**Rules, Roles, and Room for Discussion in Gadoxetic Acid-enhanced Magnetic Resonance Liver Imaging: Current Knowledge and Future Challenges**

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Since its launch onto the world medical market, gadoxetic acid has received a great deal of attention from a diverse group of researchers, including gastroenterologists, hepatologists, and abdominal radiologists. Gadoxetic acid in liver magnetic resonance (MR) imaging might be considered to have excellent utility. However, several issues remain that radiologists should keep in mind when utilizing this product. We compiled this review to introduce gadoxetic acid, describe how it should be used, highlight the situations in which it is most and least reliable, and suggest potential avenues for future research.

**Keywords:** gadoxetic acid, liver, magnetic resonance imaging

**Introduction**

Gadoxetic acid, or gadoxetate disodium (Gd-EOB-DTPA), is a recently launched liver-specific magnetic resonance (MR) contrast agent, distinguished by its capacity for rapid (<30 min) evaluation of both dynamic contrast-enhanced phase images and liver-specific phase images.

The use of gadoxetic acid in liver imaging has been the focus of a variety of studies, and in the current review, we aim to summarize the findings of that work to describe how gadoxetic acid can and should be used. We describe how to use gadoxetic acid during clinical MR examinations and focus on the results of many parameter optimization studies that aimed to standardize gadoxetic acid administration and scanning protocols during MR imaging of the liver, review the literature on the diagnostic ability of gadoxetic acid, and outline potential future uses of gadoxetic acid and issues that require further clinical and experimental evaluation.

**Rules Guiding Use of Gadoxetic Acid**

**Gadoxetic acid or extracellular gadolinium-based contrast agents?**

In most countries, 2 types of contrast agent are now available for MR imaging of the liver-extracellular gadolinium-based contrast agents (GBCAs) and liver-specific contrast agents, such as gadoxetic acid (Primovist or Eovist, Bayer Healthcare, Germany) and gadobenate dimeglumine (Gd-BOPTA).

Frydrychowicz and associates compared these latter 2 products extensively in a recent paper, and here, we focus exclusively on the characteristics that should be considered when choosing between gadoxetic acid and conventional extracellular GBCAs when performing MR imaging of the liver.

We believe that gadoxetic acid should be the first choice for liver imaging in most cases, but we should also be aware of the major disadvantages of gadoxetic acid. First, its use precludes liver equilibrium phase because signal intensity is always higher for the liver parenchyma than for vessels after the portal-venous phase. This makes it difficult to diagnose hemangioma, because pooling of contrast agent, a key feature of hemangioma, cannot be observed. Very high signal intensity on a T2-weighted image might help distinguish between hemangioma and liver malignancies, such as metastasis, but gadoxetic acid should not be used when the purpose of the MR examination is to confirm a hemangioma diagnosis rather than detect small focal liver lesions. The second disadvantage of gadoxetic acid is that its uptake is not always sufficient to provide the contrast necessary to distinguish between liver parenchyma and lesions (Fig. 1a, b). If the liver...
is not well enhanced on hepatocyte phase images, there is no reason to use gadoxetic acid for liver imaging. Several clinical parameters, including Child-Pugh score, serum bilirubin levels, and indocyanine green test results, are associated with uptake of gadoxetic acid (or signal intensity of the liver on hepatocyte phase images). No known imaging parameter predicts liver enhancement on hepatocyte phase images before gadoxetic acid administration, though liver fibrosis or stiffness as measured by MR elastography might indicate insufficient liver enhancement. We suggest using an alternative contrast agent, such as an extracellular GBCA, when previous MR examinations indicate insufficient liver enhancement after gadoxetic acid administration.

Gadoxetic acid contains half the amount of gadolinium found in extracellular GBCAs and is administered in doses that are half those of GBCAs; thus, examinations with gadoxetic acid utilize only a quarter the amount of gadolinium (0.1 mmol/kg for extracellular GBCAs versus 0.025 mmol/kg for gadoxetic acid). Contrast enhancement of the vessels is lower on the arterial phase for gadoxetic acid-enhanced images than for extracellular GBCAs. The $T_1$-shortening effect of gadoxetic acid is much larger than that of extracellular GBCAs, but that can result in equivalent or even greater contrast enhancements in the aorta. A recent study revealed that use of a slow injection rate (one mL/s) can facilitate equivalent arterial enhancements between gadoxetic acid and extracellular GBCAs. Currently, no published data compare enhancement of liver lesions on arterial phase images enhanced by gadoxetic acid and extracellular GBCAs. In our experience, however, the 2 agents provide visually equivalent enhancements.

Phase names

When using extracellular GBCAs, dynamic phases include the arterial or hepatic arterial phase followed by the portal venous phase, which is obtained about 60 to 70 s after injection; enhancement of the liver parenchyma is highest during the portal venous phase. Three to 5 min after injection, the equilibrium, delayed, or late phase begins, during which the signal intensity of the liver parenchyma decreases to the level found in the vessels. When gadoxetic acid is used as the contrast agent, the signal intensity of the liver continuously increases until it plateaus 20 min after the injection. During the hepatocyte or hepatobiliary phase, 10 to 20 min after injection, contrast between the liver parenchyma and vessels or focal liver lesions is maximal. Most researchers use the terms arterial phase and portal venous phase regardless of whether gadoxetic acid or extracellular GBCAs are used as the contrast agent. The term used to describe the phase between the dynamic and hepatocyte phases can be controversial. The term equilibrium phase should be avoided because the concentration of gadoxetic acid is consistently higher in the liver parenchyma than vessels, that is, the concentration of gadoxetic acid is never at equilibrium. The consensus report from the Second International Forum for Liver MRI used the term dynamic late phase to refer to the mid-period 2 to 3 min after administration of gadoxetic acid.

Rules for the arterial phase

Optimal arterial phase images are required for MR imaging of the liver because many focal liver

Fig. 1. Gadoxetic acid-enhanced hepatocyte phase magnetic resonance (MR) images in patients with cirrhosis with sufficient (a) and insufficient (b) liver enhancement. Precise detection of small liver lesions requires a contrast enhancement ratio, or ratio of signal intensity between the liver and spleen ($S_{Liver}/S_{Spleen}$), greater than 1.5. Hepatocellular carcinomas (HCCs) are well recognized in the liver (arrows), whereas small HCC is ambiguous in the liver with insufficient liver enhancement (arrowhead).
lesions show their own characteristic vascularity. Nonetheless, acquisition of arterial phase images of sufficient quality may be difficult because methods of contrast agent injection and the very short optimal time window for the arterial phase impact image quality.

Gradient echo sequence with 3-dimensional acquisition (3D-GRE), which has a high spatial resolution and signal-to-noise ratio, is usually used to obtain gadoxetic acid-enhanced images.\textsuperscript{13} Ringing artifacts sometimes appear on arterial phase images obtained with 3D-GRE because of \textit{k}-space inhomogeneity. Although the artifacts might include image distortion due to patient movement or respiratory motion, the truncation artifact is supposed to play a major role in ringing artifacts.\textsuperscript{14} Truncation artifacts occur because of insufficient sampling at high spatial frequencies and appear at interfaces with instantaneous transitions from high to low signal intensity, such as the interface between arteries with a high concentration of contrast agent and surrounding soft tissue.\textsuperscript{15} In addition, truncation artifacts may result when an abrupt increase in signal during signal acquisition from the inflow of contrast agent into the artery being imaged changes the amplitude of the arterial signal in the \textit{k}-space.\textsuperscript{16}

\textbf{How to avoid \textit{k}-space inhomogeneity}

Although a saline flush is mandatory after bolus injection, use of a low injection rate will help prolong the injection duration and decrease \textit{k}-space inhomogeneity.\textsuperscript{17,18} On the other hand, a high injection rate, such as 3 mL/s, results in short injection duration—one purported cause of \textit{k}-space inhomogeneity and truncation artifacts. Recent publications have recommended an injection rate of one mL/s to achieve sufficient enhancement and improve image quality.\textsuperscript{17,19} Use of a square matrix, slower injection rate, shorter scanning time, and sequential view ordering are also reported to reduce artifacts.\textsuperscript{14}

\textbf{Acquiring images during the optimal arterial phase time window}

The injection volume of gadoxetic acid, 0.1 mL/kg of body weight, is half that of extracellular GBCAs, which indicates short injection duration when using same injection rate. Since short injection duration narrows optimal time window for arterial phase, it is necessary to adjust individual factors that affect the arrival time of the contrast agent to the aorta. Bolus timing techniques, such as the use of automated bolus detection algorithms or the fluoroscopic triggering method, are particularly useful.\textsuperscript{13,17} However, there is little information on the optimal time delay after the arrival of the contrast agent to the aorta. Researchers have used delay times ranging from 7 to 15 s.\textsuperscript{17,20–22} If bolus timing cannot be manipulated as described above, timing may instead be adjusted via the test-injection method, in which a small amount (e.g., 0.5 mL) of contrast agent is injected before dynamic study to measure the length of time for the agent to reach the aorta.

\textbf{Rules for the hepatocyte phase}

\textbf{Delay before hepatocyte phase}

The hepatocyte phase, also known as the hepato-biliary phase, is the period during which the hepatocytes take up most of the contrast agent and there is maximal contrast between the liver parenchyma and vasculature, including the portal and hepatic veins. Classically, the hepatocyte phase has been defined as beginning approximately 20 min after contrast injection and lasting at least 2 hours.\textsuperscript{12,33} In one Phase II study of gadoxetic acid, the tumor-to-liver contrast plateaued 20 min after contrast injection, remained steady an additional 25 min.\textsuperscript{23} However, it is common to see hepatocyte phase images obtained only 10 to 20 min after contrast injection.\textsuperscript{24–26} Indeed, the optimal hepatocyte phase can be defined as the period of time during which there is sufficient tumor-to-liver contrast or tumor conspicuity. In other words, if tumor conspicuity is appropriate, this phase may occur as early as 10 min after injection,\textsuperscript{27} but 20 min after injection may be too early to obtain images if optimal contrast has not been achieved. In fact, in patients with normal hepatic function, sufficient liver enhancement can almost always be achieved 10 min after injection; thus, it is no longer necessary to wait 20 min to perform imaging, even for small lesions.\textsuperscript{27–29}

\textbf{Improving hepatocyte phase images}

Hepatocyte phase images are usually obtained with a low flip angle, such as 12° or 15°, as conventionally used in 3D-GRE sequences. Yet, a larger flip angle may be optimal to maximize tumor-to-liver contrast because the presence of contrast agent can shorten \textit{T}_1 relaxation time in the liver during the hepatocyte phase; recent reports suggest a 30° angle.\textsuperscript{30,31} A greater flip angle can be especially helpful when imaging patients with chronic liver disease, whose impaired hepatic function and/or gadoxetic acid uptake may make it difficult to obtain sufficient tumor-to-liver contrast.\textsuperscript{32} Respiratory-triggered high resolution 3D-GRE sequence using navigator echo has been proposed to obtain hepatocyte phase images with improved spatial
resolution, especially for the z axis. Coronal or sagittal images of good quality can be reconstructed from the isovoxel axial images with submillimeter spatial resolution.

**How to shorten examination time**

A 20-min waiting period for the hepatocyte phase is sufficient to obtain other sequences, so many researchers have attempted to shorten examination time by obtaining T2-weighted and diffusion-weighted images after gadoxetic acid administration. Acquisition of T2-weighted images after gadoxetic acid injection has been demonstrated without compromise of image contrast. Gadoxetic acid has both T2*-and T1-shortening effects. The T2*-shortening effect does not affect the image contrast of the liver on fast spin-echo T2-weighted fast spin-echo images and does not decrease tumor conspicuity or sensitivity on T2-weighted images.

This is not true, though, for the bile duct, in which a much higher concentration of excreted gadoxetic acid than in the liver parenchyma leads to a significant decrease in bile duct signals and degradation of T2-weighted MR cholangiopancreatography (MRCP). Kim and colleagues, however, reported that post-contrast MRCP is acceptable if obtained within a few minutes of gadoxetic acid injection because excretion of the contrast agent into the bile duct does not start until approximately 5 to 10 min after injection.

Diffusion-weighted images can also be obtained after gadoxetic acid administration. The presence of gadoxetic acid in the liver parenchyma does not affect tumor conspicuity or measurement of the apparent diffusion coefficient (ADC) of tumors on diffusion-weighted images. Nevertheless, the T2*-shortening effect of the contrast agent can decrease the signal intensity of the liver parenchyma, which, in turn, may affect ADC measurement in the liver parenchyma.

**Roles of Gadoxetic Acid in Liver MR Imaging**

**Improving sensitivity of small hepatic metastasis detection**

A meta-analysis published in 2010 suggested the superiority of contrast-enhanced MR imaging to contrast-enhanced CT for facilitating diagnosis of hepatic metastasis from colorectal carcinoma. In general, there is no arguing that the high contrast resolution of MR imaging improves diagnoses of small focal liver lesions. However, no publication shows the better utility of gadoxetic acid than superparamagnetic iron oxide (SPIO) for detecting small liver lesions. Combined with diffusion-weighted imaging, gadoxetic acid-enhanced MR imaging can yield better diagnostic accuracy and sensitivity than its use alone. The superiority of gadoxetic acid-enhanced MR imaging to contrast-enhanced CT in patients with liver metastases from pancreatic carcinoma has also been argued. Considering the added value of MRCP, gadoxetic acid-enhanced MR imaging can be a first-line examination for patients with suspected pancreatic carcinoma.

**Lesion characterization**

**Hemangioma versus hepatic metastasis**

Hemangiomas are liver tumors that, when small, are most frequently confused with metastatic liver tumors. Traditional MR imaging findings, such as brightness on T2-weighted images, are essential for distinguishing small hemangiomas from metastasis. On hepatocyte phase images, hemangiomas display

![Fig. 2. A case of liver metastases from rectal carcinoma. Metastasis in the posterior segment (arrow) is well visualized in contrast-enhanced computed tomography (CT) (a) and gadoxetic acid-enhanced hepatocyte phase image (b). Another small metastasis is only detected in hepatocyte phase image (b, arrow head).](image-url)
a clear, low intensity signal because they contain no hepatocytes that take up contrast agent. Thus, it is impossible to observe the most characteristic finding of hemangioma, delayed enhancement or pooling of the contrast agent, on delayed phase or hepatocyte phase images.

We suppose that gadoxetic acid has no added value for evaluating hemangioma. Thus, 2 main findings, already known as useful features in conventional dynamic CT or MR imaging, can be used to distinguish hemangioma from metastasis when gadoxetic acid-enhanced MR imaging is used—ring-like enhancement on arterial phase images, which is observed more frequently in metastasis than hemangioma (Fig. 3a), and very high signal intensity on T2-weighted images, which is more common in hemangioma than metastasis (Fig. 3b). Because they contain similar concentrations of contrast agent, hemangiomas and vessels exhibit similar signal intensities during the dynamic phases. Further, dot-like enhancements on arterial phase images (Fig. 3c) and geographic or heterogeneous enhancement of larger hemangiomas on late phase images (Fig. 3d) can also facilitate confident diagnosis of hemangioma. When comparing an ability of tumor characterization between hemangioma and metastasis, conventional GBCAs has advantage over gadoxetic acid. However, the excellent sensitivity of MR imaging with gadoxetic acid in detecting small lesions more than makes up for the disadvantages if multiparametric MR imaging evaluation is done.

**Distinguishing between focal nodular hyperplasia (FNH) and hepatic adenoma (HA)**

FNH and HA are focal lesions that develop in the liver in the absence of chronic liver disease. Both types of lesion have been linked to use of oral contraceptives and commonly observed in the livers of young women, and the lesions are characterized by the presence of hypervascularity on arterial phase images. FNH is believed to be a regenerative hyperplastic response of hepatocytes secondary to localized vascular abnormalities, is usually managed conservatively, and does not generally require resection. HA is a benign neoplasm composed of hepatocytes and is treated with surgical resection if the HA is considered at high risk for spontaneous...

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**Fig. 3.** Two major features for distinguishing liver metastasis from hemangioma are ring-like enhancement on arterial phase often observed in liver metastasis (a) and bright, homogeneous very high intensity on T2-weighted image seen in hemangioma (b). Dot-like enhancement on arterial phase (c) and geographic moderate enhancement on late phase (d) are also frequently observed in hemangioma. Note: when comparing an ability of tumor characterization between hemangioma and metastasis gadoxetic acid has no added value to conventional extracellular gadolinium-based contrast agents.
hemorrhage or malignant transformation.30,32,39,58

Recent studies have provided evidence that gadoxetic acid-enhanced MR imaging in general and hepatocyte phase images in particular greatly facilitate the differential diagnosis of these 2 lesions. Most FNHs are strongly enhanced during the arterial phase and show hyperintensity on hepatocyte phase images (Fig. 4a, b).59,60 On the other hand, hepatocyte phase images of HAs generally show hypointensity. A central scar, an anomalous portal area with abundant loose connective tissue, is a well known and specific imaging finding of FNH but not observed in all cases. However, we should be aware that such scars appear on hepatocyte phase images with much lower intensity than the remainder of the tumor.60 Although hepatocyte phase findings can aid differential diagnosis, it is also important to note that 10% of FNHs show hypointensity on hepatocyte phase images despite the fact they are non-neoplastic and benign.59,61 The central hypointense core of FNHs is generally larger in extent than the central scar observed in dynamic phases.60,62 Even in such cases, however, the peripheral hyperintense rim on hepatocyte phase might imply an uptake ability of the lesion, i.e., FNH rather than HA (Fig. 4b).60

HAs have recently been subclassified into 4 categories on the basis of genetic and pathologic features,63 but only a little has been studied on the role of gadoxetic acid for this subclassification.61

Added value for hepatocellular carcinoma (HCC)
Improving diagnosis of conventional HCCs

Arterial hypervascularity and subsequent washout are the widely recognized and accepted criteria for imaging diagnosis of HCCs.64,65 Several studies have shown that gadoxetic acid-enhanced MR imaging is useful in diagnosing conventional HCCs and, in fact, may sometimes be more reliable than dynamic contrast-enhanced 16- to 64-slice multidetector-row CT for this purpose.9,36,66,67 When using an extracellular GBCA, sensitivity and specificity of MR imaging are excellent even for small HCCs.68 However, some researchers suggest that the hepatocyte phase of gadoxetic acid might have added value to detect more HCCs than dynamic phases especially for less-experienced observers.69 This is mainly the result of the conspicuity of hypointense HCCs on hepatocyte phase images.70 The decreased uptake of gadoxetic acid, or low intensity on hepatocyte phase images, is easy to identify even if the lesion size is small, whereas washout on delayed dynamic phase CT is sometimes ambiguous. However, approximately 10% of HCCs take up gadoxetic acid and show isointensity.69 This suggests that the diagnosis of HCC should not be based solely on dynamic and hepatocyte phase images, but should also utilize conventional sequences, such as T2-weighted imaging (Fig. 5a, b).

Hypervascular pseudolesions, also known as arterial-portal shunts, typically have a rectangular or wedge shape, are commonly found at the periphery of cirrhotic livers, and may mimic small hypervascular HCCs.71 Even on extracellular GBCA-enhanced MR imaging, most hypervascular pseudolesions are easily recognized as benign, though some have a rounder shape and can be misdiagnosed as small HCCs. Uptake of gadoxetic acid, or isointensity to the surrounding liver parenchyma on hepatocyte phase images, is a key feature for confirming a hypervascular focus is benign72 (Fig. 6a, b). Although hypervascular pseudolesions can sometimes show slightly lower intensity on the hepatocyte phase, the difference in signal between the lesion and surrounding liver parenchyma is small.

Fig. 4. A case of focal nodular hyperplasia (FNH). Hypervascularity on arterial phase (a, arrow) and subsequent uptake of gadoxetic acid on hepatocyte phase (b) are the characteristic features of FNH. Note, part of the non-enhanced area is seen within the lesion (b, arrow).
Fig. 5. A case of type C cirrhosis with hypervascular hepatocellular carcinoma (HCC). Arterial enhancement is observed in the lesion (a). A part of the tumor uptakes gadoxetic acid and shows as high signal intensity on hepatocyte phase image as the liver parenchyma (b). This atypical uptake of gadoxetic acid in the HCC is not uncommon.

Fig. 6. Hypervascular pseudolesion or arterial-portal shunt in cirrhotic liver (a, b). Round hypervascular focus is observed on arterial phase (a), which uptake gadoxetic acid as well as the surrounding liver parenchyma (b). The findings suggest the lesion should be pseudolesion rather than hepatocellular carcinoma (HCC).

Fig. 7. Small hypervascular hepatocellular carcinoma (HCC) in cirrhotic liver. Faint hypervascular nodule is detected in the lateral segment on arterial phase image (a). The nodule shows clear hypointensity on hepatocyte phase (b) and hyperintensity on diffusion-weighted image (c).
Fig. 8. A case of type C chronic hepatitis with conventional small hepatocellular carcinoma (HCC) (a, b) and early HCC (c, d). Hypervascular nodule on arterial phase (a) shows clear hypointensity on hepatocyte phase image (b). This nodule is pathologically diagnosed as moderately differentiated HCC. Another small nodule without hypervascularity (c) also shows hypointensity on hepatocyte phase image (d). This nodule was surgically removed and diagnosed as early HCC. Macroscopically, the former nodule (moderately differentiated HCC) is whitish with a well defined margin (e, arrow), whereas the latter nodule (early HCC) is vaguely nodular (e, arrowhead).

Advantage of assessing multi-step hepatocarcinogenesis: assessment of hypovascular HCCs

Although hypervascularity is an established criterion for diagnosing conventional HCCs, HCCs may also show hypovascularity on arterial phase images, especially in their early stages. It is widely believed that HCC can develop in cirrhotic livers from premalignant lesions or dysplastic nodules via multi-step carcinogenesis. During this process, a pathological feature called early HCC is clearly distinguished from conventional hypervascular HCC (Fig. 8a–e). For example, early HCCs are usually smaller than 2 cm in size, and macroscopic pathological observations reveal a vaguely nodular...
appearance and the absence of a pseudocapsule surrounding the lesion. Further, early HCCs, unlike conventional HCCs, are not hypervascular, though focal hypervascularity may be observed within a lesion. Finally, early HCCs can show washout on delayed-phase dynamic CT or decreased portal perfusion on CT during arterial portography.

Though the use of conventional imaging modalities to diagnose early HCC has been challenging, the use of gadoxetic acid-enhanced MR imaging may at least partly alleviate this problem. Specifically, early HCCs may appear on hepatocyte phase images as clearly hypointense, hypovascular lesions in cirrhotic livers. Gadoxetic acid-enhanced hepatocyte phase images have been reported to have the highest sensitivity and specificity for diagnosing early HCCs. After reviewing cirrhotic liver nodules that showed atypical enhancement patterns on dynamic contrast-enhanced studies, Golferi and associates also concluded that hypointensity on hepatocyte phase images is the strongest marker of malignancy. Although some investigators have suggested that dysplastic nodules can also be seen as hypointense nodules on hepatocyte phase images, we believe that low intensity on hepatocyte phase is the key feature suggesting malignancy when assessing a cirrhotic nodule.

**Room for Discussion**

**Management of hypovascular hepatocellular nodules showing low intensity on hepatocyte phase images**

The bulk of the literature suggests that hypovascular nodules with low intensity on hepatocyte phase images can be malignant or at least premalignant. If left untreated, more than 10% of these lesions will become hypervascular or conventional HCCs within a year. Among early HCCs identified by gadoxetic acid-enhanced MR imaging, an especially important risk factor for hypervascularization is size exceeding 10 mm. However, this does not mean that this type of lesion, such as one that is hypovascular and hypointense during hepatocyte phase imaging, should always be treated as a hypervascular HCC. Future work, including prospective randomized studies, are required to determine whether it is appropriate and/or necessary to treat these early stage HCCs.

**HCCs taking up gadoxetic acid**

As discussed, low signal intensity on hepatocyte phase images can indicate the malignant transpor-
Hypervascular hepatocellular nodules showing high intensity on hepatocyte-phase imaging

The above discussion raises the question of whether hepatocellular lesions showing high intensity in the hepatocyte phase are always benign, and the answer is no. As is the case for conventional hypervascular HCCs, some hypovascular HCCs can show high signal intensity, or increased uptake of gadoxetic acid, in the hepatocyte phase. Hypovascular hepatocellular nodules showing high intensity during hepatocyte phase imaging can be early HCC\(^92\) (Fig. 10a, b) and sometimes progress to hypervascular HCCs after several months (Fig. 11). Kobayashi and colleagues reported gadoxetic acid-enhanced MR imaging findings of high grade hepatocellular lesions, or so-called early HCCs, detected by angiography-assisted CT that revealed decreased portal flow to the lesions during arterial portography and a small hypervascular focus within the tumor during hepatic arteriography. The authors reported that approximately 20% of these lesions showed isointensity on gadoxetic acid-enhanced hepatocyte phase images,\(^93\) which suggests that it might be even more difficult than expected to detect early HCCs in cirrhotic livers using only gadoxetic acid-enhanced MR images. Further studies, including those incorporating longitudinal observations, are necessary to address this issue.

It is important to remember that the signal intensity of hepatocyte phase images varies depending on hepatic function, degree of fibrosis, and portal flow. Thus, the relative intensity of lesions and liver parenchyma is not always identical among patients. Whenever hepatocyte phase intensity is discussed, it is vital to confirm enhancement by comparing signals of the liver with those of extracellular compartments, such as the spleen.

Quantitative assessment of diffuse liver disease
Because the uptake of gadoxetic acid into the liver parenchyma reflects hepatocyte function,
many researchers attempt to use gadoxetic acid-enhanced MR imaging, and especially hepatocyte phase imaging, to make non-morphological or functional assessments of the liver. For example, because the liver enhancement ratio can, with some correction, be correlated with degree of fibrosis, this technique has been used to determine stage of liver fibrosis. The ratio of hepatocyte phase enhancement has also been used to assess local hepatic function. Thus, non-morphological or quantitative MR imaging using gadoxetic acid as well as quantitative assessment using diffusion-weighted and perfusion imaging may represent the new generation of projects. For these techniques to be useful, it will be necessary to evaluate their repeatability and reproducibility and compare results from these methods with those produced by pre-existing techniques, such as laboratory analyses.

Conclusions

Compared to conventional extracellular gadolinium-based contrast agents, gadoxetic acid is better for detecting hepatic metastases, distinguishing hypervascular pseudolesions from small HCCs in patients with cirrhosis, diagnosing hypovascular HCCs, and facilitating differential diagnosis between FNH and HA. As a result, this contrast agent has changed strategies for managing patients with liver disease, and clinical guidelines will soon be revised to reflect this new trend in liver MR imaging. Although gadoxetic acid has many advantages, radiologists should be aware of its potential drawbacks and always be cautious when employing this product in clinical settings.

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