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Gadolinium Deposition in the Brain: A Systematic Review of Existing Guidelines and Policy Statement Issued by the Canadian Association of Radiologists

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Abstract

Emerging evidence has confirmed that, following administration of a gadolinium-based contrast agent (GBCA), very small amounts of gadolinium will deposit in the brain of humans with intact blood-brain barriers. The literature is evolving rapidly and the degree to which gadolinium will deposit for a particular GBCA or class of GBCAs remains undetermined. Several studies suggest that linear GBCAs deposit more gadolinium in the brain compared with macrocyclic GBCAs; however, our understanding of the molecular composition of deposited gadolinium is preliminary, and the clinical significance of gadolinium deposition remains unknown. To date, there is no conclusive evidence linking gadolinium deposition in the brain with any adverse patient outcome. A panel of radiologists representing the Canadian Association of Radiologists was assembled to assist the Canadian medical imaging community in making informed decisions regarding the issue of gadolinium deposition in the brain. The objectives of the working group were: 1) to review the evidence from animal and human studies; 2) to systematically review existing guidelines and position statements issued by other organizations and health agencies; and 3) to formulate an evidence-based position statement on behalf of the Canadian Association of Radiologists. Based on our appraisal of the evidence and systematic review of 9 guidelines issued by other organizations, the working group established the following consensus statement. GBCA administration should be considered carefully with respect to potential risks and benefits, and only used when required. Standard dosing should be used and repeat administrations should be avoided unless necessary. Gadolinium deposition is one of several issues to consider when prescribing a particular GBCA. Currently there is insufficient evidence to recommend one class of GBCA over another. The panel considered it inappropriate to withhold a linear GBCA if a macrocyclic agent is unavailable, if hepatobiliary phase imaging is required, or if there is a history of severe allergic reaction to a macrocyclic GBCA. Further study in this area is required, and the evidence should be monitored regularly with policy statements updated accordingly.

Résumé

Des données récentes confirment qu'après l'administration d'un produit de contraste à base de gadolinium (PCBG), de très petites quantités de gadolinium pénètrent le cerveau de personnes dont la barrière hémato-encéphalique est intacte. La documentation à ce sujet évolue rapidement, et l'ampleur des accumulations de gadolinium selon le PCBG ou la catégorie de PCBG demeure indéterminée. Plusieurs études suggèrent que les PCBG linéaires laissent des traces plus importantes que les PCBG macrocycliques; toutefois, notre compréhension de la composition moléculaire du gadolinium accumulé est insuffisante, et l'importance clinique de l'accumulation de gadolinium reste

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inconnue. À ce jour, aucune preuve ne permet de conclure que l'accumulation de gadolinium dans le cerveau a des conséquences indésirables pour le patient. Un groupe de radiologistes représentant l'Association canadienne des radiologistes (CAR) a été créé pour aider le milieu de l'imagerie médicale du Canada à prendre des décisions éclairées concernant l'accumulation de gadolinium dans le cerveau. Les objectifs du groupe de travail étaient les suivants : 1) examiner les résultats des études effectuées sur les animaux et les humains; 2) consulter systématiquement les lignes directrices et énoncés de position des autres organismes et des agences de santé; 3) formuler un énoncé de position fondé sur des données probantes au nom de la CAR. Selon l'évaluation des données probantes et l'examen systématique de neuf lignes directrices d'autres organismes, les membres du groupe de travail se sont entendus sur l'énoncé suivant. Les risques et les avantages de l'administration de PCBG doivent être pesés avec soin, et cette méthode doit être utilisée au besoin seulement. Il faut administrer des doses standards et ne recourir aux administrations répétées qu'en cas de nécessité. L'accumulation de gadolinium n'est pas le seul élément à considérer avant de prescrire un PCBG en particulier. À l'heure actuelle, les données sont insuffisantes pour recommander une catégorie de PCBG. Le groupe de travail a jugé inapproprié de ne pas recourir à un PCBG linéaire lorsqu'aucun agent macrocyclique n'est disponible, si une visualisation hépatobiliaire est nécessaire ou si le patient a eu une réaction allergique grave à un PCBG macrocyclique. Il recommande l'examen régulier des données à mesure que d'autres études sont disponibles, et la mise à jour des énoncés de politique en conséquence.

Key Words: Gadolinium-based contrast agents; Magnetic resonance imaging; Gadolinium deposition

Gadolinium-based contrast agents (GBCAs) are an integral component of clinical and research magnetic resonance imaging (MRI) examinations. GBCAs have been used medically since the 1980s and have an overall excellent safety record [1−7]. Adverse reactions to GBCAs are uncommon and immediate allergic reactions are rare [8]. Nephrogenic systemic fibrosis (NSF), a severe debilitating systemic disorder that has been linked to GBCA administration in patients with compromised renal function [9], has dramatically decreased in incidence with the use of newer GBCAs, rigorous screening, and cautious administration [10,11].

The recent phenomenon of gadolinium (Gd) deposition in the brain was first described in 2014 by Kanda et al [12] using T1-weighted MRI. Subsequent studies have confirmed that these signal changes correspond to Gd deposition; this occurs in patients with normal renal function and intact blood brain barriers [13−15]. Despite over 460 million dosages of Gd administered to date, there is no conclusive evidence linking Gd deposition in the brain with any adverse patient outcome.

Health organizations, radiological societies and the medical imaging community as a whole have been challenged with understanding these rapidly evolving developments, and determining what (if any) practice changes are warranted. Both the U.S. Food and Drug Administration (FDA) and Health Canada have issued communications acknowledging the phenomenon of Gd deposition, with plans for future investigations and updates to product monographs [16,17]. In September 2017, the FDA mandated a new class warning on GBCA product monographs stating that GBCA administration can result in Gd deposition, with a greater risk among linear compared with macrocyclic agents [18].

To address the needs of the Canadian medical imaging community, the Canadian Association of Radiologists (CAR) assembled a panel of academic radiologists from across Canada with interest and expertise in contrast administration. None of the working group members have any relevant disclosures to declare. The objectives of the working group were as follows: 1) to review the evidence from animal and human studies; 2) to perform a systematic review of existing policies, guidelines, and position statements issued by other organizations and health agencies with respect to Gd deposition in the brain; and 3) to formulate an evidence-based position statement on behalf of the CAR. The target audience of this policy statement is radiologists, technologists, managers and other MR imaging service providers across Canada.

Gd-Based Contrast Agents

Gd belongs to the family of rare earth heavy metals, which can be toxic in humans. For example, high concentrations of manganese, iron, and copper in the basal ganglia are associated with movement disorders such as parkinsonism [19−21]. Similarly, it is widely accepted that free elemental Gd (Gd^{3+}) can be toxic in humans, the proposed mechanisms of which are reviewed elsewhere [22,23]. To be safely used in vivo, the Gd^{3+}ion is bound to an organic ligand molecule, which forms the commercial chelate, or GBCA, that is injected intravenously for clinical use. A key component regarding the safety of a GBCA is the ability of the ligand to remain chelated to the Gd^{3+} ion while circulating in the body. Dechelation—also referred to as dissociation—of Gd^{3+} from the ligand is known to occur in human serum over several days, and occurs to a greater extent in patients who have renal insufficiency or who are on dialysis [24]. Dechelation is a complex equilibrium process determined by the chemical structure of the ligand, defined mainly by the kinetic and thermodynamic stabilities, as well as the environment, such as pH and temperature [23]. Another environmental factor is the presence of ions competing to bind with either the ligand or Gd^{3+}, and the time allowed for such exchanges—termed transmetallation—to take place. The stability of commercial GBCAs has been tested in vitro, and in order of decreasing stability can be arranged as follows: macrocyclic agents, linear ionic agents, and linear nonionic agents [24].

Evidence of Gd Deposition in the Brain From Animal Studies

Gd deposition in animals has been documented since the 1980s. A 1995 study in rats and mice found that the macrocyclic agents gadoteridol and gadoterate were associated with less soft tissue Gd deposition than the linear agents gadopentetate and gadodiamide, suggesting that the structure of the chelate had an impact on Gd dissociation and deposition [25]. Following the emergence of NSF in 2006, animal studies demonstrated that Gd deposition in different organs correlated with dissociation rates [26–28].

Recent studies have confirmed the presence of trace Gd deposits in the rat brain [29–36]. Industry-sponsored studies found higher T1-weighted signal intensity in the deep brain nuclei of rats injected with linear agents [29,30,33]. Although no signal intensity changes were found in rats injected with macrocyclic GBCA compared with saline, a non–industry-sponsored study did find such signal intensity differences [32]. Using inductively coupled plasma mass spectrometry, Gd has been detected in the brains of rats injected with both classes of agents, but more Gd deposition was found with linear agents [29–32,35]. Nevertheless, McDonald et al [32] found that Gd deposition is not universally lower with macrocyclic compared with linear agents, and intraclass differences exist which are not entirely explained by the stability of the chelate [34,37].

Studies evaluating the chemical species of Gd deposited in the rat brain have found that macrocyclic agents deposit solely as small, soluble molecules [34] that correspond to the intact chelate [35]. Conversely, linear agents deposit not only as small soluble molecules, but to a greater extent as insoluble, inorganic salts and as soluble macromolecules [34,35]. It is the soluble macromolecule form—not the intact chelated form—which is believed to account for most of the T1-hyperintense signal changes observed on MRI. This may explain, to some extent, why MRI-based studies have observed higher T1 signal with linear agents [34,38].

The implication of Gd deposition in the rat brain is unknown. Although rat studies have been performed by injecting the equivalent of 20-80 human doses over a span of several weeks, no evidence of behavioral [29,30] or histopathological [31,32,36] neurological toxicity has been identified. Moreover, the lack of dechelation observed with macrocyclic agents does not necessarily imply greater safety [39]; for example, a 1995 study found that all 3 macrocyclic agents have substantially higher neurotoxicity than gadodiamide and gadopentetate when injected intrathecally in rats [40].

Evidence of Gd Deposition in the Brain From Human Studies

Since the initial study by Kanda et al [12], subsequent studies have confirmed that signal change in the human brain on MRI following GBCA administration is due to Gd deposition [12–14,41,42]. There is evidence of a dose-response relationship, as patients exposed to more GBCA are found to have greater Gd deposition [12,41], and this phenomenon has been shown in patients with normal renal function [13] and intact blood-brain barriers [43].

Gd deposition has been observed in various structures of the brain on autopsy, including the globus pallidus and dentate nucleus, and to a lesser extent the cerebellar white matter, frontal lobe grey and white matter, pons, and thalamus [13,14]. Transmission electron microscopy has shown that the majority of Gd is deposited in the endothelial wall, and a smaller portion is found in the neural interstitium [14].

Gd deposition in the human brain has been established predominantly with linear agents [15,44–48]; however, an autopsy study by Murata et al [15] also identified Gd in the brains of patients that received exclusively macrocyclic agents. These findings have been corroborated on imaging-based studies [49,50]. Aside from GBCA type, other factors may be associated with increased Gd deposition. Younger age is likely a risk factor for Gd retention, as greater Gd-associated signal change has been shown in the dentate nucleus in younger adults compared with older adults [51]. Pediatric brain signal change has been observed with as few as 2 GBCA exposures [52]. Signal change in the brain is also greater in hemodialysis patients than in those with normal renal function [53].

A summary of studies reporting Gd deposition and the various GBCAs approved for use in Canada is provided in Table 1. Table 1 highlights that Gd deposition has been observed with both linear and macrocyclic agents on both imaging and autopsy studies of humans.

Two studies have evaluated for any association between GBCA administration and adverse patient outcome from Gd deposition in the brain. A population-based study from Ontario compared patients who underwent MRI with and without Gd, and found no association between Gd exposure and parkinsonism [67]. Another study by McDonald et al [68] used the Mayo Clinic Study of Ageing patient database to assess whether GBCA exposure (to gadodiamide) was predictive of progression from normal cognitive function to mild cognitive impairment and dementia. In a large cohort of patients that received one or more doses of GBCA, the authors found that Gd exposure was not a significant predictor of cognitive or motor impairment. Further large-scale, ideally population-based studies are required to improve our understanding regarding the risk of Gd deposition in the brain.

Systematic Review of Policy Statements

Methods

A comprehensive literature search was conducted for published guidelines or policy statements issued regarding

Table 1
Studies showing an association between a GBCA and gadolinium deposition in the brain

GBCA	Structure	Brain deposition described on imaging-based studies	Brain deposition described on pathology-based studies
Gadodiamide (Omniscan; GE Healthcare, Mississauga, ON)	Linear nonionic	Kanda et al [12][a], Errante et al [41], Quattrocchi 2015 [54], Ramalho et al [55][b,c], Ramalho et al [56][b], Ramalho et al [57][c]	McDonald et al [14]
Gadopentetate dimeglumine (Magnevist; Bayer Pharmaceuticals, Mississauga, ON)	Linear ionic	Kanda et al [12][a,d], Kanda et al [58][d], Cao et al [59], Flood et al [60], Hu et al [52], Radbruch et al [42], Tedeschi et al [61], Roberts et al [62][e], Miller et al [63][e], Schlemm [64], Tamrazi [65]	Kanda et al [13][f]
Gadoversetamide (Optimark, Guerbet Group; Roissy CdG Cedex, France)	Linear nonionic	NR	NR
Gadobenate dimeglumine (Multihance; Bracco Pharmaceuticals, Anjou, QC)	Linear ionic	Weberling et al [66]	Murata et al [15][g]
Gadoxetate disodium (Primovist; Bayer Pharmaceuticals, Mississauga, ON)	Linear ionic	NR	Murata et al [15][g]
Gadoteridol (Prohance; Bracco Pharmaceuticals, Anjou, QC)	Macrocyclic nonionic	NR	Murata et al [15][g]
Gadoterate meglumine (Dotarem; Guerbet Group, Roissy CdG Cedex, France)	Macrocyclic ionic	NR	NR
Gadobutrol (Gadovist; Bayer Pharmaceuticals, Mississauga, ON)	Macrocyclic nonionic	Stojanov et al [45], Bjornerud et al [49], Kang et al [50]	Murata et al [15][g]

GBCA = gadolinium-based contrast agent; NR = no reported studies showing gadolinium deposition in the brain.
[a] Gadodiamide and gadopentetate dimeglumine were grouped together.
[b] Different patient cohorts. Ramalho et al [55] grouped patients that received only gadodiamide, whereas Ramalho et al [56] excluded patients that received only gadodiamide.
[c] Likely overlapping cohorts. Ramalho et al [55] and Ramalho et al [57] were performed at same centre, and each includes patients that received only gadodiamide.
[d] Different patient cohorts. Different enrollment dates.
[e] Case report.
[f] Patients received a mixture of GBCA; however, all patients received gadopentate dimeglumine. One patient received an additional single dose of gadoteridol, another received an additional single dose of gadoteridol and a single dose of gadodiamide.
[g] Five received gadoteridol, 2 received gadobutrol, 1 received gadobenate dimeglumine, and 1 received gadoxetate disodium.

Gd deposition in the brain. PubMed, OVID, Medline and Embase, National Guidelines, CMA Infobase, NICE and SIGN databases were searched for the terms *gadolinium*, *deposition*, and b*rain*, c*erebral* or *cerebrum*, and *basal ganglia*. No language restrictions were applied. Our initial search on October 11, 2017, identified 72 references. Two panel members (A.F.C. and N.S.) also individually searched FDA, Health Canada, and European and Asian Regulatory Body and Radiological Society webpages for any relevant guidelines or policy statements that might have not been captured by our initial search strategy. After manually reviewing the retrieved references for potential inclusion (N.S.), 9 policy statements or practice guidelines were included for more detailed review.

Our initial intent was to appraise each reference using an internationally validated tool for assessing clinical practice guidelines (the AGREE [Appraisal of Guidelines, Research and Evaluation] II tool) [69]. However, upon further review it became apparent that policy statements published to date were insufficiently formulated and detailed enough to be critically appraised with the AGREE II tool. Therefore, each policy statement was independently reviewed by 2 panel members (A.F.C. and R.V.) for extraction of 5 predetermined data elements: using GBCA only when medically necessary; use standard dosing; avoid repeat administrations unless necessary; recommendations on selecting a class of GBCA; and need to monitor literature and update policy as required. Discrepancies were resolved by consensus.

Results

A summary of the 9 retrieved guidelines or policy statements is provided in Table 2. All 9 guidelines recommend restricting use of GBCA only when medically necessary, and a majority recommend or infer to not exceed recommended dosages, to avoid repeated GBCA administration unless clinically indicated, and to monitor the literature and adapt recommendations as required.

The policy statements disagreed on the language and recommendations made with respect to selecting a macrocyclic versus a linear GBCA. The European Medicines Agency has suspended general use of all linear GBCAs; gadoxetate and gadobenate are restricted solely for use in liver MRI, and gadopentetate may be used solely for low-dose intra-articular use [73]. Conversely,

Table 2
Summary of 9 policy statements regarding gadolinium deposition in the brain

	NIH (United States) [70]	ACR-ASNR (United States) [71]	Health Canada [16]	Australia [72]	PRAC/EMA (EU) [73]	ISMRM (international) [74]	Medsafe (New Zealand) [75]	PMDA (Japan) [76]	FDA (United States) [18]	CAR (Canada)
Authors	Malayeri et al	None	None	None	None	Gulani et al	None	None	None	Current study
Date	March 2016	May 2016	Jan 2017	July 2017	July 2017	July 2017	Aug 2017	Nov 2017	July 2015, May 2017, Dec 2017	Jan 2018
Use GBCA only when medically necessary	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Use standard GBCA dosing	No	No	Yes	Yes	Lowest dose that provides sufficient enhancement for diagnosis	No	Yes	Yes	Implied	Yes
Avoid repeat administrations unless necessary	No	No	Yes	Yes	No	Implied	No	Implied	Yes	Yes
Recommendations on how to select GBCA in context of gadolinium deposition in the brain (paraphrased)	Consider use of a macrocyclic GBCA rather than a linear agent	Consider benefit of MRI against unknown risk gadolinium deposition in the brain for each patient. Attention should be paid to pediatric and other patients who may receive many GBCA-enhanced MRI	None	None	Suspended use of IV gadodiamide, gadopentetate, and gadoversetamide Restricted use of gadoxetate and gadobenate for liver MRI, and low-dose intra-articular gadopentetate	Whether macrocyclics should be favored over linear agents is unclear. Factors to consider include: pharmacokinetics, relativity, efficacy, potential side-effects, patient age, need for repeated MRI, and cost. Institutions should weigh these factors and consider that some agents might have a greater propensity for deposition than others.	Depending on patient's individual history and circumstances macrocyclic agents may be preferable to linear agents	Considered appropriate to use macrocyclics preferentially and to use linear when macrocyclics cannot be used, for reasons such as adverse reactions or hepatobiliary imaging	Consider retention characteristics in patients at higher risk of retention (those requiring multiple doses, pregnant women, children, patients with inflammatory conditions)	Insufficient evidence to recommend one class over another; gadolinium deposition is one of several issues to consider when prescribing a GBCA, and may be a more important consideration in certain patient populations
Monitor literature and adapt policy as necessary	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes

ACR-ASNR = American College of Radiology and American Society of Neuroradiology; EU = European Union; FDA = Food and Drug Administration; GBCA = gadolinium-based contrast agent; ISMRM = International Society of Magnetic Resonance in Medicine; IV = intravenous; MRI = magnetic resonance imaging; NIH = National Institutes of Health; PMDA = Pharmaceuticals and Medical Devices Agency; PRAC/EMA = Pharmacovigilance Risk Assessment Committee of the European Medicines Agency.

Health Canada and the Australian Department of Health provide no specific recommendations [16,72]. The U.S. National Institutes of Health and Japanese Pharmaceuticals and Medical Devices Agency recommend using a macrocyclic GBCA preferentially over a linear GBCA; the Japanese Pharmaceuticals and Medical Devices Agency also notes that linear agents should not be withheld if there is a history of adverse reaction to a macrocyclic GBCA, or if hepatobiliary imaging is required [70,76]. The remaining 4 of 9 policy statements, including Medsafe (New Zealand), the American College of Radiology−American Society of Neuroradiology, U.S. FDA, and the International Society for Magnetic Resonance in Medicine, incorporated language pertaining to risk-benefit considerations of individual patients. The American College of Radiology−American Society of Neuroradiology and FDA recommended considering the issue of Gd retention particularly in those patients who may be at higher (potential) risk, such as pediatric patients and those requiring repeat doses; the FDA also mentions patients with inflammatory conditions and pregnant women [18,71]. The International Society for Magnetic Resonance in Medicine stated that it is unclear whether macrocyclics should be favored over linear agents, and that the issue of Gd deposition should be considered in addition to other factors such as GBCA efficacy, side effects, patient age, probability of the need for repeat examinations, and cost [74].

Factors to Consider When Prescribing GBCAs

In addition to the issue of Gd deposition in the brain, there are other factors to consider when prescribing a particular GBCA. Unlike Gd deposition, allergic-like reactions are known, quantifiable risks with immediate consequences [77]; a recent meta-analysis found that, although the overall risk of allergic reactions is very low, at 9.2 per 10,000 administrations, the risk of allergic-like reaction was lowest for nonionic linear agents, followed by ionic linear agents, and highest for nonionic macrocyclic agents; this trend is opposite to that of chelate stability [8]. Another issue is GBCA dosing and efficacy. For example, the linear agent gadoxetate, which provides the most efficient and efficacious method for hepatobiliary imaging, uses a standard dose that is 25% that of other GBCAs (0.025 mmol/kg) and 50% is excreted via the hepatobiliary pathway; how these factors affect Gd deposition is unknown. Lastly, the risk of NSF is not entirely explained by stability of the chelate [22]; for example, gadopentetate dimeglumine and gadobenate are both linear ionic agents, but the number of unconfounded cases of NSF associated with each one is 135 and 0, respectively [11]. In addition, there are at least 4 unconfounded cases of NSF associated with the macrocyclic agents gadoteridol and gadobutrol GBCAs [11]. Exactly how these competing benefits and risks should be weighed against each other by radiologists prescribing GBCAs is unclear, and perhaps best addressed on a case-by-case basis.

CAR Working Group Consensus Statement

The panel's consensus statement is based on appraisal of the evidence from animal and human studies performed to date, and our systematic review of 9 policy statements regarding Gd deposition in the brain. The panel acknowledged evidence demonstrating that as a class, linear GBCAs deposit more Gd than macrocyclic agents; however, there is emerging literature which suggests that within class differences exist with respect to the amount of Gd deposition in the brain, and studies directly comparing GBCAs are lacking. In addition, there is no conclusive evidence demonstrating patient symptoms or other adverse effects related to Gd deposition in the brain, although further study in assessing patient outcomes and GBCA exposure is warranted.

The CAR Working Group consensus statement is provided in Appendix 1. As with any medication, GBCA administration should be considered carefully with respect to potential risks and benefits, and only used when required. Standard dosing should be used and repeat administrations should be avoided unless necessary. The panel concluded that there is insufficient evidence to recommend one class of GBCA over another at this time. The panel considered it inappropriate to withhold a linear GBCA if a macrocyclic agent is unavailable, if hepatobiliary phase imaging is required, or if there is a history of severe allergic reaction to a macrocyclic GBCA. Further study in this area is required, and the evidence should be monitored regularly with policy statements updated accordingly.

Summary

Gd deposition in the brain is a newly described phenomenon that is evolving rapidly. To help address this issue, the CAR Gadolinium Deposition Working Group reviewed the evidence from animal and human studies performed to date, performed a systematic review of existing policy statements, and formulated a consensus statement as outlined previously. This consensus statement is intended to assist the Canadian medical imaging community in making informed decisions regarding the issue of Gd deposition in the brain, and it is anticipated that new statements will be required as more evidence emerges.

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Appendix 1. Policy Statement Issued on Behalf of the Canadian Association of Radiologists

Gadolinium-based contrast agents (GBCAs) should only be administered when medically appropriate, standard dosing should be used and repeat administrations should be avoided unless necessary. There is insufficient evidence to recommend one particular class (or agent within a class) of GBCA over another at this time. This topic requires further investigation and careful monitoring of emerging literature with potential necessary changes to recommendations depending on the development of new and credible data in the field.

Qualifying statements:

1. There is evidence supporting an association between greater degrees of gadolinium deposition in the brain among linear GBCA compared with macrocyclic GBCA. The panel agreed that Gadolinium retention is one of several important factors to consider when selecting a particular GBCA, and this may be a more important consideration in select patient populations. The panel considered it inappropriate to withhold a linear GBCA if a macrocyclic agent is unavailable, if hepatobiliary phase imaging is required, or if there is a history of severe allergic reaction to a macrocyclic GBCA.
2. There is evidence that suggests that within class differences exist as to the amount of gadolinium deposition in the brain (ie, not all linear or macrocyclic agents deposit to the same extent); however, studies directly comparing GBCAs are lacking. Further study is required to determine what, if any, importance these differences have in clinical practice.
3. There is evidence showing greater gadolinium deposition in the brain in patients who have received multiple doses of GBCA or have reduced clearance of GBCA (eg, impaired renal function). GBCA administration should neither be repeated unnecessarily nor exceed standard dosages, and should be used cautiously in patients with renal impairment.
4. To date, there is no conclusive evidence regarding patient symptoms or other adverse effects related to gadolinium deposition in the brain; however, studies evaluating patient outcomes and GBCA deposition are limited.