A Review of MR Contrast Agents

Why Gadolinium Matters Today

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Why Gadolinium Matters Today

Summary

Until approximately 2006, gadolinium-based contrast agents (GBCAs) as a class were deemed safe for patients, particularly in patients with renal impairment. However, several events have occurred since then that have altered the perception that all GBCAs are equally safe. These include the identification of nephrogenic systemic fibrosis (NSF) as a serious potential adverse event (AE), and an appreciation that gadolinium (Gd) is retained in brain, bone, and other soft-tissue organs, with unknown long-term clinical consequences. Therefore, to perform an effective, individualized risk–benefit analysis, radiologists should be familiar with the differences in properties and associated risks among GBCAs and how they relate to GBCA selection for specific applications. Here we present a summary of discussions that occurred at an Expert Panel Forum on Advancing Clinical Practice in MR Imaging, in which the experts explored the real and perceived risks associated with GBCA use. They also addressed when contrast use is appropriate and necessary and, when deemed necessary, the best practices for its use in select applications, including neuroradiology/stroke imaging, breast MR screening, and abdominal imaging. Practical administrative and cost considerations related to contrast use in the MR suite were also reviewed.

Learning Objectives

At the conclusion of this activity, participants should be able to:

- Explain recent events that have occurred that have altered the perception that all GBCAs are equally safe, including NSF and Gd retention
- Describe the various available GBCAs and their properties, with emphasis on those properties that may impact safety
- Review the relative risks and benefits of the available macrocyclic and linear GBCAs
- Summarize best practices for GBCA use in select applications, including neuroradiology/stroke imaging, breast MR screening, and abdominal imaging
- Define administrative and cost considerations that may relate to contrast use in the MR suite

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Why Gadolinium Matters Today

Gadolinium-based contrast agents (GBCAs) were first approved for magnetic resonance imaging (MRI) in 1988 based on their ability to improve soft-tissue contrast relative to noncontrast exams.[1] Since then, GBCA use has greatly expanded, and GBCAs are now used routinely in approximately 45% of MRI exams in the United States.[2,3] Until recently, available general-use GBCAs consisted of the conventional-relaxivity simple linear agents Magnevist® (gadopentetate dimeglumine), Omniscan™ (gadodiamide), and OptiMARK™ (gadoversetamide); the high-relaxivity substituted linear GBCA MultiHance® (gadobenate dimeglumine), and three macrocyclic agents: ProHance® (gadoteridol), Gadavist® (gadobutrol), and Dotarem® (gadoterate meglumine).[4-10] (Tables 1, 2) OptiMARK and Magnevist were removed from the market in 2018 and 2019, respectively, while GE introduced Clariscan™ (gadoterate meglumine), a generic version of Dotarem, in 2019.[11]

Until approximately 2006, GBCAs were deemed safe for patients, particularly those with renal impairment.

Table 1. Currently Available Gadolinium-based Contrast Agents[4-11]

GBCA	Generic Name	Structure	Ionicity	Osmolality (mOsm/kg)	Viscosity (cP, 37°C)
Omniscan™	Gadodiamide	Linear	Nonionic	650	1.4
Magnevist®*	Gadopentetate dimeglumine	Linear	Nonionic	1960	2.9
OptiMARK™	Gadoversetamide	Linear	Nonionic	1110	2.0
MultiHance®	Gadobenate dimeglumine	Linear	Ionic	1970	5.3
Dotarem®†	Gadoterate meglumine	Macrocyclic	Ionic	1350	2.4
Gadavist®	Gadobutrol	Macrocyclic	Nonionic	1603	5.0
ProHance®	Gadoteridol	Macrocyclic	Nonionic	630	1.3

*Magnevist was discontinued in the United States in Sept 2019.
†Clariscan, a generic version of Dotarem, was approved by the FDA in Nov 2019.
cP=centipoise; GBCA=gadolinium-based contrast agent.

Moreover, their safety profiles were considered comparable. Because substantial evidence demonstrated that higher doses provided additional diagnostic yield with few associated safety concerns, doses were frequently higher than the standard (approved) 0.1 mmol/kg dose. Double or even triple doses of some agents were routinely used for MR angiography and for specific central nervous system (CNS) applications.[13,14] Today only one GBCA, ProHance, retains a triple-dose (0.3 mmol/kg) indication for MRI of the CNS in adults.[8] Unfortunately, several events have occurred since 2006 that have altered the perception that all GBCAs are equally safe. These include the identification of nephrogenic systemic fibrosis (NSF) as a serious potential adverse event (AE),[15] and an appreciation that gadolinium (Gd) is retained in brain, bone, and soft-tissue organs,[16-19] with unknown long-term clinical consequences.

In this article, we present a summary of discussions from a recent Expert Panel Forum on Advancing

Table 2. Differences in Relaxivity Among GBCAs at 1.5T and 3T[12]

GBCA	r1 ($s^{-1} \cdot mM^{-1}$) @ 1.5T	r1 ($s^{-1} \cdot mM^{-1}$) @ 3.0T
MultiHance®	6.20	5.37
Gadavist®	4.61	4.46
Omniscan™	4.47	3.89
OptiMARK™	4.43	4.24
ProHance®	4.39	3.46
Magnevist®	4.25	3.76
Dotarem®	3.91	3.43

GBCA=gadolinium-based contrast agent.

Table 3. Gadolinium-based Contrast Agent Stability and Nephrogenic Systemic Fibrosis Risk[4-11,20,21]

GBCA	Thermodynamic Stability Log K_{therm}	Conditional Stability Log K_{cond} (pH 7.4)	ACR Group
Omniscan™	16.9	14.9	Group I
OptiMARK™	16.6	15.0	Group I
Magnevist®	22.5	18.4	Group I
MultiHance®	22.6	18.4	Group II
ProHance®	23.8	17.1	Group II
Dotarem®	25.6	19.3	Group II
Gadavist®	21.8	14.7	Group II

ACR=American College of Radiology; GBCA=gadolinium-based contrast agent.

Clinical Practice in MR Imaging. The primary goal of the forum was to explore the real and perceived risks associated with GBCA use and to elucidate the radiologist's role in performing the necessary risk–benefit assessment when considering contrast-enhanced MRI for specific indications. We also address two fundamental issues: 1) when is contrast necessary, and 2) what are the best practices for its use in selected applications, specifically neuroradiology/stroke imaging, breast screening, and abdominal imaging? Finally, we discuss practical administrative and cost considerations related to contrast use in MRI.

Risks vs Benefits of GBCA Use

Although the risks associated with GBCA use can be viewed as the probability of harm, the focus should center on evaluating real risk vs perceived risk. Real risk is evidence-based and determined by the severity and likelihood of harm. GBCAs vary with respect to their structure, stability, ionicity, osmolality, and viscosity, all of which can contribute to the severity and likelihood of harm. (Table 1)

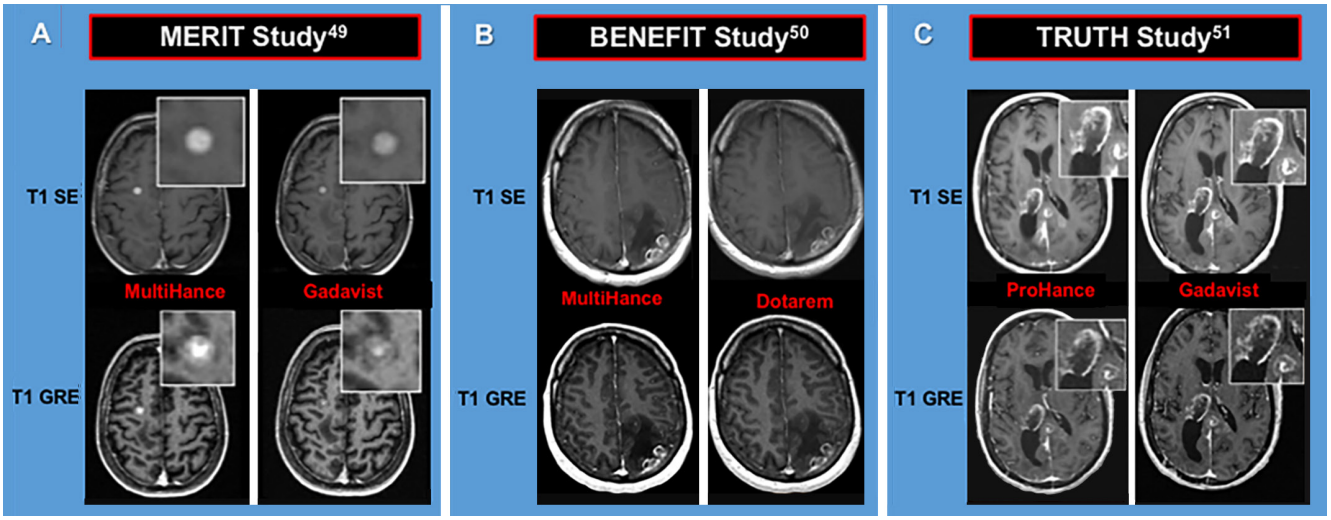
Acute Adverse Events

Based on data provided in package inserts, most AEs associated with GBCAs are mild and non-serious. Serious AEs and allergic reactions requiring hospitalization are extremely rare, occurring in about 0.008% of GBCA administrations.[21] Importantly, the rates and types of AEs are comparable across agents.[4-11] Although contrast extravasation is an indirect safety issue associated with GBCAs, potentially causing pain and swelling at the injection site, this can be limited with GBCAs that have lower viscosity and osmolality that enable greater ease of injection.[20] (Table 1)

GBCA Stability and Dechelation

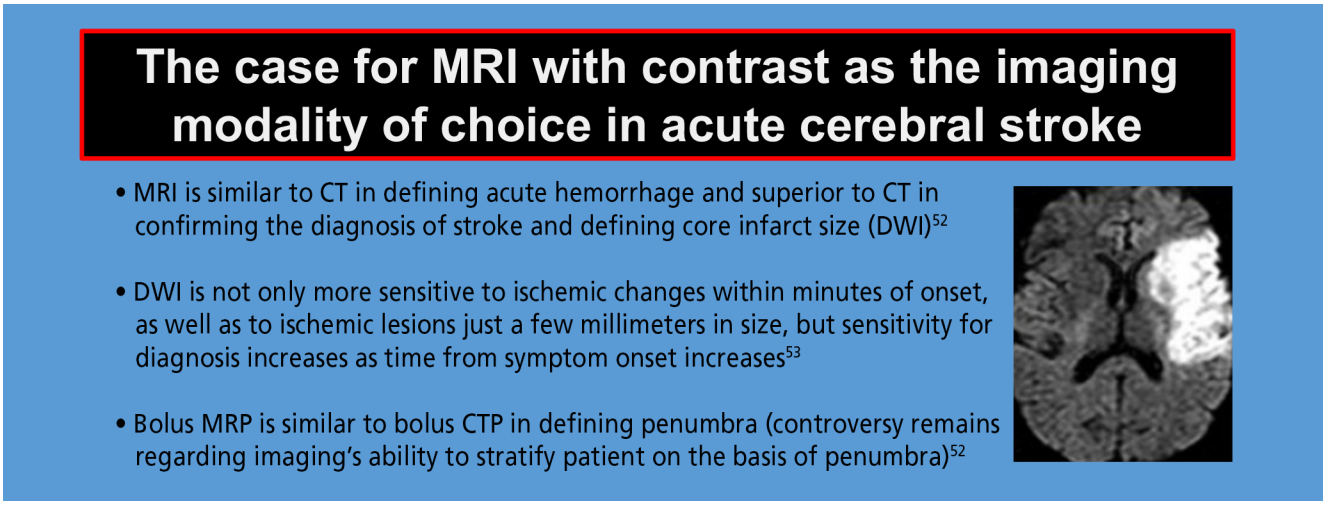
Perhaps the most clinically impactful property of GBCAs relates to their stability and potential for dechelation; ie, release of the Gd ion from the chelate structure. Macrocyclic chelates encircle the Gd ion in a molecular cage, and both in vitro and in vivo data support the greater stability of these GBCAs relative to standard relaxivity linear GBCAs, particularly relative to the nonionic linear GBCAs.[16-18] Nevertheless, there was little recognition of the potential clinical consequences of dechelation until 2006, when it was shown that the combination of severe renal insufficiency/failure, exposure to higher/repeat doses of GBCAs (primarily the least stable simple linear agents), and other less understood factors could lead to NSF in some patients.[15]

Most unconfounded cases of NSF were associated with exposure to the standard-relaxivity simple linear GBCAs, Omniscan and Magnevist; as a result, the American College of Radiology (ACR) designated these agents, along with OptiMARK, as Group I, or high-risk, agents.[21] (Table 3) These agents have since been contraindicated by the US Food and Drug Administration (FDA) for use in patients



GRE=gradient echo; SE=spin echo.

FIGURE 1. *GBCA efficacy for neuro MRI. Based on results from 3 intraindividual crossover studies, the higher relaxivity of MultiHance provided significantly improved lesion enhancement compared with equivalent doses of the macrocyclic GBCAs (A) Gadavist49 and (B) Dotarem,50 and (C) there was no significant difference in efficacy between the same Gd dose of the macrocyclic agents Gadavist and ProHance.51 To view video of Dr. Enterline's full, CE-accredited presentation, please visit Applied Radiology's RADU educational website (https://radu.appliedradiology.org) and select Online Courses.*

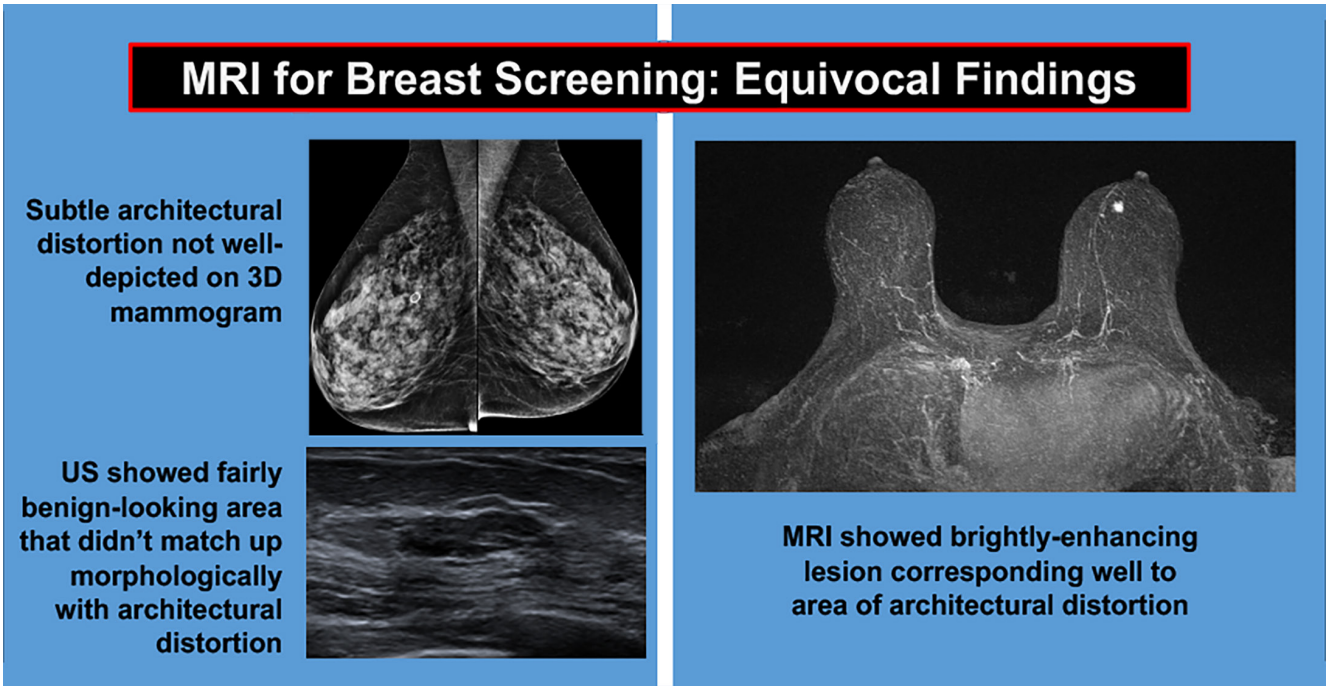


CT=computed tomography; CTP=computed tomography perfusion; DWI=diffusion-weight imaging; MRI=magnetic resonance imaging; MRP=magnetic resonance perfusion.

FIGURE 2. *Imaging acute cerebral stroke – the case for MRI. To view video of Dr. Karis' full, CE-accredited presentation, please visit Applied Radiology's RADU educational website (https://radu.appliedradiology.org) and select Online Courses.*

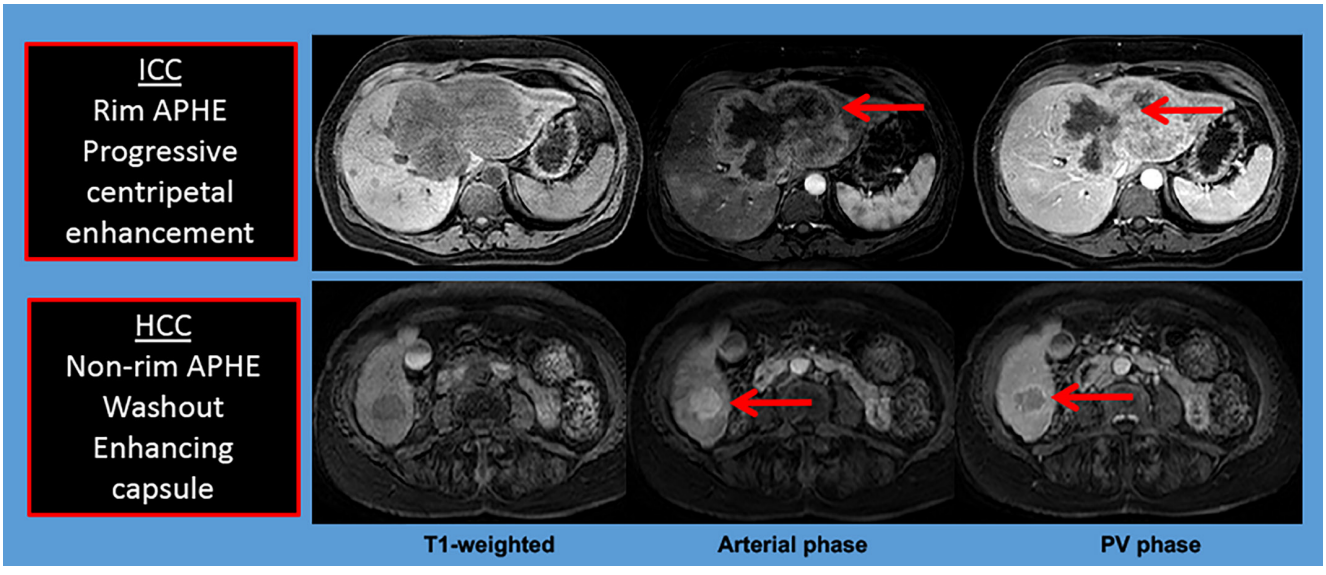
with acute kidney injury (AKI) or chronic, severe kidney disease (ie, an estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2).[4-6] Group II, or low-risk, agents include the higher-relaxivity substituted linear agent MultiHance, and the macrocyclic agents Dotarem, Gadavist, and ProHance.[21]

In 2017, the ACR made renal function screening (either by questioning the patient or measuring serum creatinine) optional for Group II agents in inpatients and outpatients.[21] Elimination of eGFR screening without increasing risk to patients is potentially beneficial in terms of both cost and time efficiency. Conversely, if Group I agents are used, an eGFR should be obtained for inpatients, while outpatients should be asked about their history of conditions that may be associated with reduced renal function.[21] Note that there is a single Group III agent, Eovist® (gadoxetate disodium), a liver-specific MR contrast agent, for which there are



MRI=magnetic resonance imaging.

FIGURE 3. *MRI for breast cancer screening: equivocal mammographic findings/problem solving in a screening 3D mammogram callback. Images courtesy of Dr. James Sancrant. To view video of Dr. Sancrant's full, CE-accredited presentation, please visit Applied Radiology's RADU educational website (https://radu.appliedradiology.org) and select Online Courses.*

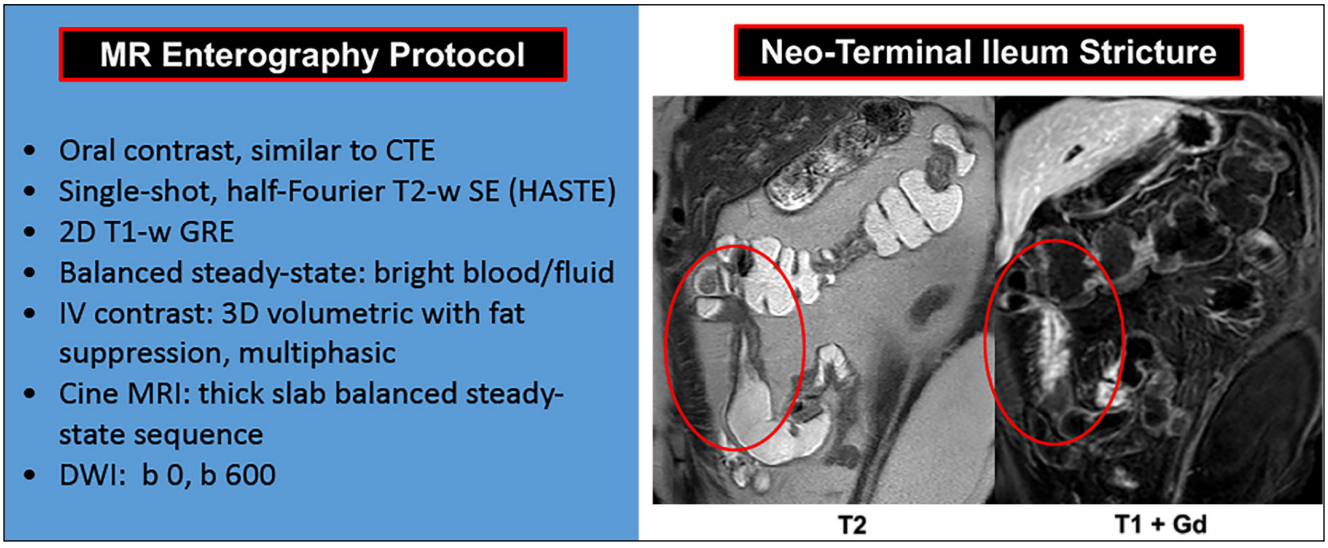


HCC=hepatocellular carcinoma; ICC=intrahepatic cholangiocarcinoma; PV=portal venous.

FIGURE 4. *Use of contrast-enhanced MRI to differentiate mass-forming ICC from HCC. Images courtesy of Dr. Kristen Porter. To view video of Dr. Porter's full, CE-accredited presentation, please visit Applied Radiology's RADU educational website (https://radu.appliedradiology.org) and select Online Courses.*

limited data regarding NSF risk, but for which few, if any, unconfounded cases of NSF have been reported.[21] Changes in clinical practice such as screening high-risk patients for renal dysfunction, use of the lowest effective contrast dose, and use of a Group II GBCA appears to have eliminated NSF risk in patients referred for contrast-enhanced MRI.

A second change with regard to the perceived safety profile of linear vs macrocyclic GBCAs occurred in 2014 with a publication that demonstrated increased signal in the dentate



CTE-computed tomography enterography; DWI=diffusion-weighted imaging; Gd=gadolinium; GRE=gradient echo; SE=spin echo.

FIGURE 5. *Follow up of a patient with recurring Crohn's disease who had already undergone a resection of the terminal ileum. As is typical in Crohn's, the recurring disease occurred in the neo-terminal ileum. The thickened wall of the neo-terminal ileum is evident, with some mucosal high signal intensity on T2, indicating the presence of edema (A); after contrast, there is even greater evidence of stricturing disease (B). Images courtesy of Dr. Jorge Soto. To view video of Dr. Soto's full, CE-accredited presentation, please visit Applied Radiology's RADU educational website (https://radu.appliedradiology.org) and select Online Courses.*

nucleus and globus pallidus on noncontrast T1 MRI scans in patients with a history of having received gadolinium-based contrast.[19] Although this initial study investigated only patients who received Magnevist or Omniscan, subsequent studies found that T1 hypersignal on noncontrast T1 MR images occurred more frequently with linear GBCAs than with macrocyclic agents. This caused many to speculate that, as with NSF, the linear GBCAs dechelate more readily, leading to long-term Gd retention in the brain and body.[23-29] Gd retention has since been identified even after exposure to low GBCA doses in patients with normal renal function,[30-31] and in the presence of an intact blood-brain barrier.[32] This indicates that Gd retention likely occurs to a greater or lesser extent in all patients who receive a GBCA. Among macrocyclic GBCAs, visible hypersignal has been seen so far only after multiple injections of Gadavist and Dotarem.[33-39] Among linear GBCAs, greater Gd retention has been observed after Omniscan than after Magnevist, MultiHance, or Eovist.[22,29,31,32,40-43] Notably, knowledge that Gd is retained in body tissues is not new; several studies have long shown that Gd is retained in bone and body tissues.[16-18]

Although frequently considered a marker for Gd retention, visible T1 hypersignal is actually a very poor indicator. Although many disease conditions unrelated to Gd can cause hyperintensity in the dentate nucleus and globus pallidus, the brain has been shown to retain Gd even in the absence of visible hyperintensity or demonstrable T1 shortening. Unequivocal demonstration of Gd retention comes from tissue sampling studies using inductively coupled plasma mass spectrometry (ICP-MS). Such studies provide far superior sensitivity for quantifying Gd than studies based on analysis of MRI signal intensity.[22]

Using ICP-MS, Murata et al demonstrated the presence of Gd in the brain following administration of all GBCAs available in the U.S. at the time, including macrocyclic agents.[29] Gd was also detected in bone at much higher levels than in the brain.[29] Unfortunately, the study was performed on tissue samples from a relatively small number of human decedents (N=9) who, in some cases, passed away only days after contrast administration. Hence, further confirmatory studies are needed in a larger population. Gd retention studies are performed more easily in animals. Two recent such studies comparing Gd retention among macrocyclic agents 28 days after exposure confirmed that differences do exist, with significantly lower levels of Gd noted with ProHance than with Dotarem and Gadavist in the cerebellum, cerebrum, kidneys, liver, and skin.[44,45] A third study performed in rats demonstrated Gd clearance differences among the macrocyclic agents in the first weeks and months after administration, with ProHance clearing much more rapidly than Gadavist and

Dotarem.[43] This might be clinically significant given that one rat year equates to roughly 30 human years, and might be of particular relevance when imaging very young patients, whose brain and cognitive function are still developing.

In May 2017, the FDA stated that although Gd retention has been observed, no adverse health effects have been identified and no restrictions on GBCA use are warranted. However, the agency cautioned that GBCA use should be limited wherever possible.[46] The FDA also stated that, based on the literature, Gd retention levels appear to be greater with linear agents than with macrocyclic agents.At about the same time, a summit meeting of drug industry representatives, medical professionals, and FDA personnel met to discuss Gd retention and the possible implications and future actions.[47] It was decided that new language would be added to the prescribing information for GBCAs, warning of the potential for Gd retention, particularly with linear agents, and recommending that risk minimization measures be practiced in at-risk populations. Notably, the European Medicines Agency (EMA) position differs markedly from the FDA's, with all simple linear agents removed from the market and leaving only macrocyclic GBCAs available for general use, along with the substituted linear agents MultiHance and Primovist (Eovist) for liver imaging.[48]

With no unequivocal evidence of clinical sequelae from retained Gd, assessing the real risk of Gd retention is difficult. GBCAs have been approved and used routinely in clinical practice for more than 30 years, with some 450 million doses administered worldwide with little acute or long-term adverse reactions. However, until further long-term studies confirm that no adverse clinical outcomes are associated with Gd retention, careful GBCA selection and use is warranted in at-risk populations.

Serial Imaging

Care should be taken in patients requiring serial MRI examinations, particularly those with seizures or multiple sclerosis (MS), and in young women with dense breasts who require MRI for breast cancer screening or monitoring. Contrast should be used primarily in cases where it has the greatest potential to impact patient management. Moreover, macrocyclic GBCA use is considered prudent in such cases to minimize the potential risks of Gd retention.

Pediatric Patients

Most MRI examinations in children require contrast.These include workups of neoplasia, infections, and inflammatory processes, particularly at initial diagnosis, with exceptions for most congenital and/or structural disorders.The potential impact of Gd retention in pediatric patients remains unknown, as long-term data are unavailable. However, logic would dictate, and trends support, that macrocyclic agent use in children would be prudent. In this regard, animal studies have shown ProHance to be cleared more rapidly than Gadavist and Dotarem, resulting in lower levels of Gd retention in the first weeks and months.[43-45] If the human situation reflects that of animals, then the first 5 weeks of rat life would correspond to approximately 3 human years. In these patients, less Gd would be retained if ProHance were used.

On the other hand, whereas all the macrocyclic agents (Dotarem, Gadavist, and ProHance) and the substituted linear agent MultiHance, are approved for use in children older than 2 years of age, only Dotarem, Gadavist, and MultiHance have a neonate indication.[7-10] Among these agents, MultiHance is unique in possessing higher r1 relaxivity, meaning that greater signal is obtained at equivalent dose or equivalent signal at lower dose compared with all other GBCAs. (Table 2) MultiHance has a flexible dosing indication in neonates and infants, allowing for doses of 0.05 – 0.1 mmol/kg.[7] Thus, a lower dose and, potentially, lower levels of retained Gd are possible with MultiHance.

Improving Outcomes with Contrast-Enhanced Imaging for Select Applications

The Expert Panel Forum on Advancing Clinical Practice in MR Imaging highlighted contrast use in several applications. "Why Gadolinium Matters Today," a presentation delivered by David Enterline, MD, provided an overview of similarities and differences among linear and macrocyclic GBCAs. A summary of select efficacy data is shown in Figure 1, along with a link to the full video presentation.

In "Contrast Enhanced MR Acute Stroke Protocol in the ED," John Karis, MD, discussed the goals of acute stroke MR imaging, as well as some of the technical and practice considerations in imaging this condition. (See Figure 2 for the conclusions of his presentation and a link to the full video.)

James Sancrant, DO, spoke on various aspects of breast MRI screening, including indications, performance, and protocols. Dr. Sancrant presented a case in which breast MRI was used

to image a patient who underwent 3D mammogram and ultrasound. While, both modalities generated equivocal results, breast MRI clearly showed a brightly-enhancing lesion. (Figure 3) A link to the video presentation is provided in the figure legend.

"Contrast-enhanced MR of the Abdomen and Pelvis," by Kristin Porter, MD, PhD, outlined the ACR's appropriateness criteria for abdominal and pelvic MR imaging and discussed a number of cases highlighting the use of contrast-enhanced MRI of the liver and urologic system, and pelvic imaging in women. Figure 4 shows an example of a hepatic application for MRI, the differentiation of mass-forming intrahepatic cholangiocarcinoma (ICC) from hepatocellular carcinoma (HCC). (See the figure legend for a link to the full video presentation.)

Contrast-enhanced MRI of the bowel was the focus of a presentation by Jorge Soto, MD, who reviewed indications and shared his institution's protocols for the procedure. Dr. Soto also showed several examples of patients undergoing MRI for Crohn's disease, rectal carcinoma, perianal fistulas, and other conditions. See Figure 5 for a summary of Dr. Soto's findings in the follow-up of a patient with recurrent Crohn's disease who had undergone resection of the terminal ileum.

Contrast-Enhanced MRI: Practice Considerations

Economic considerations are vital in today's healthcare environment. Practice considerations including the selection and utilization of MR contrast can impact workflow, which in turn affects costs. For example, GBCA-enhanced imaging can increase scan time, but also potentially reduces the need for additional and/or unnecessary imaging, which may lead to overall cost savings. Decisions related to which GBCA(s) a practice uses can have economic implications: one may choose to stock several GBCAs to allow for selection of an optimal agent based on an individualized risk-benefit assessment or, alternatively, only 1 or 2 agents based on pricing or contractual constraints. In either case, an increasing number of practices are choosing to use a macrocyclic agent based on their safety profile with respect to NSF risk and Gd retention, particularly if the applications include pediatric applications and/or serial imaging.

Radiologists are not always directly involved in GBCA selection at their institution. In such cases, communication between the Radiology Department, hospital administration and/or contrast decision making committees, is important. An evidence-based case can be made by the Radiologists when macrocyclic or higher-relaxivity agents offer the possibility of improved diagnostic confidence, help to address potential medico-legal issues, or simply provide physicians and patients with greater peace of mind.

Conclusion

Contrast-enhanced MRI is fundamental to clinical practice and is faster and more efficient than many other diagnostic procedures. To perform an effective, individualized risk–benefit analysis, radiologists should be familiar with the differences in properties and associated risks among GBCAs and how these relate to agent selection for specific applications.

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