

Contrast Media for Liver MRI: Which One to Choose?
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Overview: In this lecture, I will provide an overview of the different available gadolinium-based contrast agents, with specific attention on dynamic contrast enhanced imaging and delayed hepatobiliary phase imaging. The dual blood supply of the liver will be reviewed and its importance on understanding the detection and characterization of focal liver lesions. The behavior of the dual blood supply will be exploited with extracellular gadolinium-based contrast agents using rapid dynamic T1-weighted imaging for liver lesion characterization. Further, we will discuss the use of hepatobiliary contrast agents that take up gadolinium into functioning hepatocytes and how this behavior can be exploited on delayed T1-weighted imaging for liver lesion characterization, as well as biliary imaging. The chemical composition, relaxivity, pharmacokinetics of these agents, and how these properties may impact the choice of contrast agent for a particular application, will be discussed. Modifications to imaging protocols that may be helpful for specific contrast agents will be discussed, including strategies for optimization of delayed hepatobiliary imaging. Finally, a set of guidelines currently in use at the University of Wisconsin for choosing between an extracellular contrast agent and a hepatobiliary contrast agent will be provided as a “cheat sheet” to assist users in their choice and dosing of different contrast agents for liver imaging.

Dual blood supply of the liver: The liver is unique in that it is one of the few organs in the body with a dual blood supply, specifically the hepatic artery which is a branch of the celiac axis / aorta, and the portal vein, which routes venous drainage from the gut and the spleen into the liver. Under normal circumstances, the hepatic artery provides approximately 20-25% of the total blood supply to the liver with the portal vein providing the remaining 75-80%. Blood flow from the hepatic arterioles and portal venules enters hepatic sinusoids at the level of the portal triad within a hepatic lobule. Blood enters the hepatic sinusoids and filters to across the hepatic lobule and collects in the hepatic venule, for subsequent drainage into the hepatic veins, inferior vena cava and right atrium. In the presence of focal hepatic pathology, such as a malignant hypervascular tumor, the hepatic arterial blood supply is commonly parasitized such that the majority of the tumor blood supply derived from the hepatic artery. These so called “hypervascular” lesions can be detected through dynamic contrast enhanced imaging, particularly in the late arterial phase when hypervascular tumors are avidly enhancing, while the back ground liver has yet to enhance. Subsequent washout or equilibration of these lesions provides additional important characterization of these tumors. Finally, the blood pool phase at 2-5 minutes is extremely helpful for additional characterization, particularly for characterization of lesions of vascular origin such as hemangiomas. Conventional extracellular gadolinium-based contrast agents provide an excellent means of performing dynamic contrast enhanced imaging in combination with rapid breathhold 3D fast saturated spoiled echo T1-weighted imaging

techniques. Further, high relaxivity agents which increase the amount of T1 shortening during the contrast bolus provide the advantage of greater SNR and CNR to improve lesion detection and confidence of characterization.

Hepatobiliary phase: Contrast agents that are taken up differentially in to functioning hepatocytes, in comparison to normal cells of non-hepatocyte origin or abnormal cells of tumors such as malignancy can provide excellent SNR and CNR for lesion detection and characterization. Such agents include the use of superparamagnetic oxides (SPIOs) which preferentially are taken into Kupffer cells (macrophages that reside in the liver). Using T2* weighted imaging, areas of normal liver that contain Kupffer cells that have taken up as SPIOs appear dark while lesions with abnormal cells such as metastases ie., non-hepatocytes, will remain bright. Unfortunately, although SPIOs are FDA approved, they are no longer available in the US market. Further, the side effects of some agents limited patient acceptance and practical widespread use. Newer agents that may be available on the market soon, may address these limitations. Therefore, in this talk, we will focus the discussion on the use of new hepatobiliary gadolinium-based agents that rely on a similar principle for characterization of liver lesions.

Available contrast agents: There are five broad categories of contrast agents which have been described as liver imaging for MRI. These include:

Superparamagnetic oxides (SPIOs): As discussed above, the use of SPIOs has been described in combination with T2* weighted imaging for detection and characterization of focal liver lesions. By exploiting the differential uptake of SPIOs into normal liver, via Kupffer cells, detection and characterization of liver lesions is possible. The primary agent that is FDA approved in the United States is Feridex (Bayer Healthcare, Wayne, NJ). Due to relatively low interest, likely resulting from a well known side effect of back pain during administration, as well as the inconvenience of using these agents (they require approximately 30 minutes of infusion), these agents are no longer available on the market. Related SPIO agents in Europe eg. Resovist (Bayer Healthcare, Berlin, Germany) are still in use and may be available in the United States in the future. Due to their low availability, however, they will not be discussed further in this lecture.

1. Extracellular gadolinium contrast agents: The EC-GBCAs have been the mainstay of dynamic contrast enhanced imaging during the last 20 years. These agents include gadopentetate dimeglumine (Magnevist), gadoteridol (ProHance), gadodiamide (Omniscan), gadoversetamide (OptiMARK), and gadoteric acid (Dotarem, Guerbet, Paris, France). Further, a new high concentration gadolinium-based contrast agent, gadobutrol (Gadovist, Bayer Healthcare, Berlin, Germany), has recently been introduced into the US market. Overall, all of the use agents overall have an excellent safety profile (please see discussion below regarding safety and NSF) and have a similar pharmacokinetics, although with some minor differences in relaxivity. The pharmacokinetic differences between these agents are insignificant and are more based on differences in relaxivity, local preference, safety profile and cost considerations. They provide an excellent means of enhancement of the liver during the dynamic phase in combination with fat-suppressed rapid T1-weighted 3D spoiled gradient echo methods. The typical dose for extracellular gadolinium contrast agents is 0.1 mmol/kg, although

lower doses, such a 0.05 mmol/kilogram of high relaxivity agents may be appropriate. All extracellular gadolinium contrast agents are excreted primarily through the kidneys with little or no hepatic excretion,

2. **Intravascular gadolinium-based contrast agents:** Recently, an intravascular gadolinium-based contrast agent was approved in the United States, although it has been in use for several years in Europe. This agent, gadofosveset trisodium (Ablavar, Lantheus Pharmaceuticals, Boston, MA; Vasovist, Bayer Healthcare, Berlin, Germany) has a degree of albumin binding then slows the tumbling rate, and therefore greatly increases its relaxivity. The approved indication in the United States for Ablavar is vascular imaging, and there are relatively few publications on the use of intravascular contrast agents for liver imaging. It has potential for high-resolution steady state arterial, portal venous and hepatic venous imaging in the liver as well as the potential for quantitative perfusion imaging. There are few / no reports on the use of this agent for liver imaging, and therefore it will not be further discussed in this lecture.
3. **Primary gadolinium-based contrast agents:** Mangafodipir trisodium (Teslascan, GE Healthcare, London, UK) is a manganese based hepatobiliary contrast agent that is rapidly taken up into hepatocytes and subsequently excreted in the bile. There was significant interest in this agent in the 1990s for liver lesion characterization as well as biliary imaging on delayed imaging. Although this agent is FDA approved, it has been withdrawn from the market largely due to the lack of interest, and some concerns regarding side effects. The lack of interest is likely related to the fact that mangafodipir performs poorly during the dynamic contrast enhancement. For these reasons it will not be discussed further in this lecture.
4. **Mixed extracellular hepatobiliary gadolinium-based contrast agents:** there are currently two gadolinium-based contrast agents with mixed extracellular and hepatobiliary contrast behavior. These include:
 - a. Gadobenate dimeglumine (Multihance, Bracco Diagnostics, Princeton, NJ) is a high relaxivity gadolinium-based contrast agent with a variety of uses including imaging in the CNS and other regions of the body. It has gained wide acceptance for use in the liver due to its high relaxivity and excellent contrast enhancement patterns and high SNR / CNR performance during dynamic contrast enhanced imaging. There are numerous reports in the literature describing the use of Multihance for liver imaging, although it is important to note the liver imaging is an off-label use of this agent. Interestingly, approximately 4-5% of Multihance is taken up into hepatocytes and subsequently excreted into the bile. This has lead to a variety of applications using Multihance for hepatobiliary imaging including T1-weighted MR cholangiography and the characterization of liver lesions such as focal nodular hyperplasia (FNH) versus hepatic adenoma (HA). It has also been used for the detection of metastases and the detection and characterization of hepatocellular carcinoma. The main disadvantage of Multihance is that the hepatobiliary phase peaks at approximately 1-2 hours, typically too long for a single setting to perform delayed T1-weighted imaging. For this reason, delayed

imaging typically requires a short interval follow-up study at 1-2 hours after the initial injection of contrast. Such images provide excellent additional information for biliary imaging and lesion characterization but do provide logistical challenges in busy clinical practices. The typical contrast dose for liver imaging is 0.1 mmol/kg although there are multiple reports of using lower doses such as 0.05 mmol/kg, particularly at higher field strengths where the improved SNR of 3T can compensate for the decreased enhancement from a lower dose.

- b. Gadoteric acid (Eovist, Bayer Healthcare, Wayne, NJ; Primovist, Bayer Healthcare, Berlin, Germany) was introduced to the United States in July 2008 as a new liver specific gadolinium-based contrast agent. It was in use for several years prior to this in Europe and elsewhere in the world. It has a mixed extracellular and hepatobiliary contrast enhancement pattern. Approximately 50% of Eovist is taken up into the liver and subsequently excreted into the bile. The remaining 50% is excreted through the kidney. This behavior has multiple implications and dramatically changes the pharmacokinetics of the agent, including during the dynamic phase. Specifically, the late arterial phase with Eovist is very similar to Multihance as well as extracellular gadolinium-based contrast agents, however, as early as the portal venous phase, there is obvious and apparent uptake of gadolinium into the hepatocytes. This is very apparent at approximately 5 minutes and peaks at approximately 20 minutes when there is significant uptake of contrast into hepatocytes and excretion into bile ducts. Further, as a result of the rapid uptake into the liver, the concentration of Eovist in the blood pool rapidly decreases, much faster than extracellular agents and Multihance. It is important to understand these differences in behavior of the pharmacokinetics in order to correctly identify a variety of liver lesions. For example, hepatic hemangiomas behave very similarly in the arterial portal venous phase using Eovist, however, given the factor that the blood pool is rapidly being cleared of gadolinium and the liver is rapidly taking up gadolinium, hemangiomas typically appear relatively hypointense to liver, in contradistinction to hemangiomas seen with extracellular agents or with Multihance where it appears relatively hyperintense. With all contrast agents, in the equilibrium phase, the hemangiomas will follow the blood pool as expected by its underlying physiology. Understanding the physiology of a lesion and the coupling with the pharmacokinetics of a particular contrast agent is critical in understanding the imaging appearance of a lesion. These pharmacokinetics will be explored during this lecture.

So which contrast agent do I use? As a general philosophy, I recommend using an extracellular contrast agent (eg. Magnevist) or a high relaxivity agent that has a predominance of extracellular behavior (eg. Multihance) for applications that predominantly require information to be obtained during the dynamic contrast enhanced phase or for applications in the abdomen that require or necessitate excellent visualization of the vascular. Applications that focus primarily on biliary visualization as well as liver lesion where distinction between hepatocytes and lesions not containing hepatocytes is of primary importance, would favor the use of an agent with strong hepatobiliary behavior, such as Eovist. Please see the end of the syllabus for the current

guidelines at the University of Wisconsin that are used to decide which contrast agent to use for liver imaging. A particular advantage of using Multihance (compared to a pure extracellular agent) is, that should a case appear where delayed imaging is required but was not anticipated, delayed imaging at 1-2 hours can still be obtained containing hepatobiliary information thus capturing the hepatobiliary behavior. However, when it is anticipated that delayed hepatobiliary imaging should be performed, Eovist is preferred. Finally, it is important to note that for applications **not** related to the liver or bile ducts, Eovist should not be used.

Timing and protocol modifications: The basic protocol for liver imaging at the University of Wisconsin includes:

- Localizers
- In- and opposed- phased imaging
- T2-weighted imaging
- Pre, late arterial, portal venous and equilibrium phase at fat-saturated T1 weighted 3D spoiled gradient echo imaging during the infusion of contrast.

This is the basic protocol that is used in combination with extracellular contrast agents as well as Multihance. If delayed imaging is needed after injection of Multihance, the patient is brought back to the department between 1-2 hours and additional T1-weighted imaging is performed. This is typically performed with a slightly higher flip angle, approximately 20-30°, in order to improve the SNR and CNR performance because gadolinium is taken up into hepatocytes and excreted into the bile ducts with relatively high concentration with relatively short T1. Increasing the flip angle slightly provides great improvement in the overall image quality of these delayed images.

When using Eovist, the protocol can be modified slightly. First, a 20 minute delayed image should **always** be performed when using Eovist in order to capture a good hepatobiliary phase. In addition, we commonly perform a 5 minute delayed hepatobiliary phase which provides excellent visualization of the liver with excellent enhancement of the hepatocytes, but without significant biliary excretion. In order to improve overall sequence efficiency, it has been documented by multiple investigators that T2-weighted imaging can be performed after the dynamic phase of contrast injection during the period prior to the 20 minute delayed Eovist enhanced images. It is critical to note, however, that heavily T2-weighted MRCP imaging should always be performed **before** the administration of gadoxetic acid. This occurs because even small amounts of gadoxetic acid within the bile result in significant T2 shortening that will cause significant T2 shortening of the bile, and will corrupt MRCP images. This is usually of little consequence for standard T2-weighted imaging because the concentration of gadolinium in the liver is not sufficient to cause significant T2 shortening. In principle, in- and opposed- phase imaging can also be performed after the administration of Eovist acid, however, this is a relatively rapid pulse sequence requiring one or two breathholds and we usually perform these sequences pre-contrast. Finally, if you include diffusion weighted imaging in your protocol, it is important to note that all gadolinium agents will increase the apparent diffusion coefficient (ADC) slightly. This is of little consequence for qualitative applications, but may be important for quantitative applications. Therefore, I recommend performing DWI before contrast if ADC is important, and before or after, depending on workflow, if only qualitative features of DWI are needed.

When imaging at 20 minutes with Eovist, our group has shown (Nagle, et al., ISMRM 2009) that using a much higher *flip angle of approx 35-40°* provides improved T1-weighting with dramatic improvements in SNR and CNR when using 0.05 mmol/kg of Eovist. On some vendors, the maximum flip angle for T1-weighted 3D spoiled gradient echo imaging is locked at 15° maximum. I recommend using other 3D T1-weighted sequences such as typical MRA pulse sequences that allow a higher flip angle in order to improve the T1-weighting, to maximize the efficacy of this contrast agent on delayed imaging. Considerable improvement in the overall image quality can be obtained by increasing the flip angle. These observations have been confirmed by other groups (Bashir, et al., European Radiology, 2010). When imaging with higher flip angles, the overall SNR of the liver becomes relatively high with dark vessels and lesions of non-hepatocyte origin becoming very dark as well. One useful technique for visualization of these small lesions is the use of minimum intensity projection (minIP), which turns vessels into branching structures while focal lesions remain relatively spherical. I recommend using a 10 mm thin slab minIP reconstructed every 5 mm, reconstructed in 2 planes (axial, coronal) for detection of small liver lesions.

With regard to dose of contrast agent, at our institution, we typically use 0.1 mmol/kg of Multihance. Imaging of the liver with gadobenate is an off label use although 0.1 mmol/kg is a standard dose commonly used for many applications in the body. In our experience, this provides excellent contrast enhancement while also being mindful of reasonable exposure to gadolinium and also mindful of cost considerations. Eovist is FDA approved for characterization of liver lesions when used at a dose of 0.025 mmol/kg, which is the package insert dose. In our experience, as well as confirmed by quantitative studies during the dynamic phase, a dose of 0.025 mmol/kg is inadequate for enhancement of the liver, vascular structure and liver lesions during the dynamic phase. For this reason at our institution, as well as a growing number of institutions, a weight based dose of 0.05 mmol/kg of gadoxetic acid is used. At some institutions, a straight volume of 10 ml (1 bottle) is also used, and may be a good balance of cost and sufficient dose. From a safety and consistency perspective, however, I would recommend using a weight based dosing of 0.05mmol/kg.

Safety considerations: it has been several years since the FDA issued its first warnings on the use of gadolinium-based contrast agents in patients with acute and chronic renal failure. As a result of judicious use of contrast agents and avoiding the use of gadolinium-based agents in patients with renal failure when appropriate, as well as a general awareness of nephrogenic systemic fibrosis (NSF), there have been no reported cases in the 2-3 years. Regardless, the FDA warning remains in effect and the use of all gadolinium-based contrast agents should be avoided when possible to avoid this potentially lethal condition. In many cases, however, the diagnostic information that can be obtained from these gadolinium-based agents far outweighs the small risk of developing NSF and it may be highly appropriate to administer contrast agent despite the FDA warning. Recently, both the FDA and the American College of Radiology (ACR) issued modified recommendations on the use of gadolinium-based contrast agents based on differences in the incidence of NSF with specific contrast agents. These were divided in to three broad categories of agents as follows:

Group 1: agents associated with the greatest number of NSF cases: Magnevist (gadopentetate dimeglumine), Omniscan (gadodiamide), and Optimark (gadoversetamide)

Group 2: agents associated with few, if any, unconfounded cases of NSF: Multihance (gadobenate dimeglumine), Prohance (gadoteridol), Dotarem (gadoteric acid), Gadobutrol (gadobutrol).

Group3: agents that have only recently appeared on the market in the United States: Ablavar (gadofosveset), Eovist (gadoxetic acid).

The ACR and FDA recommend that Group 1 agents not be used in any circumstance in patients with renal failure and, if gadolinium agents must be used, to rely on those listed in Group 2 agents. Group 3 agents are relatively new and there are limited data, however, no unconfounded cases of NSF have been reported with Group 3 agents. Of particular note for Eovist, the lower dose in combination with the dual excretion pathway (renal, hepatic) provides a mechanistic way through which this agent may be safer; however, there is no evidence that conclusively demonstrates this. Similarly, the 4-5% hepatic excretion of Multihance may also confer additional safety in patients with renal failure by providing an alternative pathway; again, however, there is no inclusive evidence to demonstrate that this mechanism confers additional safety.

Conclusions: the choice of contrast agents is highly varied with a wide number of important and interesting agents available for both dynamic and delayed hepatobiliary imaging of the liver with MRI, providing a large tool box to facilitate accurate detection and characterization of MRI. In combination with a rich variety of pulse sequences and inherent contrast mechanisms, these various contrast agents have played an instrumental role in establishing MRI as the gold standard for evaluation of hepatobiliary diseases. It is my firm belief that a single contrast agent is not sufficient to maximize the full potential benefit of MR for detection and characterization of liver lesions. I recommend that clinicians consider the use of two agents, one that is primarily extracellular in behavior, with which they are comfortable for dynamic phase imaging, and a second agent with hepatobiliary action for delayed imaging. At our institution we have chosen Multihance as our primary extracellular contrast agent, noting that Multihance has some hepatobiliary behavior, and Eovist as our primary hepatobiliary agent, noting that it does have good dynamic contrast enhancement behavior, particularly at 0.05mmol/kg. This is one possible solution, however, other available agents have been demonstrated to provide excellent quality contrast enhancement imaging of the liver and multiple factors including loco-regional needs and economic considerations must be considered when deciding which agents to choose.

Clinical Guidelines for Gadolinium Based Contrast Agents for Hepatobiliary Imaging with MRI at UW-Madison

Background: the following guidelines for liver MRI contrast enhanced imaging are based on the reported literature and our experience using “Eovist”, a new hepatobiliary gadolinium based contrast agent. It is intended as a general guideline for residents and fellows protocoling studies, to decide when Eovist should be used. It is intended as a guide to improve uniformity of practice, while balancing special needs of particular patients, and to be mindful of the relative cost of Eovist (cost of Eovist is higher than other agents).

Imaging Protocol: when Eovist is used, at least one high resolution T1 weighted sequence should be acquired at ≥ 20 minutes. High flip angle (30-40°) with high spatial resolution should be used, preferably with navigators.

Dose: the FDA approved package insert dose of Eovist is 0.025mmol/kg. Quantitative data demonstrate that 0.05mmol/kg provides adequate dosing for dynamic imaging. Dosing should be weight-based to avoid inadvertent high doses in small patients. If calculated dose 1ml greater than nearest bottle volume, dose should be reduced to reduce cost. eg. 10ml is OK if the calculated dose is 11ml.

General Principle: Eovist is preferred for bile duct imaging and lesion characterization using delayed imaging; Multihance is preferred for vascular imaging and characterization of lesions using dynamic imaging

General Applications / Indications:

1. Cirrhotic Liver

Major indications: HCC screening/evaluation, complications of portal hypertension

Recommended Agent: Multihance 0.1mmol/kg

Alternative Agent: Eovist 0.05mmol/kg acceptable for specific problem solving of a particular focal liver lesion (eg. atypical nodule)

2. Metastatic Disease

a. With prior imaging (MRI, CT, and /or US)

Major indications: follow known metastatic disease, improve characterization of extent of disease seen on other imaging, liver segment volume measurements prior to resection

Recommended Agent: Eovist 0.05mmol/kg

Alternative Agent: Multihance 0.1mmol/kg with delayed imaging acceptable, but Eovist preferred

b. No prior liver imaging

Major indications: known malignancy, no known metastatic disease (“rule out liver metastases”)

Recommended Agent: Multihance 0.1mmol/kg

Alternative Agent: Eovist 0.05mmol/kg acceptable, but Multihance preferred. Eovist acceptable in some circumstances

3. Pre-liver transplantation

Major indications: evaluate liver anatomy including vascular anatomy, unsuspected pathology (eg. HCC, PV thrombus)

Recommended Agent: Multihance 0.1mmol/kg

Alternative Agent: Eovist should not be used only except in unusual circumstances, eg. in combination with other imaging (eg. CT)

4. Complications of Liver Transplantation

a. Biliary Complications

Major indications: biliary leak, anastomotic stenosis, etc

Recommended Agent: Eovist 0.05mmol/kg with Roux-En-Y protocol

b. Vascular Complications

Major indications: hepatic arterial or portal venous stenosis/occlusion/thrombosis

Recommended Agent: Multihance 0.1mmol/kg

c. Biliary and Vascular complications suspected (uncommon)

Major indications: biliary leak/stenosis, vascular complication

Recommended Agent: Multihance 0.1mmol/kg for dynamic phase. Consider Eovist 0.025mmol/kg immediately after dynamic phase imaging with Multihance, followed by Roux-En-Y protocol

5. Living Related Liver Donor (uncommon)

Major indications: Liver & vascular anatomy, liver segment volumes, if CT is contraindicated (CT is preferred modality for this indication)

Recommended Agent: If MRA is not needed, use Eovist 0.05mmol/kg. If MRA is needed, use Multihance 0.1mmol/kg. Consider giving Eovist 0.025mmol/kg after dynamic phase imaging with Multihance.

6. Biliary Disease

a. Primary Sclerosing Cholangitis

Major indications: evaluate for complications of PSC, including strictures, biliary obstruction, stones, cholangiocarcinoma

Recommended Agent: Eovist 0.05mmol/kg

Alternative Agent: Multihance 0.1mmol/kg with delayed imaging. Eovist highly preferred.

b. Other Biliary Disease

Major indications: intrahepatic biliary stones, bile leak (eg. trauma), choledochal cyst / Caroli’s disease. Generally, prior imaging with MRI, CT or US is available but is not necessary, depending on clinical history

Recommended Agent: Eovist 0.05mmol/kg

Alternative Agent: Multihance 0.1mmol/kg with delayed imaging. Eovist highly preferred.

7. Characterization of FNH vs Adenoma

Major indications: incompletely characterized focal liver lesion with high suspicion for FNH or hepatic adenoma. Prior imaging with MRI, CT or US required. Prior MRI not required.

Recommended Agent: Eovist 0.05mmol/kg

Alternative Agent: Multihance 0.1mmol/kg with delayed imaging

8. Characterization of Liver Lesion (Other)

Major indications: incompletely characterized focal liver lesion felt unlikely to be FNH or hepatic adenoma. Prior imaging with MRI, CT or US is generally available, but not strictly required, depending on clinical history.

Recommended Agent: Multihance 0.1mmol/kg

Alternative Agent: Eovist 0.05mmol/kg is a very reasonable alternative depending on clinical scenario

9. Evaluation of non-hepatic abdominal pathology or symptomatic patient with no prior imaging / relevant history

Recommended Agent: Multihance 0.1mmol/kg. Should not use Eovist for non-hepatobiliary applications.