Magnetic resonance imaging of the cirrhotic liver in the era of gadoxetic acid

Francesco Agnello, Marco Dioguardi Burgio, Dario Picone, Federica Vernuccio, Giuseppe Cabibbo, Lydia Giannitrapani, Adele Taibbi, Antonino Agrusa, Tommaso Vincenzo Bartolotta, Massimo Galia, Roberto Lagalla, Massimo Midiri, Giuseppe Brancatelli

Section of Radiological Sciences, DIBIMED, University of Palermo, 90127 Palermo, Italy

Section of Gastroenterology, DIBIMIS, University of Palermo, 90127 Palermo, Italy

Section of Internal Medicine, DIBIMIS, University of Palermo, 90127 Palermo, Italy

Department of General Surgery, Urgency, and Organ Transplantation, University of Palermo, 90127 Palermo, Italy

Author contributions: Agnello F and Brancatelli G were guarantors of integrity for entire study; Agnello F, Dioguardi Burgio M, Galia M, Midiri M and Brancatelli G wrote and revised the manuscript for important intellectual content; Agnello F, Picone D, Vernuccio F, Giannitrapani L and Taibbi A performed the literature research; Agnello F, Cabibbo G, Agrusa A, Bartolotta TV, Lagalla R and Brancatelli G edited the manuscript; and all authors approve the final version of submitted manuscript.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Correspondence to: Giuseppe Brancatelli, MD, Section of Radiological Sciences, DIBIMED, University of Palermo, Via del Vespri 127, 90127 Palermo, Italy. gbranca@yahoo.com

Telephone: +39-91-6552348
Fax: +39-91-6552324

Received: May 16, 2015
Peer-review started: May 20, 2015
First decision: June 23, 2015
Revised: July 22, 2015
Accepted: September 30, 2015
Article in press: September 30, 2015
Published online: January 7, 2016

Abstract

Gadoxetic acid improves detection and characterization of focal liver lesions in cirrhotic patients and can estimate liver function in patients undergoing liver resection. The purpose of this article is to describe the optimal gadoxetic acid study protocol for the liver, the unique characteristics of gadoxetic acid, the differences between gadoxetic acid and extra-cellular gadolium chelates, and the differences in phases of enhancement between cirrhotic and normal liver using gadoxetic acid. We also discuss how to obtain and recognize an adequate hepatobiliary phase.

Key words: Hepatobiliary contrast materials; Gadoxetic acid; Cirrhosis; Magnetic resonance imaging; Liver

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Hepatobiliary contrast materials improve detection and characterization of focal liver lesions in cirrhotic patients and can measure liver function. Familiarity with unique characteristics of gadoxetic acid is crucial to achieve an optimal magnetic resonance examination of the liver. In this review, we discuss the protocol for gadoxetic acid enhanced magnetic resonance imaging of the liver and describe differences.
between gadoxetic acid and extra-cellular contrast materials.


INTRODUCTION

Several studies have demonstrated the added value of hepatobiliary contrast agents in the detection and characterization of focal liver lesions in cirrhotic patients compared with extra-cellular gadolinium chelates and contrast enhanced computed tomography (CT)\(^1\-^4\). Hepatobiliary contrast agents are first distributed in the extracellular fluid compartment, subsequently taken up by functioning hepatocytes, and then excreted into the biliary system\(^5\-^6\). Thus, hepatobiliary contrast agents can differentiate lesions that contain functioning hepatocytes, such as regenerative nodules and most dysplastic nodules, from hepatocellular lesions without functioning hepatocytes, such as most hepatocellular carcinomas (HCCs) and nonhepatocellular lesions, such as cyst, hemangioma, cholangiocarcinoma, metastases\(^7\).

There are two commercially available hepatobiliary contrast agents: gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (gadoxetic acid; Eovist/Primovist; Bayer-Healthcare, Leverkusen, Germany) and gadobenate dimeglumine (Multihance, Bracco, Italy). Both of them allow evaluation of lesion vascularity and hepatobiliary function. However, approximately 50% of the injected dose of gadoxetic acid is eliminated by functioning hepatocytes, while only 3%-5% gadobenate dimeglumine undergoes the same pathway of excretion\(^5\-^6\). Therefore, using gadoxetic acid, higher hepatobiliary uptake results in greater enhancement of liver parenchyma\(^8\).

Another unique feature of gadoxetic acid is the rapid hepatocellular uptake (starting at approximately 90 s after injection)\(^9\), which results in an overlap between extracellular and hepatobiliary phases (the so-called "transitional phase"). Rapid uptake of gadoxetic acid allows acquisition of the hepatobiliary phase at 20 min after contrast injection\(^1\). Hepatocellular uptake of gadobenate dimeglumine starts no sooner than 40 min after contrast injection\(^9\). Therefore, the extracellular phase of gadobenate dimeglumine is "pure" (it shows no overlap with the hepatobiliary phase, similar to what can be obtained with any extracellular contrast agent), and the hepatobiliary phase is typically acquired 60-180 min after contrast injection\(^9\). Thus, with gadobenate dimeglumine, dynamic and hepatobiliary images are acquired in two separate sessions, increasing examination time and patient discomfort. For these reasons, gadoxetic acid is generally preferred over gadobenate dimeglumine when acquisition of hepatobiliary phase is deemed necessary for the management of patients. The main disadvantage of liver magnetic resonance imaging (MRI) with gadoxetic acid is the contrast cost: the purchase price of gadoxetic acid is approximately twice that of gadobenate dimeglumine. As MRI reimbursements in the public sector are fixed, many institutions use gadobenate dimeglumine instead of gadoxetic acid for economic reasons.

In this review, we describe the optimal MRI study protocol of the liver and the differences in phases of enhancement between cirrhotic and normal liver using gadoxetic acid. We also illustrate the differences in phases of enhancement between gadoxetic acid and extracellular contrast agents and discuss how to obtain and recognize an adequate hepatobiliary phase.

WHY GADOXETIC ACID IN THE CIRRHOTIC LIVER

The need for an accurate detection and characterization of HCC represents the main reason for the increasing use of gadoxetic acid in cirrhotic patients\(^10\-^12\). The ability to detect HCC with gadoxetic acid depends on the differences in hepatocellular contrast uptake between HCC and the surrounding liver\(^14\). On hepatobiliary phase, HCCs are typically hypointense due to the absence of functioning hepatocytes, while the liver parenchyma enhances due to hepatocellular uptake of gadoxetic acid. Consequently, HCC to liver contrast and HCC detection rate are increased\(^4\).

Hepatobiliary phase hypointensity also helps differentiate HCCs from dysplastic and regenerative nodules. Since hepatocellular uptake of gadoxetic acid decreases during hepatocarcinogenesis, hepatobiliary phase hypointensity suggests a diagnosis of HCC over that of dysplastic and regenerative nodules, which are typically iso- or hyperintense\(^13\-^16\). Typical imaging appearance of HCC includes moderate arterial enhancement and venous wash-out\(^17\). Using these criteria, however, several small HCCs can be missed because of absence of venous wash-out or, more rarely, arterial enhancement\(^18\). The hypointensity on hepatobiliary phase helps to correctly characterize small HCCs\(^13\-^19\). Hepatobiliary phase hypointensity, however, is not specific for the diagnosis of HCC because it can be found in any non-hepatocyte containing lesion (e.g., hemangiomas, cholangiocarcinomas, metastases)\(^20\).

Another application of gadoxetic acid is the preoperative evaluation of patients scheduled for liver resection\(^21\-^22\). Recent studies have reported that quantitative analysis of hepatocellular uptake of gadoxetic acid can be used to estimate liver function and to predict the risk of liver failure after major hepatic resection.
resection\textsuperscript{[21, 22]}. Hepatocellular uptake of gadoxetic acid correlates with indocyanine green clearance and uptake of radiopharmaceutical agents\textsuperscript{[22, 23]}. The advantages of gadoxetic acid over traditional methods, such as indocyanine green clearance and hepatic scintigraphy with radiopharmaceutical agents, include anatomic resolution (\textit{i.e.}, liver function can be evaluated at segmental or subsegmental level) and the absence of ionizing radiation\textsuperscript{[24]}. 

**OPTIMAL STUDY PROTOCOL OF THE LIVER**

An ideal MRI liver protocol should evaluate both liver parenchyma and vessels and should aid in detection and characterization of hepatic lesions. Typically, MRI liver protocol includes T2-weighted turbo or fast spin-echo (with and without fat saturation) sequences, gradient-recalled echo (GRE) T1-weighted in- and opposed-phase sequence, diffusion-weighted (DW) sequence, and contrast-enhanced three-dimensional T1-weighted GRE sequence with fat suppression. Field-strength magnets of 1.5 Tesla or greater are recommended to obtain high-quality liver imaging\textsuperscript{[25]}. Contrast administration should be performed through a power injector. The use of a saline solution is strongly recommended because it reduces the dose of contrast material remaining in the dead space (\textit{e.g.}, the brachial vein) and shortens the arrival time of contrast material in the hepatic arteries\textsuperscript{[26]}. Contrast enhanced images are obtained on vascular, transitional, and hepatobiliary phases\textsuperscript{[26]}. Vascular phases include the late hepatic arterial and portal venous phases\textsuperscript{[26]}. Late hepatic arterial phase is crucial to detect and characterize hypervascular lesions\textsuperscript{[27]}. Demonstration of moderate enhancement of intrahepatic portal veins, slight enhancement of liver parenchyma, and no enhancement of hepatic veins indicate an appropriate timing\textsuperscript{[28]}. Achieving an adequate arterial phase with gadoxetic acid is more challenging than with conventional extra-cellular contrast materials. Due to the higher T1-relaxivity, gadoxetic acid has one-half lower contrast volume and one fourth lower Gd-content per kg than those of conventional extra-cellular contrast materials\textsuperscript{[29]}. Thus, gadoxetic acid injection duration and time to peak aortic enhancement are shorter than those of conventional extra-cellular contrast materials\textsuperscript{[29]}. In addition, the administration of gadoxetic acid has been associated with acute self-limited dyspnea, and consequent severe motion artifacts\textsuperscript{[30]}. By definition, acute self-limited dyspnea is limited to the hepatic arterial phase images, and respiratory motion artifacts are absent in other sequences\textsuperscript{[30]}. The exact cause remains unknown. A relationship between higher gadoxetic acid doses and chronic obstructive pulmonary disease has been reported\textsuperscript{[31]}. Because the dyspnea is transient (10-20 s), a potential solution in order to overcome the artifacts is to acquire more than one arterial phase image. This approach is advantageous because: (1) acquisition of a greater number of phases increases the likelihood to obtain at least one diagnostic arterial phase image; and (2) reducing the acquisition time of each phase minimizes the opportunity for motion\textsuperscript{[30]}. 

There are methods for achieving an optimal an optimal hepatic arterial phase. The most frequently used is a fixed delay (approximately 25-30 s) between the start of contrast injection and data acquisition. This method, however, is often inadequate because it does not take into account injection- or patient-related factors (\textit{e.g.}, cardiac output) that influence circulation time. Indeed, arterial phase images are frequently obtained either too early (\textit{i.e.}, before portal venous enhancement) or too late (\textit{i.e.}, when contrast is already in the hepatic veins)\textsuperscript{[32]}. Another option is the test bolus technique, in which a small test bolus (1-2 mL) of contrast material is injected to calculate contrast material arrival time. Although this technique is effective with extra-cellular contrast materials, it is not recommended in gadoxetic acid enhanced MRI because hepatocellular uptake of the bolus can increase liver signal intensity, and the removal of bolus volume from the pre-filled syringe can leave insufficient contrast to administer during the dynamic phases of the study. The use of a fluoroscopic system (MR SmartPrep, GE Medical Systems, Milwaukee, WI, United States; CARE Bolus, Siemens Medical Solutions, Erlangen, Germany; Bolus-Track, Philips Medical Systems, Best, The Netherlands) is preferable\textsuperscript{[16]}. This technique is based on real-time monitoring of the bolus arrival at the level of the vessel of interest (typically the suprarenal abdominal aorta) with a 2D fluoroscopic sequence. Arterial phase acquisition can be started manually or automatically with a trigger threshold. The optimal scan delay for late hepatic arterial phase is 15-20 s after the peak aortic enhancement, which corresponds to the time necessary to synchronize the arrival of contrast material in the main portal vein with central k-space filling\textsuperscript{[26]}.

The injection of contrast material breaks k-space homogeneity and can cause truncation artifacts\textsuperscript{[33]}. These artifacts appear as dark or bright lines at interfaces between high and low signal intensity structures (\textit{e.g.}, enhanced arteries and surrounding liver parenchyma) and alter anatomic details of structures\textsuperscript{[34]}. Several methods of minimizing truncation artifacts truncation artifacts have been proposed. One option is to use a larger volume of contrast material by diluting gadoxetic acid with saline\textsuperscript{[35]}. Alternatively, a slow (1 mL/s) injection rate, which results in natural dilution of the contrast in the vascular space, can be used\textsuperscript{[35]}. In addition, to increase k-space homogeneity, the larger contrast volume provides a wider temporal window of hepatic arterial phase. Tamada et al\textsuperscript{[36]} compared arterial phase images obtained with three different techniques: diluted gadoxetic acid administered at conventional rate of 3 mL/s; undiluted gadoxetic acid administered at conventional rate of 3
hepatocytes through a canalicular multispecific organic anion transporting polypeptide 1B3 (OATP1B3) as early as 90 s after contrast injection, but this process takes several minutes before all contrast is taken up by hepatocytes. Thus, gadoxetic acid “transitates” from interstitial space to intracellular space. That is why we refer to this phase as the transitional phase, indicating the transition of gadoxetic acid from the extracellular spaces to the hepatocellular spaces. On 10 min and 20 min phase (hepatobiliary phase), the intrahepatic vessels show hypointensity to the liver, while the bile ducts (arrows) show hyperintensity; these findings indicate an adequate hepatobiliary phase. Also note kidney hypointensity to the liver, which indicates normal hepatobiliary elimination of gadoxetic acid and adequate hepatobiliary phase. In contrast, extracellular contrast materials are equally distributed between vascular spaces and interstitial spaces. Hepatocellular uptake of gadoxetic acid explains higher signal intensity of liver parenchyma with gadoxetic acid than with extracellular contrast materials. Earlier elimination of gadoxetic acid from the vessels leads to earlier de-enhancement and, therefore, lower signal intensity.

They concluded that the injection rate of 1 mL/s with undiluted gadoxetic acid was preferable to the other two methods. Portal venous phase is acquired 50-70 s after gadoxetic acid injection. On portal venous phase, the liver parenchyma shows intense enhancement, and the portal and hepatic veins are fully and maximally enhanced. The interval time (2-5 min after gadoxetic acid injection) between perfusion phase and hepatobiliary phase is termed “transitional phase”, and, therefore, should not be confused with or referred to as the equilibrium phase that is typically obtained at the same time delay with extracellular contrast agents (Figures 1 and 2). The transitional phase is obtained 3 min after the start of contrast injection. Gadoxetic acid shows uptake by hepatocytes through a canalicular multispecific organic anion transporting polypeptide 1B3 (OATP1B3) as early as 90 s after contrast injection, but this process takes several minutes before all contrast is taken up by hepatocytes. Thus, gadoxetic acid “transitates” from interstitial space to intracellular space. That is why we refer to this phase as the transitional phase, indicating the transition of gadoxetic acid from the extra-cellular space to the hepatocellular space (Figures 1 and 2). In contrast, extra-cellular contrast materials are equally distributed between vascular spaces and interstitial spaces. Hepatocellular uptake of gadoxetic acid explains higher signal intensity of liver parenchyma with gadoxetic acid than with extracellular contrast materials. Earlier elimination of gadoxetic acid from the vessels leads to earlier de-enhancement and, therefore, lower signal intensity.
intensity of intrahepatic vessels with gadoxetic acid than with extra-cellular contrast materials (Figure 2).[39]

Hepatobiliary phase is acquired 10–20 min after the start of contrast injection. Since the injection of gadoxetic acid does not compromise tissue contrast on T2-weighted images and diffusion-weighted images, these sequences can be acquired in the interval between the 3 min phase and the hepatobiliary phase, thus reducing the total examination time.[40–42] DW images can help to differentiate hypovascular HCC from high-grade dysplastic nodules and can predict the progression of hypovascular hypointense nodules on hepatobiliary phase into hypervascular HCC.[43,44] That is, hyperintensity on high-b-value DW images suggests a diagnosis of HCC and is strongly associated with progression of hypovascular nodules into hypervascular HCC.[43,44]. The adjunct of DW images, however, does not significantly improve the diagnostic accuracy of MRI with hepatobiliary contrast materials in the detection of HCC.[45,46]. Most small HCCs are imperceptible on DW images because they have cellular density and microscopic architecture relatively similar to that of surrounding cirrhotic liver.[46].

DIFFERENCES IN PHASES OF ENHANCEMENT BETWEEN GADOXETIC ACID AND EXTRA-CELLULAR CONTRAST MATERIALS

Although gadoxetic acid allows dynamic imaging during the hepatic arterial, portal venous, and 3 min phases, some enhancement characteristics are different from those of extracellular contrast materials[1,39] (Figure 2). Gadoxetic acid shows a biphasic enhancement pattern in the liver[1]. The first phase (arterial + portal venous) is due to distribution in the vascular compartment. The second phase is due to hepatocellular uptake of gadoxetic acid by the canalicular multispecific OATP1B3 and starts 90 s after injection.[1]. Extra-cellular contrast materials distribute in the extracellular fluid compartments, and, as the name implies, they are not taken up by the hepatocytes.[1]. Liver enhancement peaks on portal venous phase and then decreases.[39]. Vascular enhancement is higher and longer with extracellular contrast materials than with gadoxetic acid.[39]. It has been reported that, on hepatic arterial phase, aorta and liver parenchymal enhancement is weaker.[39]. Since most HCCs are hypervascular, this can influence their detection and characterization.[1,39]. On portal venous phase, the signal intensity of liver parenchyma is comparable between gadoxetic acid and extra-cellular contrast materials, but the signal intensity of portal vein is lower with gadoxetic acid than with extra-cellular contrast materials.[39]. Thus, the evaluation of portal and hepatic veins can be suboptimal with gadoxetic acid.[39]. Since HCC invasion into portal or hepatic vein and portal vein thrombosis influence treatment options and can preclude surgical resection and liver transplantation, vascular evaluation can reduce the advantages of gadoxetic acid.

DIFFERENCES IN PHASES OF ENHANCEMENT BETWEEN CIRRHOTIC AND NORMAL LIVER WITH GADOXETIC ACID

Cirrhosis is characterized pathologically by distortion of hepatic architecture due to marked bridging hepatic fibrosis and regenerative nodule formation.[47]. The number of normal hepatocytes is reduced, and biliary excretion is impaired.[34,48]. Cirrhosis alters liver perfusion with a reduction in portal inflow and a compensatory increase of arterial inflow.[11]. Thus, on hepatic arterial phase, liver enhancement is higher in cirrhotic patients than in normal-liver patients.[49]. On portal venous phase, however, liver enhancement is superimposable in cirrhotic patients and normal-liver patients.[49]. At 3 min and in the hepatobiliary phases, liver enhancement is higher in normal patients than in cirrhotic patients and shows an inverse correlation with the severity of cirrhosis.[49]. This is because hepatic fibrosis and the reduction in the number of functioning hepatocytes decrease the hepatocellular uptake of gadoxetic acid.[49]. Pharmacokinetic analysis demonstrated that liver signal intensity shows a stepwise increase from the hepatic arterial phase to the hepatobiliary phase in patients with normal liver and in patients with Child-Pugh class A and B cirrhosis (Figure 1); on the other hand it does not significantly change from portal venous phase to 20 min hepatobiliary phase in patients with Child-Pugh class C cirrhosis.[49] (Figure 3). The consequence is that oftentimes, at 20 min, the vessels will not be “dark” enough in patients with Child-Pugh class C cirrhosis, resulting in a suboptimal hepatobiliary phase. Thus, in our practice, acquisition of hepatobiliary phase beyond the conventional 20 min delay may be useful in patients with impaired hepatic function in order to allow the hepatocytes more time to take up contrast from the extracellular space.[40,51]. Conversely, in normal-liver patients, a hepatobiliary delay of 10 min after gadoxetic acid injection is sufficient.[52]. Unlike normal liver, cirrhotic liver can show heterogeneous enhancement on the hepatobiliary phase, which can further complicate the detection and characterization of hepatic nodules.[49]. The heterogeneity directly correlates with Child-Pugh class.[49]. Enhancement of biliary tree is delayed in patients with cirrhosis compared with normal-liver patients.[48].

Tschirch et al.[52] compared the visualization of biliary tree between cirrhotic patients and normal-liver patients and found that 16/40 (40%) cirrhotic patients showed sufficient visualization of the biliary tree within 30 min of injection, and 21/40 (53%) cirrhotic patients showed sufficient visualization of the biliary tree within 180 min of injection. In contrast, in their series, all
normal-liver patients showed sufficient visualization of the biliary tree within 30 min of injection\cite{48}.

**ADEQUACY OF HEPATOBILIARY PHASE**

In patients with normal hepatic function, gadoxetic acid is equally eliminated by biliary excretion and glomerular filtration\cite{6}. Impaired hepatic function results in a compensatory increase of renal elimination and more prolonged plasma half-life of gadoxetic acid in cirrhotic patients than in normal-liver patients\cite{36}. The consequence is typically a decrease of contrast between liver parenchyma and portal vein\cite{33}. Visual evaluation of the signal intensity of the liver relative to the portal vein or kidney can help radiologists assess adequacy of the hepatobiliary phase\cite{34,38}. Specifically, brighter signal intensity of the liver parenchyma compared with the portal vein and kidney indicates an adequate hepatobiliary phase, while persistent contrast within the portal vein and brighter or equal signal intensity of the kidney compared with the liver parenchyma indicates an inadequate hepatobiliary phase\cite{36,39} (Figures 3 and 4). Opacification of the biliary tree shows no correlation with the severity of cirrhosis and cannot be used alone to evaluate adequacy of the hepatobiliary phase\cite{48} (Figure 4).

The uptake of gadoxetic acid does not depend only on the hepatic function but also on the hepatic blood flow\cite{33}. Motosugi et al\cite{33} reported that most patients with Child Pugh Class A cirrhosis and inadequate hepatobiliary phase had considerable arterial-portal and portal-systemic shunts. The shunts decrease the hepatic blood flow and hepatic retention of gadoxetic acid\cite{33}. Other causes of reduced hepatobiliary phase enhancement include severe steatosis (Figure 5), hepatic fibrosis, and iron overload\cite{54-57}. An inadequate hepatobiliary phase may impair detection and characterization of focal liver lesions because the contrast between focal liver lesions and the liver parenchyma is reduced\cite{58}. These patients should be evaluated with alternative modalities, such as contrast-enhanced CT and contrast-enhanced ultrasound, in order to avoid misdiagnosis. To date, however, no liver function test can predict whether the hepatobiliary phase result will be adequate.

Recent studies have demonstrated that increasing the flip-angle from 10°-15° to 30°-40° can improve detection and conspicuity of focal hepatic lesion,
particularly of small lesions\textsuperscript{[44-46]}. Larger flip angle maximizes T1-contrast and results in better differentiation between tissues with short T1-relaxation times, such as liver parenchyma with gadoxetic acid uptake and tissues with long T1-relaxation times, such as lesions without functioning hepatocytes\textsuperscript{[59-61]}. Larger flip angle, however, increases specific absorption rate (SAR) in patient tissue\textsuperscript{[59]}. 

CONCLUSION

Gadoxetic acid enhanced liver MRI is emerging as a powerful tool in the diagnostic workup of cirrhotic patients and provides unique information related to lesion vascularity and hepatobiliary function. Use of gadoxetic acid improves detection and characterization of focal liver lesions, and hepatocellular uptake can be used as a measure of liver function. Thus, radiologists involved in liver imaging need to be familiar with the state-of-art MRI study protocol of the liver and the unique characteristics of gadoxetic acid.

REFERENCES


Quantitative evaluation of liver function with use of gadoxetic acid-enhanced MR imaging: role in imaging the hepatocellular carcinoma.


Gadoxetic acid-enhanced MRI of cirrhotic liver

Agnello F et al.

**References**


