintense HCCs (25,26). Kitao et al (26) reported that HCC with β-catenin gene mutation showed higher OATP1B3 expression, a pseudoglandular pattern, bile production, and hyperintensity during the HBP. In addition, investigators in other studies have reported that HCCs with β-catenin gene mutation, as compared with HCCs without this mutation, are associated with accelerated bile production (79), higher OATP1B3 expression (80), and a favorable prognosis (81). The investigators in these studies also reported that both hepatocyte nuclear factor 4α activation and β-catenin activation correlate with hyperintense HCCs (25).

Hepatocyte nuclear factor 4α has been shown to suppress hepatocyte proliferation and HCC growth (82) and is the central regulator of bile acid conjugation in hepatocytes (83). Such genetic-molecular study findings can explain the clinical and pathologic differences in HCCs. Given these imaging study developments, gadoxetic acid–enhanced MRI can be an effective imaging method, with findings that serve as biomarkers of HCC that reflect the genetic and molecular background of these tumors, or so-called radiogenomics.

FNH and FNH-like lesions are important differential diagnoses of the hyperintense HCC seen during the HBP because they also show iso- or hyperintensity during this phase (84). Findings in a previous study (84) indicated that arterial phase hyperenhancement with a washout pattern at dynamic CT and a lower apparent diffusion coefficient are important findings that favor a diagnosis of HCC. Some atypical intrahepatic mass–forming cholangiocarcinomas may be categorized as LR-5 or LR-TIV lesions in the LI-RADS, resulting in a false-positive diagnosis of HCC (85).

### Retention of Gadoxetic Acid in the Extracellular Space

#### Fibrotic Tumors

Gadoxetic acid is a valuable contrast agent in liver MRI because it has the combined properties of liver-specific contrast material and conventional extracellular contrast material (86). Thus, both the hepatocyte-specific phase and the dy-
namic perfusion phase can be evaluated at gadoxetic acid–enhanced MRI. Liver lesions that have expanded extracellular volume, such as fibrosis and necrosis, possibly demonstrate gadoxetic acid retention in the extracellular space during the HBP owing to the properties of gadoxetic acid that are similar to those of conventional extracellular contrast material.

Figure 8. HCC (green hepatoma) in a 79-year-old man with hepatitis B–related cirrhosis. (a) Axial T1-weighted MR image shows a tumor (arrow) with slight hypointensity. (b) Axial arterial phase T1-weighted MR image shows enhancement of the tumor (arrow). (c) On the axial HBP MR image, the tumor (arrow) is hyperintense, indicating uptake of gadoxetic acid. (d) Photograph of the surgically resected specimen shows a greenish nodule. (e) Photomicrograph shows moderately differentiated HCC consisting of pseudoglandular patterns (arrowheads), trabecular patterns, and bile plugs (arrow). (Hematoxylin-eosin stain; original magnification, ×200.)
It is well known that areas of delayed or prolonged liver tumor enhancement at conventional extracellular contrast-enhanced CT or MRI correspond to fibrotic stroma at histopathologic examination (87). Similarly, liver tumors with fibrous stroma, such as cholangiocarcinoma and metastatic adenocarcinoma, possibly are iso- to hyperintense during the HBP of gadoxetic acid–enhanced MRI because of gadoxetic acid retention in the extracellular space (Fig 9). In previous studies (88,89), almost 80% of cholangiocarcinomas demonstrated gadoxetic acid retention in the extracellular space. In addition, 47%–70% of metastatic carcinomas also show retention of gadoxetic acid in the extracellular space (90–92). Such gadoxetic acid retention in the extracellular space is often observed in the center of the tumor, representing fibrotic stroma or degeneration. Thus, this enhancement pattern during the HBP is referred to as a targetoid pattern.

Despite the retention of gadoxetic acid in the extracellular space, gadoxetic acid–enhanced MRI is useful for detecting metastatic adenocarcinoma (6). Even in the setting of disappearing colorectal metastases after chemotherapy, gadoxetic acid–enhanced MRI is superior to contrast material–enhanced CT in the assessment of these lesions (93).

Park et al (94) reported interestingly that the aberrant expression of OATP1B3 in colorectal cancer liver metastases is associated with mixed hypointensity during the HBP. This finding suggests that the signal intensity of metastatic adenocarcinoma during the HBP may be affected by not only the amount of extracellular tissue but also the aberrant expression of OATP1B3. They also reported that such signal intensity during the HBP was associated with worse survival rates (94). Similarly, patients with colon cancer whose immunohistochemical results indicate OATP1B3 overexpression have worse progression-free survival rates than do patients with scant or negative OATP1B3 expression (95). Given these imaging study developments, gadoxetic acid–enhanced MRI can be an effective imaging method, with findings that serve as biomarkers of metastatic carcinoma and reflect the genetic-molecular background of these tumors (ie, radiogenomics), as well as HCCs.

Some neuroendocrine tumors with a higher fibrous content may show more delayed enhancement that is best visualized during the delayed phase of imaging with extracellular contrast agents (96). Thus, fibrotic neuroendocrine tumors also can show iso- to hyperintensity during the HBP of gadoxetic acid–enhanced MRI (Fig 10). However, such enhancement during the HBP, which is due to retention of gadoxetic acid in the extracellular space, tends to be lower compared with the enhancement related to transporter uptake of gadoxetic acid (17).

**Hemangioma**

Hemangioma is the most common benign hepatic neoplasm and is found in less than or equal to 20% of the population (11). Most patients with hemangiomas have no symptoms, but they become symptomatic if the tumor enlarges.

At MRI, hemangioma appears as a well-defined mass. It can have a heterogeneous appearance if there are areas of thrombosis, fibrosis, or degeneration. Markedly hyperintense lesions at T2-weighted MRI are characteristic imaging findings (11). At conventional extracellular contrast–enhanced MRI, hemangiomas typically show peripheral nodular enhancement followed by centripetal enhancement, referred to as filling in, during the later phases (11). The prolonged...
and delayed enhancement is secondary to contrast material entering the multiple vascular channels and slowly filling the lesion (11). This filling in of hemangioma can be seen during the HBP of gadoxetic acid–enhanced MRI, reflecting the blood pool, especially when there is suboptimal clearance of contrast material from the blood pool (Fig 11). Some hemangiomas may show slight central high signal intensity, even during the early HBP beyond the transitional phase (19). Tamada et al (97) reported that 47% of hemangiomas show intratumoral enhancement during the HBP.

High-flow hemangiomas may show relative hypointensity during the transitional phase owing to the uptake of gadoxetic acid in the normal surrounding liver parenchyma. This is referred to as the “pseudowashout” sign, which is not considered true contrast material washout, as is seen in HCC (98).

**Peritumoral Retention**

Peritumoral retention during the HBP of gadoxetic acid–enhanced MRI appears as a hyperintense rim surrounding the tumor. This rim is occasionally observed in HCCs (Fig 12). In the Yoneda et al study (99), peritumoral retention with partial enhancement was observed in 50% of HCCs. Histopathologically, peritumoral retention corresponds to *peritumoral hyperplasia*, which is defined as a rim of hyperplastic hepatocytes surrounding the tumor. Peritumoral hyperplasia is also observed in other hepatic tumors, such as neuroendocrine tumors, gastrointestinal stromal tumors, metastatic colon carcinomas, hemangiomas, and hepatoblastomas (100). Thus, these tumors also can show peritumoral retention during the HBP of gadoxetic acid–enhanced MRI (Figs 13, 14).

The pathogenesis of peritumoral hyperplasia remains controversial. Perfusion abnormality due to tumor vascular invasion is considered to be
Figure 11. Hemangioma in a 42-year-old man. (a) Axial T2-weighted MR image shows the lesion (arrow) with marked hyperintensity. (b) On an axial T1-weighted MR image, the lesion (arrow) is hypointense. (c) Axial arterial phase T1-weighted MR image shows peripheral enhancement of the lesion (arrow). (d) On an axial HBP MR image, the lesion (arrow) is hypointense, with marked ventral hyperintense foci (ie, filling in) (arrowhead).

Figure 12. HCC in a 73-year-old woman. (a) Axial arterial phase T1-weighted MR image shows enhancement of the tumor (arrow). (b) On an axial HBP MR image, the lesion (arrow) is hypointense and surrounded by a hyperintense rim, indicating peritumoral retention.
a major possible cause. Peritumoral hyperplasia is commonly seen in hypervascular neoplasms (100). In addition, portal venous invasion (100) or hepatic venous invasion (99) is more frequently observed in tumors with peritumoral hyperplasia. Such vascular invasion causes increased arterial blood flow in the peritumoral liver parenchyma and consequent hepatocyte hyperplasia.

Another pathogenesis of peritumoral hyperplasia could be regenerative changes in hepatocytes compressed by the tumor (99). Tumors such as HCC, neuroendocrine tumor, and gastrointestinal stromal tumor usually show expansive growth and do not show the type of infiltrative growth seen with adenocarcinomas. Such expansive growth can cause strong compression of the liver parenchyma and regenerative changes of hepatocytes, causing peritumoral retention.

The differential diagnosis of liver tumors that show peritumoral retention includes FNH and FNH-like lesions, which appear as ring or doughnut-like lesions during the HBP. Peritumoral retention is observed in the adjacent liver parenchyma outside the tumor, while ring or doughnut-like enhancement is observed in the lesion. Precisely recognizing the tumor margin by referring to the findings seen with other sequences is important for differential diagnosis.

**Biliary Tract Enhancement**

Gadoxetic acid is eliminated in approximately equal proportions by the liver (43.1%–53.2%) and by the kidneys, with renal glomerular filtration and subsequent excretion (41.6%–51.2%) (20). After being taken up by hepatocytes, gadoxetic acid is excreted from these cells into the
biliary canaliculi. Excretion into the bile ducts causes biliary luminal enhancement as early as 5–10 minutes after the injection. A 20-minute delay after the gadoxetic acid injection (ie, the HBP) may be sufficient for adequate biliary evaluation (20). Such biliary enhancement during the HBP is sometimes useful for diagnosing hepatic liver mass lesions.

Intraductal Papillary Mucinous Neoplasm of the Bile Duct

IPNB is a subtype of bile duct carcinoma (101). The histopathologic and immunohistochemical features of IPNB are similar to those of intraductal papillary mucinous neoplasms of the pancreas. Thus, IPNB is considered to be a “counterpart” disease of pancreatic intraductal papillary mucinous neoplasms. The imaging findings of IPNB include papillary or polypoid growth of the tumor along the bile duct, with expansive and significant dilatation of the bile duct upstream or downstream of the tumor (102). Dilatation of the bile duct has a cystic appearance and is usually connected with the involved bile ducts (102). For this reason, IPNB is usually diagnosed by using endoscopic retrograde cholangiopancreatography to determine the presence of mucin in the dilated bile duct (103).

The usefulness of gadoxetic acid–enhanced MRI in the diagnosis of IPNB has been reported. During the HBP, IPNB demonstrates a dilated enhanced bile duct with filling defects caused by mucin retention or a solid component of the tumor (Fig 15) (104–106). Note that when there is a large amount of mucin in a bile duct, it results in marked bile duct dilatation and obvious impaired liver function. In this setting, the hepatocellular uptake of gadoxetic acid and secretion of this agent into the bile duct have obviously decreased and led to nonenhancement of the biliary ducts during the HBP (106). The addition of diffusion-weighted imaging to the gadoxetic acid–enhanced MRI examination has the potential to improve the conspicuity of intraductal tumors in IPNB and is helpful in determining tumor invasiveness (107).

Malignant Lymphoma

Primary lymphoma of the liver is a rare malignant tumor, accounting for fewer than 1% of extranodal lymphomas. In contrast, hepatic extension (ie, secondary malignant lymphoma) in stage IV lymphoma has been observed in 15% of cases (15,16). Primary lymphomas of the liver are mainly large B-cell non-Hodgkin lymphomas. The risk factors for hepatic lymphomas are hepatitis C virus infection, Epstein-Barr virus infection, human immunodeficiency virus infection, and autoimmune disease (15,16).

At MRI, lymphomas of the liver are homogeneously hypointense to isointense on T1-weighted images and hyperintense on T2-weighted images. The signal intensity at T1- and T2-weighted MRI may be heterogeneous owing to foci of hemorrhage and necrosis. T2-hypointense tumors with a peripheral rim of hyperintensity also have been reported. The increased signal intensity around the lesion has been attributed to the inflammatory response elicited by the lymphomatous lesion and the resultant surrounding edema. The highly cellular nature of lymphoma typically results in markedly restricted diffusion. The majority of these lesions demonstrate minimal to no enhancement during all phases. The other pattern is that of enhancement of the lesion rim with a central nonenhancing area, resulting in a target-
like appearance of the lesion (108). Vascular structures such as portal and hepatic veins in the tumor, with no distortions in size or direction, are highly suggestive of malignant lymphoma (109). Similarly, nondistorted enhancing biliary ducts in the tumor are useful imaging findings in the diagnosis of malignant lymphoma (Fig 16) (110).

**Relative Signal Intensity and Differential Diagnosis of Hyperintense Liver Masses during the HBP**

The majority of FNHs, FNH-like lesions, and NRHs are iso- to hyperintense during the HBP because they are composed of nonneoplastic hyperplastic hepatocytes. Therefore, marked hyperintensity can be seen during the HBP.

In addition, these lesions often demonstrate ring or doughnut-like enhancement. The differential diagnosis of those among these lesions that have ring or doughnut-like enhancement includes liver tumors that show peritumoral retention during the HBP. Peritumoral retention corresponds to peritumoral hyperplastic hepatocytes surrounding the tumor; thus, peritumoral retention can also show marked hyperintensity during the HBP. Precise recognition of the tumor margin is important for the differential diagnosis.

Dysplastic nodules may be hyperintense, isointense, or hypointense during the HBP, depending on the grade of malignancy. Unlike HCCs, dysplastic nodules demonstrate no definite enhancement during the arterial dominant phase. Approximately 10%–15% of HCCs are hyperintense during the HBP. B-HCA and I-HCA lesions also can show hyperintensity during the HBP. The differentiation between benign nodules (eg, FNH, FNH-like nodules, and NRH) and tumor lesions (eg, HCC and HCA) is relatively easy when it is based on imaging features, including hemodynamic findings, and other features, as described earlier. However, differentiating HCC from HCA with use of imaging alone is often difficult. Additional clinical information is necessary for differential diagnosis, and biopsy is sometimes needed when it is difficult to make the differential diagnosis.

The hyperintensity caused by gadoxetic acid retention in the extracellular space tends to be lower compared with the hyperintensity caused by transporter uptake of gadoxetic acid (17). However, some hemangiomas can show strong hyperintensity due to the filling-in phenomenon. Comparison of the imaging findings of conventional extracellular contrast-enhanced CT and MRI is important for the differential diagnosis.

Biliary tract enhancement is caused by the physiologic excretion of gadoxetic acid into the bile ducts and therefore is usually strong. IPNB can show a dilated enhanced bile duct with filling defects caused by mucin retention or a solid component of the tumor. Enhanced nondistorted biliary ducts in the tumor are useful imaging findings in the diagnosis of malignant lymphoma. The differential diagnosis of hyperintense liver masses seen during the HBP is summarized in Figure 17.

**Conclusion**

Hepatic mass lesions without functioning hepatocytes commonly show hypointensity during the HBP of gadoxetic acid–enhanced MRI. However, it is important to identify the specific causes of hyperintensity seen during the HBP. Understanding these causes is useful not only for precise imaging-based diagnosis but also for understanding the pathogenesis of hepatic mass lesions. In other words, gadoxetic acid–enhanced MRI has a
recently identified role in the characterization of hepatic masses, including disease and molecular conditions, in addition to its conventional role in facilitating higher detectability of hepatic lesions.

Disclosures of Conflicts of Interest.—T.N. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: received unrestricted research grants from Bayer AG and Philips Healthcare. Other activities: disclosed no relevant relationships.

References


