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The Use of Contrast-Enhanced MRI in 'At Risk' Patient Populations

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The Use of Contrast-enhanced MRI in At-risk Patient Populations

Program Description

Gadolinium-based contrast agents (GBCAs) have been used to improve the sensitivity and specificity of magnetic resonance imaging (MRI) for decades. These contrast agents differ in their structure and ionicity which, in turn affect their stability; ie, the likelihood of dechelation and release of free gadolinium (Gd) ions. The safety profiles of the available GBCAs correlate with their stability: more stable agents are associated with a lower risk of nephrogenic systemic fibrosis (NSF) and less Gd deposition in brain, bone, and other tissues. Several patient populations are considered especially vulnerable to Gd exposure, including children, the elderly, the renally impaired, and those that require repeat MRI exams. The benefits of contrast-enhanced MRI are widely recognized; however, prudence dictates that contrast use be limited to cases where the results are likely to contribute significantly to diagnosis and/or patient management. Perhaps most importantly, contrast should not be withheld when it is expected that the clinical benefit will outweigh any potential risk.

Learning Objectives

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

- Identify patient populations at increased risk of experiencing an adverse event following administration of a gadolinium-based contrast agent (GBCA) during contrast-enhanced MRI;
- Discuss risk factors related to the use of each of the specific GBCAs in these patient populations;
- Summarize alternative approaches for the clinical management of at-risk patients.

Authors

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Target Audience

- Radiological Technologists
- Radiology Administrators
- Related Imaging Professionals

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The Use of Contrast-enhanced MRI in At-risk Patient Populations

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Gadolinium-based contrast agents (GBCAs) for magnetic resonance imaging (MRI) have been used for decades to increase soft-tissue contrast, characterize pathological structures, and detect vascularization and tissue perfusion.[1] With over 450 million doses administered worldwide, GBCA safety and efficacy have been well established.[2] Available GBCAs include: Dotarem® (gadoterate meglumine), Clariscan™ (gadoterate meglumine; a generic of Dotarem), Gadavist® (gadobutrol), ProHance® (gadoteridol), MultiHance® (gadobenate dimeglumine), and Omniscan™ (gadodiamide).[3-8] Magnevist® (gadopentetate dimeglumine) and OptiMARK® (gadoversetamide) have been discontinued in the US.

All GBCA contrast agents are made up of a gadolinium (Gd) ion bound to an organic ligand to form a chelate, and these agents can be classified on the basis of ligand structure (linear or macrocyclic) and ionicity (ionic or nonionic).[1,3-10] (Table 1) The specific combination of properties of each GBCA have long been known to affect the stability of the Gd-ligand chelate, resulting in differences in their tendency to dissociate and release free Gd ions, with important potential safety implications. Here we review the short- and long-term adverse effects associated with GBCAs, and strategies to optimize safe GBCA use in at-risk patient populations.

Short-term GBCA Tolerability

Most acute adverse reactions to GBCAs are mild and physiologic. They include coldness, warmth, pain at the injection site, nausea with or without vomiting, headache, paresthesia, and dizziness.[11,12] In general, the rates of these reactions are low and comparable among the GBCAs; however, the largest, single-center study of acute reactions to date did show some minor differences in reaction rates among them.[13] (Figure 1) Specifically, among the agents studied, the GBCA with the lowest rate of overall reactions was the macrocyclic agent Dotarem (the same molecule as Clariscan), at 12 per 10,000 injections, and the second lowest was the linear agent Omniscan, at 19 per 10,000. Severe reactions were found to be rare (1 per 50,000 injections); indeed, none were reported for Dotarem or Omniscan during the study time frame.

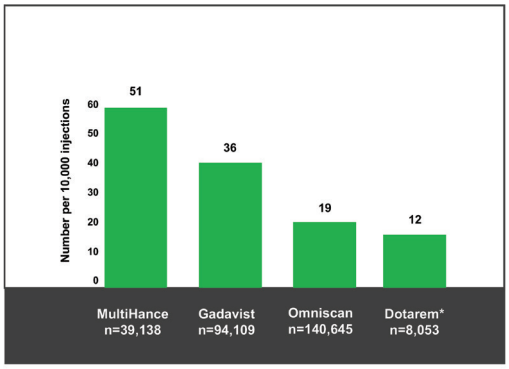
A main risk factor for acute reactions to GBCAs include a previous reaction to a GBCA; this can be an indication for corticosteroid prophylaxis, and it may also be prudent under such circumstances to use a different GBCA. Additionally, those with asthma and other allergies are at increased risk for an acute, allergic-like reaction, but here again the rate is low.[12] Overall, GBCAs are very well tolerated; however, personnel trained in recognizing and managing reactions should be immediately available should one occur.[12]

Table 1. Extracellular Gadolinium-based Contrast Agents.[1,3-10]

GBCA*	Ionic	Nonionic
Macrocyclic	Dotarem® Clariscan™	ProHance® Gadavist®
Linear	MultiHance® Magnevist®	Omniscan™ OptiMARK®

*Magnevist and OptiMARK have been discontinued in the United States.GBCA=gadolinium-based contrast agent.

Figure 1. Acute reaction rates by GBCA used per 10,000 injections.[13]

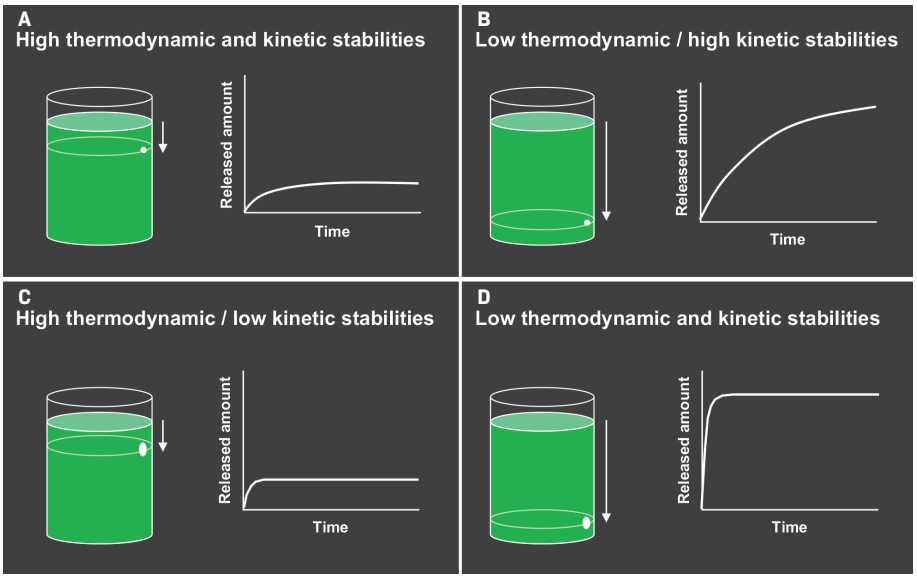


*Dotarem is the same molecule as Clariscan

Long-term GBCA Safety

The two main long-term safety concerns with GBCA administration are nephrogenic systemic fibrosis (NSF) and Gd retention in the organs and tissues in the body,

Figure 2. Model representing thermodynamic vs kinetic stability: the ''liquid'' represents free Gd which can leak out of the container via a hole; the level of the hole represents thermodynamic stability, ie, the volume of Gd release; the diameter of the hole represents kinetic stability, ie, the speed of Gd release. The lower the hole (B, D), the greater volume of Gd loss, and the lower the thermodynamic stability; the larger the hole (C, D), the faster the Gd loss, and the lower the kinetic stability.[15]



as evidenced by T1 hyperintensity on noncontrast scans in patients having received a GBCA in the past. Both relate to GBCA chelate stability; ie, how tightly the Gd ion is bound to its ligand. Chelate stability is difficult to measure in vivo. Consequently, it is inferred from two stability constants that are measured in vitro: the conditional thermodynamic stability constant (Log K_{cond}) and the kinetic stability constant ($T_{1/2}$).[14] Conditional thermodynamic stability reflects how much of the Gd dissociates; it is denoted as "conditional" because it is measured at physiologic pH. Kinetic stability reflects how fast dissociation occurs. This measurement is taken under acidic conditions, which are required to observe any dissociation within a reasonable time period.

The effects of the thermodynamic and kinetic stabilities can be graphically depicted by a beaker of liquid with a hole in it, where the liquid represents free Gd that can leak out, or be released.[15] (Figure 2) The height of the hole represents the thermodynamic stability, and the diameter of the hole represents the kinetic stability. The higher the hole on the side of the beaker (Figures 2A and 2C), the lower the overall volume of Gd released; the smaller the diameter of the hole (Figures 2A and 2B), the slower the speed of Gd release.[15]

The conditional thermodynamic and kinetic stability constants for various GBCAs are shown in Figure 3.[14] Based on the conditional thermodynamic stability (how much Gd dissociates), ionic GBCAs are much more stable than nonionic GBCAs because the ionic bond is stronger than the nonionic bond. Note that this a logarithmic scale, so seemingly small differences are actually quite large.

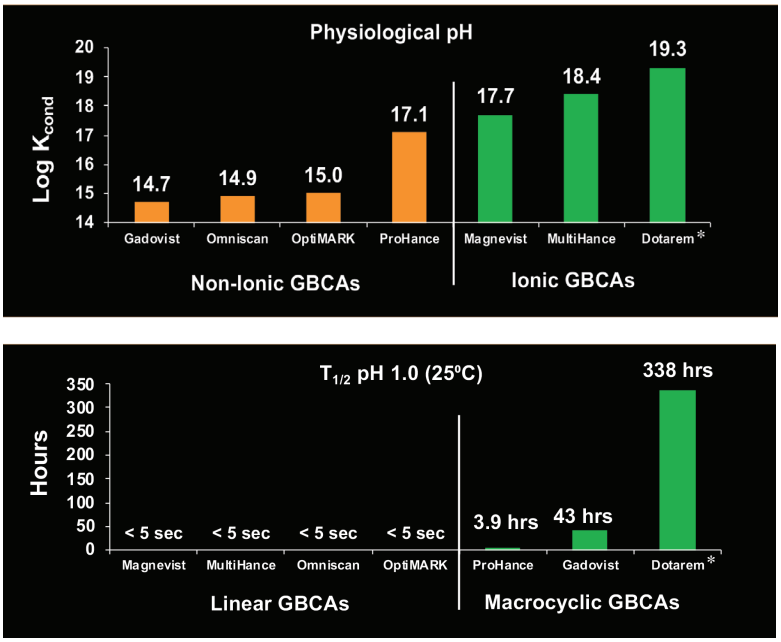
Based on the kinetic stability (how quickly dissociation occurs), the linear GBCAs are much less stable, dissociating almost immediately (< 5 sec), while the macrocyclic agents dissociate much more slowly—on the order of hours and days.[14] In the experiment shown in Figure 3, Dotarem did not exhibit dissociation after 338 hours, the timepoint at which the experiment was terminated. In summary, the nonionic linear GBCAs are the least stable, and the ionic macrocyclic GBCAs are the most stable, with the remainder falling in between.

Nephrogenic Systemic Fibrosis

Nephrogenic systemic fibrosis is a rare but serious disease observed in patients with end-stage renal disease receiving high and/or multiple doses of less stable GBCAs. GBCA clearance is known to be slower in these patients, presumably permitting a greater accumulation of free Gd not seen in patients with normal kidney function, particularly in those receiving less stable GBCAs.[16] This free Gd is believed to be taken up by macrophages, triggering a systemic fibrotic process within the body that can be fulminant and, in rare cases, fatal.[16]

As one might expect, unconfounded NSF cases (ie, those occurring after administration of only one GBCA) are limited almost exclusively to the linear GBCAs (with the exception of the linear agent MultiHance), even when adjusting for the number of doses administered.[3,17-26] (Table 2) The only agent for which no unconfounded NSF cases have been reported is Dotarem.[3,26] Such observations led the American College of Radiology (ACR) to stratify GBCAs into three groups according to NSF risk: Group I (Omniscan, Magnevist, and OptiMARK) are associated with the greatest number of NSF cases; Group II (MultiHance, Gadavist, Dotarem, Clariscan and ProHance) are associated with few, if any, unconfounded NSF cases; and Group III (Eovist), for which data remain limited, but few cases have been reported.[12] (Table 3) Since the implementation of guidelines limiting exposure of at-risk patients to Group II GBCAs, the incidence of NSF

Figure 3. (A) Conditional thermodynamic and (B) kinetic stabilities of GBCAs.[14]



*Dotarem is the same molecule as Clariscan. GBCA-gadolinium-based contrast agent.

has dropped and today, new cases are exceedingly rare.

Gadolinium Retention

Retention of Gd in both bone and brain tissue was demonstrated some time ago.[27,28] Moreover, it was recognized in these early studies that the amount of Gd retention was higher after administration of lower stability GBCAs. Interestingly, in 2011, a publication demonstrating hyperintensity on noncontrast brain scans of patients attributed their findings to the fact that the patients had received brain irradiation.[29] Other studies attributed observed signal changes to a specific subtype of multiple sclerosis (MS).[30] However, interest in Gd retention has been renewed by a large number of studies performed since 2014 showing hyperintensity on noncontrast brain scans of patients with normal renal function who had received GBCAs in the past.[31-36]

Taken together, these publications suggest that cumulative GBCA dosing is associated with T1 hyperintensity in patients with normal renal function who have been exposed to linear GBCAs. In addition, the presence of Gd has been confirmed in tissue using inductively coupled plasma mass spectrometry (ICP-MS) and, using ICP-MS, Gd retention has been shown to occur with all GBCAs.[36,37] To date, whether the Gd seen using ICP-MS is free or chelated and, if chelated, whether it is chelated to its ligand or another macromolecule, is not known.[2] Notably, although Gd retention has been well established by many investigators, no associated clinical sequalae have been definitively found to date.

GBCA Use in At-risk Populations

Pediatric Patients

The benefits of contrast-enhanced MRI in children are well recognized. For indicated pathologies, contrast improves the sensitivity and specificity of MRI, while avoiding the use of radiation. In addition, in children with CNS tumors, use of MRI often means the ability to avoid invasive procedures that might be needed to make a diagnosis, such as CSF sampling to exclude metastatic disease. New advances, such as artificial intelligence (AI) and others, are being successfully used to address the many challenges inherent to pediatric imaging, including the small size of anatomic structures, limited breath-holding capability, and motion artifacts.

Unfortunately, many children with brain tumors and recurrent disease require periodic surveillance. Often, these children are asymptomatic, and recurrence is diagnosed solely by MRI.[38-41] Multiple contrast-enhanced MRI scans can quickly add up to significant cumulative doses of Gd. While the risks in children are similar to those in adults, given the potential for large exposures over a lifetime and the vulnerability of these patients, it is important to assess the risks associated with GBCAs, including hypersensitive reactions, NSF, and Gd retention.

Acute allergic-like reactions are even more rare in children than they are in adults. In 2 large studies, the frequency of pediatric acute reactions ranged from 0.04% to 0.10%.[42,43] Moreover, NSF is even more rare in children: there have been only 23 reported cases, the youngest being 6 years of age.[12,44] Although there are no published reports of NSF in neonates, in theory they may be at risk for NSF if given low-stability Gd agents. In a prospective, multicenter, and observational study to assess the overall safety and efficacy of Dotarem (the same molecule as Clariscan) in 1,631 pediatric patients, only a single adverse event was recorded (vomiting), and no suspicions of NSF were reported at 3-month follow-up.[45]

Table 2. Nephrogenic Systemic Fibrosis Rates with Each GBCA[3,17-26]

	GBCA	No. of Unconfounded NSF Cases	No. of Injected (millions)	NSF Rate (per million)	EU/US Approval Year
Linear/ nonionic	Omniscan	197	>40	4.9	1993/ 1993
	OptiMARK*	8	>5	1.6	2007/ 2000
Linear/ ionic	Magnevist*	74	>100	0.74	1988/ 1988
	MultiHance	1	>42	<0.01	1997/ 2004
Macrocyclic/ nonionic	Gadavist	3	>27	0.11	2003/ 2011
	ProHance	1	>34	<0.01	1992/ 1992
Macrocyclic/ ionic	Dotarem**	0	>65	0	1989/ 2013

*Magnevist and OptiMARK have been discontinued in the United States.
**Dotarem is the same molecule as Clariscan.
GBCA=gadolinium-based contrast agent; NSF=nephrogenic systemic fibrosis.

Table 3. ACR Manual classification of GBCAs relative to NSF risk.[12]

Group I: Agents associated with the greatest number of NSF cases:
Gadodiamide (Omniscan™ – GE Healthcare)
Gadopentetate dimeglumine (Magnevist®* – Bayer HealthCare Pharmaceuticals)
Gadoversetamide (OptiMARK®* – Guerbet)
Group II: Agents associated with few, if any unconfounded cases of NSF:
Gadobenate dimeglumine (MultiHance® – Bracco Diagnostics)
Gadobutrol (Gadavist® – Bayer HealthCare Pharmaceuticals)
Gadoteric acid (Dotarem® – Guerbet; Clariscan™ – GE Healthcare)
Gadoteridol (ProHance® – Bracco Diagnostics)
Group III: Agents for which data remain limited regarding NSF risk, but for which few, if any, unconfounded cases of NSF have been reported:
Gadoxetate disodium (Eovist® – Bayer HealthCare Pharmaceuticals)

*Magnevist and OptiMARK have been discontinued in the United States.

As for adults, studies in children have raised concerns for Gd retention in sensitive tissues of the body, including the brain, after repeat exposures.[46] Evaluations of hyperintensity within the brains of children after repeated Gd exposure show a pattern that is similar to that seen in adults.[47-62] There is generally a stronger signal intensity with increasing doses of linear agents that is not seen with the more stable macrocyclic agents. Also, as in adults, studies in children have shown the corresponding presence of Gd within the brain at autopsy.[63-66] Specifically, the average concentration of Gd was higher with exposure to the linear agents compared to the macrocyclic agents, but all agents that were tested demonstrated at least some Gd in the brain.[66] (Figure 4) At transmission electron microscopy, Gd can be seen as spherical, electron-dense deposits surrounding blood vessels.[65] (Figure 5)

Figure 6 shows images from a child diagnosed with a tumor at two months of age, and by age six, the patient had already received 22 doses of Gd contrast, with visible dentate hyperintensity.

As mentioned, no study thus far has found evidence of any clinical consequence of Gd deposits in the brain; however, it is important to remember that the pediatric brain is known to be sensitive to very small amounts of metals and other man-made chemicals; eg, lead.[67] Therefore, the fetus and developing child arguably bear the highest risk from the effects of Gd exposure.

Importantly, comparisons of retained Gd in the brain and bone tissues at autopsy have found that bone levels were 23 times higher, suggesting that the hyperintensity in the brain seen using less-stable agents could be a marker for even higher Gd levels elsewhere in the body.[37] Also this may be important, in that pediatric patients are being exposed to large cumulative doses of Gd at a time when they are actively undergoing bone formation.

In light of all of these findings, practices are changing how they approach contrast administration in children. In a 2011 survey of pediatric radiology chairs in the US and Canada, most respondents reported using contrast agents considered by the ACR to be Class I agents; ie, those with a higher association with NSF.[68] By 2016, a survey of pediatric physicians with 690 respondents, showed a shift to the more stable Class II agents.[69] In fact, over half of respondents reported recently switching to solely using macrocyclic agents. The stated reason was concern about Gd deposition within the brain. Of those respondents who said they were still considering a switch, most indicated they were most likely to switch to the higher stability macrocyclic agent gadoterate meglumine.

Another recent shift, likely

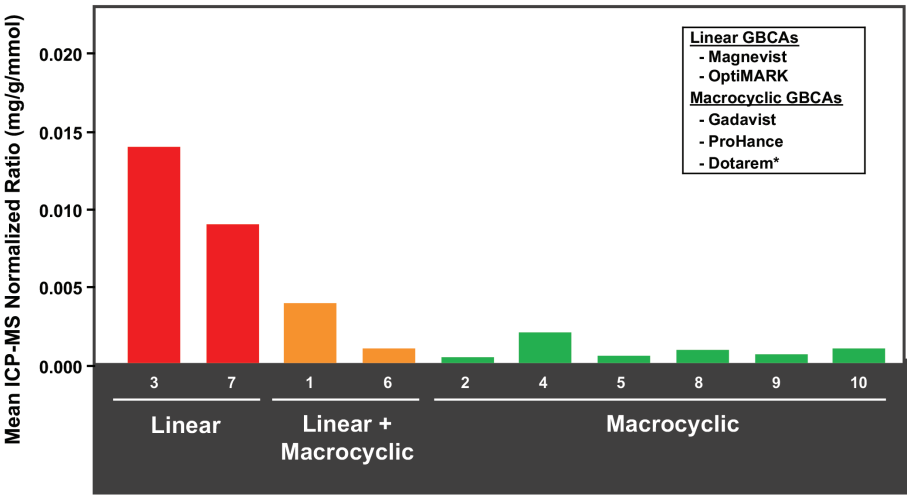
driven by increased awareness of the large cumulative doses administered to pediatric patients, has been to question whether Gd is necessary for surveillance MRI. Several studies have evaluated whether contrast informed patient management decisions in children with optic pathway gliomas[70] and low-grade gliomas.[71,72] In short, the authors concluded that Gd use, particularly for surveillance, should be individualized to the patient and disease. All these studies were retrospective, so prospective studies are needed to confirm when Gd is necessary for patient surveillance. Note that for tumor follow-up, as of 2020, the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group continues to recommend postcontrast imaging for many tumor types.[73-75]

Given the clinical benefits of MRI in children, addressing the concerns of family members around the issue of Gd contrast administration is important. Many patients and their caregivers believe the patient is receiving a "dye;" they are unaware that GBCAs are Food and Drug Administration (FDA)-approved drugs that have been used for decades. In a 2018 communication, the FDA made the following recommendation:

"All MRI centers should provide a Medication Guide the first time an outpatient receives a GBCA injection or when the information is substantially changed. In general, hospital inpatients are not required to receive a Medication Guide unless the patient or caregiver requests it."[76]

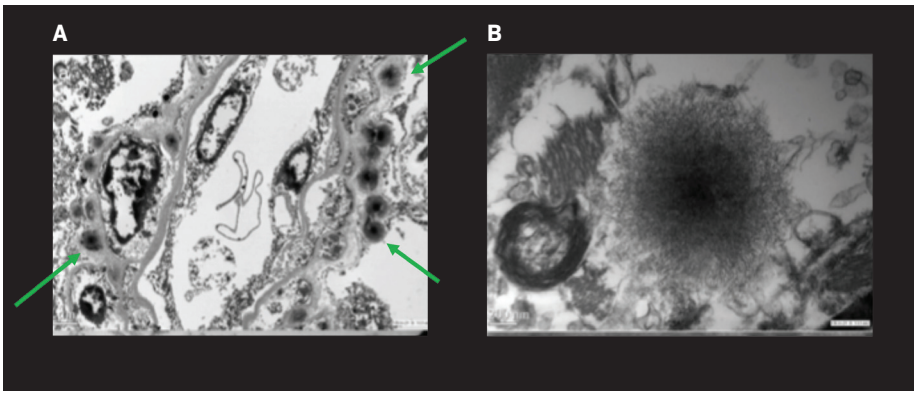
Health care professionals and patients can access the patient Medication Guides, according to the GBCA drug name, on the Medication Guides webpage.[77] In a recent publication, a group from the Seattle Children's Hospital provided excellent guidance on how to discuss concerns about contrast usage with families of patients.[78]

Figure 4. Mean ICP-MS Gd deposition ratios, normalized per mmol of total GBCA delivered, in 10 children grouped by structure of GBCA received. Patients 3 and 7 received only linear agents; patients 1 and 6 received at least one dose of a linear agent, in addition to macrocyclic agents; and the remaining patients received only macrocyclic agents. Each data point represents the result of analysis from a discrete specimen of normal brain tissue. Children who received linear Gd agents were more likely to have a higher ICP-MS normalized Gd deposition ratio than those who received only macrocyclic agents.[66]



*Dotarem is the same molecule as Clariscan.
GBCA=gadolinium-based contrast agent.

Figure 5. Pediatric autopsy study of Gd deposition from a 16-year-old with optic pathway glioma who received 49 doses of a linear GBCA (28 doses of MultiHance and 21 doses of Omniscan). Transmission electron microscopy (TEM) confirms Gd deposits around perivascular space with intraparenchymal extension. (A) TEM of the dentate nucleus demonstrates spherical electron-dense deposits surrounding blood vessels (green arrows); (B) Higher magnification TEM reveals that these deposits contain a more electron dense core and a less dense periphery comprised of filamentous bands measuring approximately 6 nm in diameter.[65]



The authors suggest reassuring patients and their families by letting them know that GBCAs have been in use safely for decades, and over 450 million intravenous doses of contrast agents have been administered. Also, patients and their families may not realize that several GBCAs are available, and it can be reassuring to know their doctor has selected the one most appropriate for the specific examination and patient. Parents are understandably concerned and often a thoughtful and transparent conversation is all that is needed.

In summary, for pediatric patients, it is important to 1) carefully consider whether contrast is needed; 2) consider the retention

Figure 6. Pediatric Gd deposition in a 2-month–old child. (Images courtesy of D Roberts, MD)

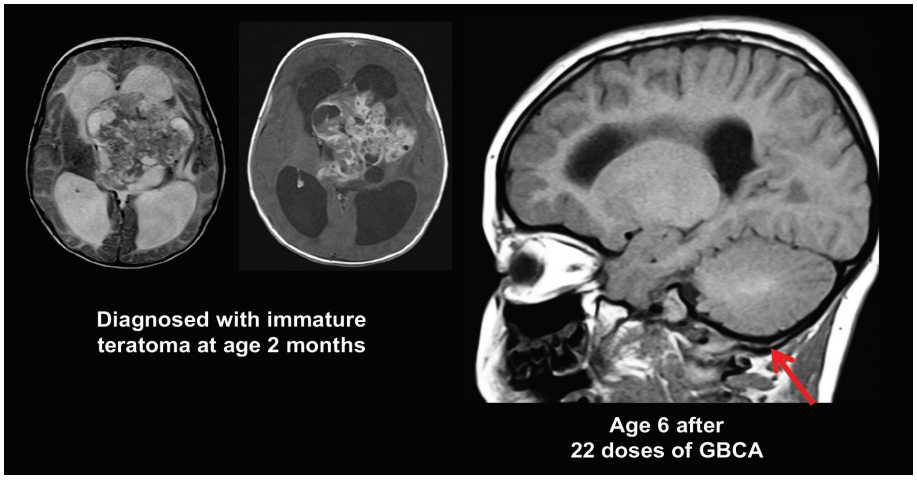


Figure 7. 26-year-old with a history of multiple sclerosis. (Images courtesy of L. Tannenbaum, MD)

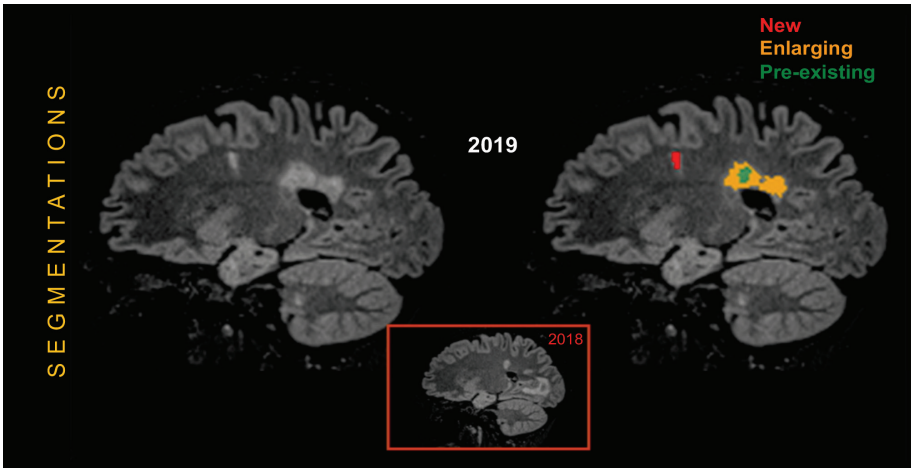
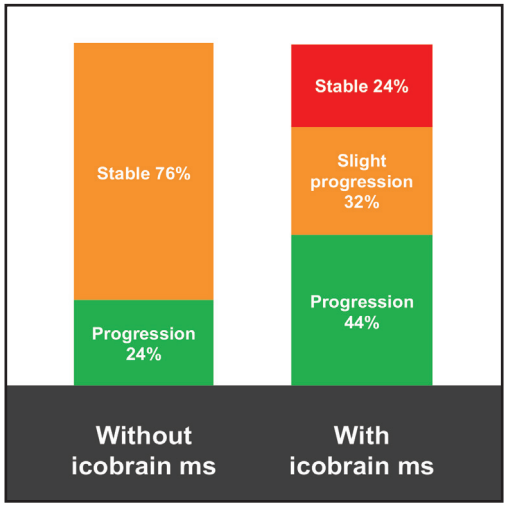


Figure 8. Increased sensitivity with icobrain ms: 20% increase in progression and 32% increase in slight progression.[84]



characteristics when choosing a GBCA, particularly for patients expected to undergo repeated dosing; 3) minimize repeated GBCA imaging studies, particularly closely-spaced MRI studies, whenever possible; and 4) accurately record the agent, the dose, and the cumulative dose. Finally, it is critical that no clinically necessary GBCA MRI scan be avoided or deferred without considering the clinical befits in relation to the potential risks of a contrast agent.

Patients Requiring Repeat MRI Exams

Repeat MRI exams are often required for specific patient populations under certain circumstances. These typically include screening for diseases such as cancer in high-risk patients, and for surveillance following diagnosis and/or treatment for tumors, multiple sclerosis, and inflammatory bowel disease.

Contrast-enhanced MRI is essential for tumor imaging, particularly for obtaining information on the location, classification, and grade of lesions; assisting in biopsy; aiding in treatment planning; and enabling clinicians to monitor response to therapy.[79] Since the discovery of NSF and the observation that Gd can accumulate in bodily tissues, regulatory and clinical guidelines have begun to emerge on contrast-enhanced imaging. Currently there are no specific guidelines limiting the dose or frequency of Gd administration; the FDA recommends only minimizing repeat GBCA studies when possible, particularly closely-spaced studies.[26] That said, the FDA also recommends that no contrast-enhanced MRI exam deemed to be necessary should be avoided or deferred. Many radiologists reiterate this point — reserve GBCA use for cases in which it has the potential to impact outcomes.

With the recognition that GBCAs should be used judiciously, a new appreciation has emerged for alternative, noncontrast techniques. A main reason to use a GBCA is to increase sensitivity to a lesion or pathology, since a missed disease can lead to mistreatment or undertreatment.[88] Therefore, Gd can often be given for initial diagnosis and characterization of tumors, but then less routinely for surveillance. It may be prudent to evaluate whether follow-up MRI exams truly require Gd to effectively monitor lesions; ie, whether they provide additional information that will impact treatment. Examples of cases where Gd may not be needed for surveillance

include macroadenoma, vestibular schwannoma, and meningioma. Additionally, alternative sequences and technical advances have made lower-contrast and noncontrast imaging a viable option for many patients. For example, artificial intelligence-based tools may reduce the dose of or even eliminate the need for contrast agents.[81]

Patients with MS are typically imaged on a regular basis and also when they experience flares. These patients often receive significant cumulative doses of Gd. According the Consortium of MS Centers (CMSC), GBCAs are "necessary for the accurate initial diagnosis of patients experiencing a first clinical attack of symptoms consistent with MS and for following patients with highly active disease or sudden, unexpected declines."[82] However, "GBCAs are optional, although helpful, in many other clinical scenarios, especially when noncontrast MRI can provide answers."[82] This is particularly the case in patients with stable, quiescent MS disease – contrast may not provide additional useful information.

Contrast is often deemed necessary in MS patients with active disease; changes over time are important to determine whether treatment is effective or if the disease is progressing. However, obtaining an accurate count or characterization of lesions is challenging, even with contrast. Side-by-side visual assessment of scans is time-intensive and subjective. In addition, detecting and quantifying subtle changes in lesion volume and number, as well as brain volume loss, can be challenging.

Artificial intelligence tools can help to better segment white matter lesions in patients with MS; better segmentation reveals changes in lesion volume faster and more accurately than can the human eye, providing accurate and quantitative information on T1 hyperintensities and FLAIR hyperintensities. One example is icobrain ms, a software tool that helps radiologists assess subclinical MRI metrics and predict/monitor disability progression and treatment response.[83] (Figure 7) Artificial intelligence has also been shown to standardize and improve reporting speed and sensitivity, as well as to decrease intra- and inter-reader variability. [84-89] (Figure 8) Such standardization has been shown to positively impact the quality of care and efficiency of workflows.

Renally Impaired/Elderly Patients

In patients with renal failure, Gd elimination is slowed, resulting in a prolonged circulation time. Specifically, in renally insufficient patients, the elimination half-life of Gd in plasma increases substantially from hours to days, depending on renal function.[90] Therefore, with respect to NSF and Gd retention, renally impaired and elderly patients require special care when contrast-enhanced MRI is deemed necessary. The elderly in particular are vulnerable, as their renal dysfunction may be asymptomatic.

Since NSF was observed in patients with end-stage renal disease, many of whom were elderly, care has been taken to avoid Gd contrast whenever possible and to use only those GBCAs deemed to be lowest risk; ie, the ACR Group II agents. This has all but eliminated new cases of NSF. Indeed, the risk of NSF is considered so low with Group II agents that, per the ACR, kidney function screening in potentially at-risk patients is considered optional, even in the elderly.[12]

With regard to Gd retention, studies have demonstrated that hyperintensity develops earlier and at lower cumulative doses in renally impaired or older patients with poor renal function.[91,92] Therefore, recommendations to use the lowest effective dose of a GBCA at the least appropriate frequency would apply in these cases. However, with no known adverse effects associated with Gd retention, it remains important to consider the benefits that may be provided by contrast. More than likely, there is less concern for long-term clinical sequalae from Gd retention in the elderly than in pediatric patients.

Conclusions

Recognizing the significant benefit derived from contrast-enhanced MRI, guidelines nonetheless recommend using such imaging only when it appears more likely than noncontrast imaging to contribute to diagnosis and/or patient management. Moreover, a GBCA that offers the best combination of safety and efficacy should be selected, based on the need for repeat imaging and the patient's age and level of renal function. Small amounts of Gd are likely to be retained in the body regardless of the GBCA selected. Therefore, ensuring that the benefit of a contrast-enhanced MRI outweighs any potential risk of adverse effects is critical.

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