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Review

Gadolinium-Based Contrast Agents: Updates and Answers to Typical Questions Regarding Gadolinium Use

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Gadolinium-based contrast agents have expanded the diagnostic usefulness and capability of magnetic resonance imaging. Despite their highly favorable safety profile, these agents have been associated with nephrogenic systemic fibrosis in a small number of patients who have advanced kidney disease. Recently, trace amounts of gadolinium deposition in the brain and other organs have been reported after contrast exposure, even in patients with normal renal function. In this review, we provide a brief overview of recent updates and discuss typical clinical situations related to the use of gadolinium-based contrast agents. ***(Tex Heart Inst J 2022;49(3):e217680)***

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Magnetic resonance imaging (MRI) is an important diagnostic method with high spatial resolution that provides exquisite soft-tissue contrast without the need for ionizing radiation or a potentially nephrotoxic contrast agent. The use of a gadolinium (Gd)-based contrast agent (GBCA) further increases the diagnostic sensitivity and capabilities of MRI. In the United States (US), GBCAs are used in 30% to 45% of the approximately 40 million MRI procedures performed each year.[1] Since receiving US regulatory approval in 1988, GBCAs have come into widespread clinical use. In addition to having a favorable safety profile,[2] GBCAs are unlikely to cause or worsen renal insufficiency, and they precipitate anaphylactoid reactions in no more than 0.01% of cases.[3]

At the turn of the recent millennium, a rare systemic ailment called nephrogenic systemic fibrosis (NSF) was observed after GBCA exposure in some patients who had existing advanced chronic kidney disease (CKD).[4-6] Trace amounts of Gd of uncertain clinical significance have been observed in other organs after GBCA exposure, even in patients with normal renal function.[7]

In this review, we discuss updates and answer typical questions related to GBCA classification, GBCA and NSF, and GBCA use during dialysis, pregnancy, and breastfeeding. In addition, we discuss recent findings of Gd deposition in the brain.

Classification of Gadolinium-Based Contrast Agents

Gadolinium ion (Gd^{3+}) is a heavy metal with 7 unpaired orbital electrons. In its free ionic form, Gd^{3+} is highly toxic and can disrupt calcium-mediated signal pathways; therefore, it must be bound with an appropriate ligand to form a sufficiently stable complex that enables its excretion intact.[8] The chemical nature of GBCAs has been reviewed elsewhere.[2,7-9] Gadolinium-based contrast agents can be classified as ionic or nonionic, or in accordance with their linear or cyclic structures. In general, cyclic GBCAs, which have a rigid, cage-like structure, are more stable than are linear

GBCAs, and they have a higher stability constant and substantially lower dissociation rate.[7,8]

The American College of Radiology's most recent GBCA classification is based on the associated risk of developing NSF (Table I).[10]

Gadolinium-Based Contrast Agents in Patients With Nephrogenic Systemic Fibrosis

In the early 2000s, a small number of patients with advanced CKD and previous GBCA exposure showed signs of skin edema and erythema in their extremities that sometimes worsened into thickened, woody, and contracted skin.[4,5] In addition, the sclerosing process could extend to other organs and tissues, such as the lungs, diaphragm, esophagus, myocardium, skeletal muscle, and dura mater. This condition, termed NSF,[5,11] was primarily associated with the use of less stable linear GBCAs in patients with advanced CKD, and it rarely developed when cyclic GBCAs were used.[9]

The pathogenesis of NSF, previously reviewed by Cheong and associates,[12] most likely involves the dissociation of free and toxic Gd^{3+} through transmetallation by endogenous metal ions such as Zn^{2+} or Cu^{2+}.

Increased awareness among practicing clinicians regarding the relationship among NSF, advanced CKD, and less stable linear (Group I) GBCAs has led to changes in clinical practice, including the use of more-stable GBCAs. Furthermore, clinical research uncovering the potential underlying mechanisms of NSF, together with guidance regarding GBCA use provided by the US Food and Drug Administration (FDA) and several professional societies,[7,10,13-17] has reduced or eliminated the incidence of NSF.[18-22] Beyond 2008, Attari and colleagues[19] noted only 7 out of 639 biopsy-confirmed NSF cases after GBCA administration, further supporting a decline in the incidence of NSF.

With respect to NSF, macrocyclic (Group II) GBCAs have been relatively safe.[19,23-26] In the Gadobutrol in Renally Impaired Patients Study[25]—a prospective international, multicenter, open-label study in which gadobutrol-enhanced MRI was used—no NSF was reported during the 2-year follow-up period; 284 of 908 patients (31.3%) had an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2. In a recent meta-analysis of 16 studies, comprising 4,931 patients with stage 4 or 5 CKD who were given a Group II GBCA and were monitored for up to 72 months, no NSF was reported.[26]

Few investigators have studied the safety of using gadoxetic acid (a Group III GBCA, primarily for hepatobiliary imaging),[27,28] although no NSF was noted during follow-up in patients who had moderate or severe CKD.[27] In studies of Group II gadobenate dimeglumine use in patients with severe CKD,[21,22,29] none of the patients developed NSF during the study period.

Gadolinium-Based Contrast Agents in Patients With Chronic Kidney Disease

In 2017, the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency suspended the use of high-risk linear Group I GBCAs (gadodiamide, gadopentetate dimeglumine, and gadoversetamide),[13] although gadopentetate dimeglumine can be used during an MRI arthrogram.[13] Gadobenate dimeglumine and gadoxetic acid are now limited to hepatobiliary imaging only. Gadopentetate dimeglumine and gadoversetamide have been discontinued in the US, whereas gadodiamide is still available, albeit with a contraindication warning for patients with acute kidney injury (AKI) and those with an eGFR <30 mL/min/1.73 m^2.

TABLE I. Gadolinium-Based Contrast Agents Classified by Risk of Nephrogenic Systemic Fibrosis

	Cyclic	Linear
Ionic	Gadoteric acid (Dotarem, Guerbet; Clariscan, GE Healthcare)	Gadobenate dimeglumine (MultiHance, Bracco Diagnostics Inc.)
		Gadoxetic acid (Eovist, Bayer HealthCare Pharmaceuticals Inc.)
		Gadopentetate dimeglumine (Magnevist, Bayer HealthCare Pharmaceuticals Inc.)
Nonionic	Gadoteridol (ProHance, Bracco Diagnostics Inc.)	Gadodiamide (Omniscan, GE Healthcare)
	Gadobutrol (Gadavist, Bayer HealthCare Pharmaceuticals Inc.)	Gadoversetamide (OptiMARK, Guerbet)

Green = Group II gadolinium-based contrast agents (GBCAs), associated with few or no unconfounded cases of nephrogenic systemic fibrosis (NSF); yellow = Group III GBCAs, associated with only a few administrations with no unconfounded cases of NSF; red = Group I GBCAs, associated with the highest number of cases of NSF. Most GBCAs are renally excreted except for gadobenate dimeglumine (3% biliary excretion) and gadoxetic acid (50% biliary excretion).

Adapted with permission from: ACR Committee on Drugs and Contrast Media. ACR manual on contrast media. Available from: https://www.acr.org/-/media/ACR/files/clinical-resources/contrast_media.pdf [2021; cited 2021 Mar 3].[10]

Various professional societies have provided fairly similar recommendations regarding GBCA use in patients with CKD.[7,10,14-16] No special precautions are typically necessary for patients with stage 1, 2, or 3 CKD. Furthermore, when a Group II GBCA is being used for a clinically indicated study, it is unnecessary to measure eGFR or avoid GBCA administration in patients with advanced CKD who are not undergoing dialysis. For patients undergoing hemodialysis, the next treatment session can be scheduled as soon as possible after MRI, preferably within a few hours.

Group II (macrocyclic) GBCAs should be used whenever possible, given their exceedingly low to nonexistent risk for inducing NSF.[14-16,23] Hepatobiliary imaging may necessitate the only available class III GBCA (gadoxetic acid), which also imposes minimal NSF risk.[15,16,27,28]

The MRI physician can play an important role in optimizing imaging protocols to minimize the required total GBCA dose. In general, when multiple GBCA doses are expected in an urgent situation, imaging should not be delayed simply because of NSF risk. When multiple doses are anticipated for elective imaging, a delay of longer than 24 hours or dialysis between doses in dialysis-dependent patients may improve GBCA clearance.[7]

In patients with advanced CKD or undergoing dialysis, the use of GBCA in MRI studies should be evaluated on a case-by-case basis. Specifically, clinicians should consider whether non–contrast-enhanced MRI will provide sufficient information or whether any other imaging method can provide information similar to that obtained from MRI with GBCA enhancement.

Typical Questions Related to Gadolinium-Based Contrast Agent Uses

What is the Recommended Dose for a Single Session?

In general, only the FDA-approved GBCA dose should be administered during a single imaging session. The approved dose is 0.1 mmol/kg, except for the liver-specific gadoexetic acid dose (0.025 mmol/kg). Nonetheless, imaging physicians can make exceptions according to imaging requirements.[10] The use of a lower-than-recommended GBCA dose for NSF prevention is not supported by evidence[15,16] and may compromise image quality.[16,23,30]

What is the Recommended Time Interval Between Gadolinium-Based Contrast Agent Administrations?

In patients with normal renal function, GBCAs have a half-life of approximately 1.5 hours[31]; thus, more than 95% of an injected dose is eliminated within 24 hours.[9] However, the mean half-life is prolonged to 5.6 hours in patients with moderate CKD and to 9.2 hours in those with severe CKD, and it can be as long as 30 hours when the GFR is <5 mL/min.[9,31] Hemodialysis removes GBCAs with ~70% clearance after 1 session and >95% clearance after 3 sessions.[32] Thus, the following guidelines for the repeat administration of GBCA are recommended:

1) In patients with normal renal function, GBCA can be readministered after 24 hours if a GBCA-enhanced MRI examination is clinically necessary.[9] The European Society of Urogenital Radiology recommends at least 4 hours between GBCA injections in patients with an eGFR >30 mL/min/1.73 m^2.[14] The most recent joint consensus statement from the American College of Radiology and the National Kidney Foundation states that "if multiple urgent Group II or Group III GBCA doses are indicated, subsequent dose(s) should not be delayed for fear of NSF."[7]
2) For patients undergoing hemodialysis, 3 dialysis sessions will clear >95% of a GBCA. For this reason, GBCA can be readministered one week later for a nonurgent, clinically indicated study.[14]
3) For nondialysis outpatients with suspected advanced (severe) CKD, GBCA can be administered one week apart for a nonurgent, clinically indicated study, taking into account the prolonged half-life of GBCA in patients with severe CKD.[14]

Is Routine Evaluation of Renal Function Necessary?

According to the most recent recommendations from the Canadian Association of Radiologists, eGFR estimation is no longer needed for outpatients, because Group II and Group III GBCAs are associated with an exceedingly low to nonexistent risk for NSF.[16] The American College of Radiology and National Kidney Foundation consensus statement suggests that eGFR evaluation is not mandatory for any Group II GBCA, but that it is necessary for Group III GBCAs.[7]

It is important to ascertain whether an outpatient is undergoing dialysis so that the next dialysis session can be facilitated, preferably as soon as feasible, after GBCA administration.[7,15] For inpatients, even those given a Group II GBCA, the imaging team should be alert for AKI along with concurrent medical issues, because AKI is a risk factor for NSF.[12] An available alternative imaging method should be considered for patients with AKI. However, if MRI with GBCA is clinically indicated in the presence of AKI and no alternative imaging method is available, MRI with GBCA should be performed and not delayed, given the very low risk for NSF for a standard GBCA dose.[7] In this situation, a Group II GBCA should be used. Figure 1 shows an overview of GBCA administration.

Do Gadolinium-Based Contrast Agents Cause Acute Kidney Injury?

Administering an FDA-approved dose of GBCA is not generally associated with postcontrast AKI, especially in patients with normal renal function.[9,14,33,34] Using a higher-than-approved dose or an intra-arterial injection are well-described risk factors for GBCA-associated postcontrast AKI.[9,34]

When Should Hemodialysis and Peritoneal Dialysis Be Performed After Gadolinium-Based Contrast Agent Administration?

Hemodialysis effectively removes GBCAs.[32] Dialysis should optimally be performed as soon as possible after GBCA administration.[7,15,35] However, no clear-cut evidence supports the hypothesis that hemodialysis prevents NSF in at-risk populations.[15,36] Therefore, hemodialysis should not be initiated solely to prevent NSF.

Even though it is not feasible to perform dialysis as soon as possible after MRI with GBCA, the benefit of MRI with use of a GBCA outweighs the risk of NSF, so MRI should still be performed if clinically indicated. The patient should then continue with regularly scheduled dialysis after MRI.[7]

Peritoneal dialysis should continue after GBCA administration. Insufficient data are available to support switching from peritoneal dialysis to hemodialysis.[30]

Is Gadolinium-Based Contrast Agent Administration Safe During Pregnancy?

Magnetic resonance imaging is increasingly used during pregnancy because of its ability to depict detailed cross-sectional anatomy without the use of ionizing radiation. Despite theoretical concerns regarding the safety of MRI with GBCA administration during pregnancy, no harm has yet been attributed to MRI during any trimester of pregnancy. However, prospective and longitudinal studies are lacking. The gestational outcomes of 397 pregnant women who underwent MRI with GBCA administration from 2003 through 2015 were compared with those of 1,418,451 pregnant women who were not exposed to MRI.[37] The number of stillbirths and neo-

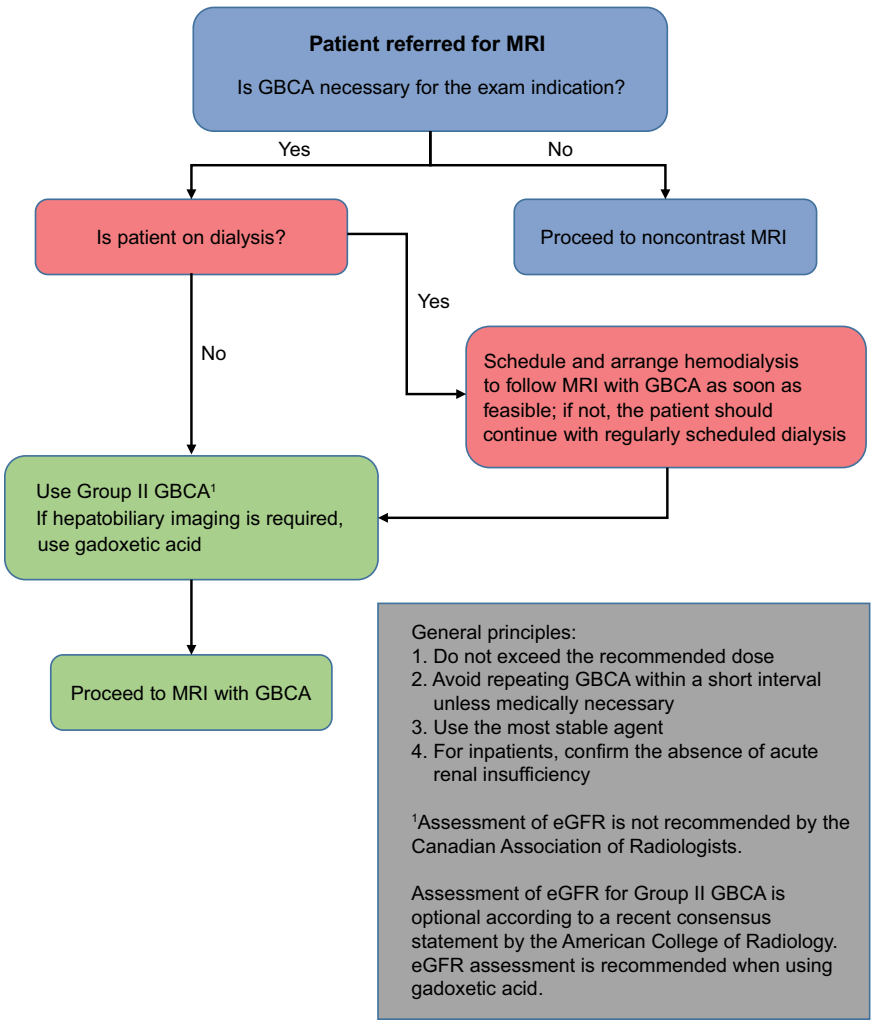

Fig. 1 *Flow chart shows an overview of GBCA administration.*

eGFR = estimated glomerular filtration rate; GBCA = gadolinium-based contrast agent; MRI = magnetic resonance imaging

natal deaths in the exposure group was 7 (1.8%), compared with 9,844 (0.7%) in the nonexposure (control) group (adjusted relative risk, 3.70; 95% CI, 1.55–8.85). Of note, the control group underwent no MRI, rather than noncontrast MRI, and whether GBCAs were administered during the first trimester was not specified.

Teratogenicity has not been reported after GBCA administration during pregnancy.[37,38] Although no randomized trials have been performed to evaluate the use of GBCA during pregnancy, a prospective study of 26 women who underwent MRI with use of a GBCA during the first trimester showed no evidence of teratogenesis or mutagenesis at follow-up.[39]

According to the most recent recommendations, Group II GBCAs should be used during pregnancy only if the potential benefits justify the unknown risk to the fetus.[10,14,40]

Is GBCA Administration Safe in Breastfeeding Mothers?

In women with normal renal function, <0.04% of a GBCA dose is excreted into breast milk within the first 24 hours after it is administered. Infants absorb <1% of this small amount from their gastrointestinal tract. The expected systemic dose absorbed by the infant is <0.0004% of the intravascular dose given to the mother; therefore, the likelihood of an adverse effect from such a small amount of GBCA absorbed from breast milk is remote,[10] suggesting that no breastfeeding interruption is required after GBCA administration.[10,40,41]

Gadolinium Deposition

Kanda and colleagues[42] first reported the observation of T1-weighted hyperintensities in the dentate nucleus and globus pallidus during the brain MRI of patients with normal renal function who had received multiple doses of linear GBCAs in the past. In tissues with similar MRI findings, Gd deposits were detected by using spectroscopy and electron microscopy.[43] Gadolinium deposition in other brain regions and extracranial organs has also been reported, even in patients with normal renal function.[7] Gadolinium deposition in the brain is thought to be a kinetic process,[44] suggested after studies in rodents revealed that the accumulation of intact Gd-chelate molecules of both linear and macrocyclic GBCAs in the brain was progressively eliminated over time. On the other hand, dechelated Gd (predominantly from linear GBCAs) binding to soluble macromolecules led to permanent deposition.[45,46]

One proposed mechanism of Gd accumulation in tissues is competition with other metals for the contrast agent chelator.[47] The result is transmetallation, whereby endogenous metals such as Fe^{3+}, Zn^{2+}, Cu^{2+}, and Ca^{2+} have a high affinity for the chelator and release Gd^{3+}, which is deposited in the tissue as Gd phosphate.[47] The iron-rich basal ganglia are heavily invested with metal transporters that may favor the accumulation of insoluble Gd.

Studies that compare the degree of Gd deposition associated with various GBCAs are lacking.[30] A few autopsy and imaging studies of the brain have revealed evidence of Gd deposits from both Group I and II GBCAs, with much greater Gd deposition for Group I (linear) GBCAs than from Group II GBCAs, presumably reflecting the more stable nature of Group II GBCAs.[30,47] Although no negative health effects from Gd brain deposition have been identified,[13,17,23,30] further research and longer-term monitoring are warranted.

Recommendations for GBCA use that are specifically related to Gd brain deposition include using GBCAs only when medically necessary, not exceeding the recommended dose, and avoiding repeated GBCA administration unless clinically indicated.[30] Given that comparison studies of GBCAs are limited, the more stable Group II (macrocyclic) GBCAs are generally the best option, unless hepatobiliary imaging is required. When macrocyclic GBCAs are not available, or if the patient has a history of severe allergic reaction to Group II GBCAs, Group I linear agents may be used after the risk-to-benefit ratio is considered.[30]

Conclusions

Gadolinium enhances MRI capabilities. In its chelated form, it can be safely administered in most patients at the approved doses. Nephrogenic systemic fibrosis has been observed in a small subset of patients with advanced CKD; most of these cases are related to Group I GBCAs. During the last decade, increased understanding of the role of chelating agents has led to the implementation of processes that have effectively eliminated the incidence of NSF. Although most GBCAs are cleared from the body, trace amounts may accumulate in tissues, most notably the brain, even in patients with normal renal function. However, the clinical significance of this accumulation is currently unknown, and no adverse health effects have been observed. The low risk of GBCA administration in high-risk patients (such as in patients with advanced CKD) should be balanced against the risk of denying patients a clinically well-indicated contrast-enhanced MRI examination, especially with the newer and safer Group II GBCAs.

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References

1. Kanal E. Gadolinium based contrast agents (GBCA): safety overview after 3 decades of clinical experience. Magn Reson Imaging 2016;34(10):1341-5.
2. Runge VM. Safety of magnetic resonance contrast media. Top Magn Reson Imaging 2001;12(4):309-14.
3. Behzadi AH, Zhao Y, Farooq Z, Prince MR. Immediate allergic reactions to gadolinium-based contrast agents: a systematic review and meta-analysis. Radiology 2018;286(2):471-82.
4. Cowper SE, Su LD, Bhawan J, Robin HS, LeBoit PE. Nephrogenic fibrosing dermopathy. Am J Dermatopathol 2001;23(5):383-93.
5. Grobner T. Gadolinium--a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis [published erratum appears in Nephrol Dial Transplant 2006;21(6):1745]? Nephrol Dial Transplant 2006;21(4):1104-8.
6. Ting WW, Stone MS, Madison KC, Kurtz K. Nephrogenic fibrosing dermopathy with systemic involvement. Arch Dermatol 2003;139(7):903-6.
7. Weinreb JC, Rodby RA, Yee J, Wang CL, Fine D, McDonald RJ, et al. Use of intravenous gadolinium-based contrast media in patients with kidney disease: consensus statements from the American College of Radiology and the National Kidney Foundation. Radiology 2021;298(1):28-35.
8. Rofsky NM, Sherry AD, Lenkinski RE. Nephrogenic systemic fibrosis: a chemical perspective. Radiology 2008;247(3):608-12.
9. Perazella MA. Current status of gadolinium toxicity in patients with kidney disease. Clin J Am Soc Nephrol 2009;4(2):461-9.
10. ACR Committee on Drugs and Contrast Media. ACR manual on contrast media. Available from: https://www.acr.org/-/media/ACR/files/clinical-resources/contrast_media.pdf [2021; cited 2021 Mar 3].
11. Marckmann P, Skov L, Rossen K, Dupont A, Damholt MB, Heaf JG, Thomsen HS. Nephrogenic systemic fibrosis: suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. J Am Soc Nephrol 2006;17(9):2359-62.
12. Cheong BYC, Muthupillai R. Nephrogenic systemic fibrosis: a concise review for cardiologists. Tex Heart Inst J 2010;37(5):508-15.
13. European Medicines Agency. PRAC confirms restrictions on the use of linear gadolinium agents [Internet]. Available from: https://www.ema.europa.eu/en/documents/referral/gadolinium-article-31-referral-prac-confirms-restrictions-use-linear-gadolinium-agents_en.pdf [2017 Jul 7; cited 2021 Mar 3].
14. European Society of Urogenital Radiology. ESUR guidelines on contrast agents [Internet]. Available from: http://www.esur.org/fileadmin/content/2019/ESUR_Guidelines_10.0_Final_Version.pdf [2018 Mar; cited 2021 Mar 3].
15. Schieda N, Blaichman JI, Costa AF, Glikstein R, Hurrell C, James M, et al. Gadolinium-based contrast agents in kidney disease: a comprehensive review and clinical practice guideline issued by the Canadian Association of Radiologists. Can J Kidney Health Dis 2018;5:2054358118778573.
16. Schieda N, Maralani PJ, Hurrell C, Tsampalieros AK, Hiremath S. Updated clinical practice guideline on use of gadolinium-based contrast agents in kidney disease issued by the Canadian Association of Radiologists. Can Assoc Radiol J 2019;70(3):226-32.
17. U.S. Food and Drug Administration. FDA drug safety communication: FDA warns that gadolinium-based contrast agents (GBCAs) are retained in the body; requires new class warnings [Internet]. 2018. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-gadolinium-based-contrast-agents-gbcas-are-retained-body [updated 2018 May 16; cited 2021 Mar 3].
18. Thomsen HS. Nephrogenic systemic fibrosis: a serious adverse reaction to gadolinium - 1997-2006-2016. Part 1. Acta Radiol 2016;57(5):515-20.
19. Attari H, Cao Y, Elmholdt TR, Zhao Y, Prince MR. A systematic review of 639 patients with biopsy-confirmed nephrogenic systemic fibrosis. Radiology 2019;292(2):376-86.
20. Bruce R, Wentland AL, Haemel AK, Garrett RW, Sadowski DR, Djamali A, Sadowski EA. Incidence of nephrogenic systemic fibrosis using gadobenate dimeglumine in 1423 patients with renal insufficiency compared with gadodiamide. Invest Radiol 2016;51(11):701-5.
21. Altun E, Martin DR, Wertman R, Lugo-Somolinos A, Fuller ER 3rd, Semelka RC. Nephrogenic systemic fibrosis: change in incidence following a switch in gadolinium agents and adoption of a gadolinium policy--report from two U.S. universities. Radiology 2009;253(3):689-96.
22. Martin DR, Krishnamoorthy SK, Kalb B, Salman KN, Sharma P, Carew JD, et al. Decreased incidence of NSF in patients on dialysis after changing gadolinium contrast-enhanced MRI protocols. J Magn Reson Imaging 2010;31(2):440-6.
23. Alfano G, Fontana F, Ferrari A, Solazzo A, Perrone R, Giaroni F, et al. Incidence of nephrogenic systemic fibrosis after administration of gadoteric acid in patients on renal replacement treatment. Magn Reson Imaging 2020;70:1-4.
24. McWilliams RG, Frabizzio JV, De Backer AI, Grinberg A, Maes BD, Zobel BB, Gottschalk A. Observational study on the incidence of nephrogenic systemic fibrosis in patients with renal impairment following gadoterate meglumine administration: the NSsaFe study. J Magn Reson Imaging 2020;51(2):607-14.
25. Michaely HJ, Aschauer M, Deutschmann H, Bongartz G, Gutberlet M, Woitek R, et al. Gadobutrol in renally impaired patients: results of the GRIP study. Invest Radiol 2017;52(1):55-60.
26. Woolen SA, Shankar PR, Gagnier JJ, MacEachern MP, Singer L, Davenport MS. Risk of nephrogenic systemic fibrosis in patients with stage 4 or 5 chronic kidney disease receiving a group II gadolinium-based contrast agent: a systematic review and meta-analysis. JAMA Intern Med 2020;180(2):223-30.
27. Lauenstein T, Ramirez-Garrido F, Kim YH, Rha SE, Ricke J, Phongkitkarun S, et al. Nephrogenic systemic fibrosis risk after liver magnetic resonance imaging with gadoxetate disodium in patients with moderate to severe renal impairment: results of a prospective, open-label, multicenter study. Invest Radiol 2015;50(6):416-22.
28. Starekova J, Bruce RJ, Sadowski EA, Reeder SB. No cases of nephrogenic systemic fibrosis after administration of gadoxetic acid. Radiology 2020;297(3):556-62.
29. Nandwana SB, Moreno CC, Osipow MT, Sekhar A, Cox KL. Gadobenate dimeglumine administration and nephrogenic systemic fibrosis: is there a real risk in patients with impaired renal function? Radiology 2015;276(3):741-7.
30. Costa AF, van der Pol CB, Maralani PJ, McInnes MDF, Shewchuk JR, Verma R, et al. Gadolinium deposition in the brain: a systematic review of existing guidelines and

policy statement issued by the Canadian Association of Radiologists. Can Assoc Radiol J 2018;69(4):373-82.
31. Aime S, Caravan P. Biodistribution of gadolinium-based contrast agents, including gadolinium deposition. J Magn Reson Imaging 2009;30(6):1259-67.
32. Okada S, Katagiri K, Kumazaki T, Yokoyama H. Safety of gadolinium contrast agent in hemodialysis patients. Acta Radiol 2001;42(3):339-41.
33. van der Molen AJ, Reimer P, Dekkers IA, Bongartz G, Bellin MF, Bertolotto M, et al. Post-contrast acute kidney injury - Part 1: definition, clinical features, incidence, role of contrast medium and risk factors: recommendations for updated ESUR Contrast Medium Safety Committee guidelines. Eur Radiol 2018;28(7):2845-55.
34. Ledneva E, Karie S, Launay-Vacher V, Janus N, Deray G. Renal safety of gadolinium-based contrast media in patients with chronic renal insufficiency. Radiology 2009;250(3): 618-28.
35. Prince MR, Zhang HL, Roditi GH, Leiner T, Kucharczyk W. Risk factors for NSF: a literature review. J Magn Reson Imaging 2009;30(6):1298-308.
36. Yee J. Prophylactic hemodialysis for protection against gadolinium-induced nephrogenic systemic fibrosis: a doll's house. Adv Chronic Kidney Dis 2017;24(3):133-5.
37. Ray JG, Vermeulen MJ, Bharatha A, Montanera WJ, Park AL. Association between MRI exposure during pregnancy and fetal and childhood outcomes. JAMA 2016;316(9): 952-61.
38. Gui B, Cambi F, Micco M, Sbarra M, Petta F, Autorino R, et al. MRI in pregnant patients with suspected abdominal and pelvic cancer: a practical guide for radiologists. Diagn Interv Radiol 2020;26(3):183-92.
39. De Santis M, Straface G, Cavaliere AF, Carducci B, Caruso A. Gadolinium periconceptional exposure: pregnancy and neonatal outcome. Acta Obstet Gynecol Scand 2007;86(1):99-101.
40. Committee opinion no. 723: guidelines for diagnostic imaging during pregnancy and lactation [published erratum appears in Obstet Gynecol 2018;132(3):786]. Obstet Gynecol 2017;130(4):e210-6.
41. Sachs HC, Committee On Drugs. The transfer of drugs and therapeutics into human breast milk: an update on selected topics. Pediatrics 2013;132(3):e796-809.
42. Kanda T, Ishii K, Kawaguchi H, Kitajima K, Takenaka D. High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material. Radiology 2014;270(3):834-41.
43. McDonald RJ, McDonald JS, Kallmes DF, Jentoft ME, Murray DL, Thielen KR, et al. Intracranial gadolinium deposition after contrast-enhanced MR imaging. Radiology 2015;275(3):772-82.
44. Radbruch A. Gadolinium deposition in the brain: we need to differentiate between chelated and dechelated gadolinium. Radiology 2018;288(2):434-5.
45. Frenzel T, Apte C, Jost G, Schöckel L, Lohrke J, Pietsch H. Quantification and assessment of the chemical form of residual gadolinium in the brain after repeated administration of gadolinium-based contrast agents: comparative study in rats. Invest Radiol 2017;52(7):396-404.
46. Robert P, Fingerhut S, Factor C, Vives V, Letien J, Sperling M, et al. One-year retention of gadolinium in the brain: comparison of gadodiamide and gadoterate meglumine in a rodent model. Radiology 2018;288(2):424-33.
47. Choi JW, Moon WJ. Gadolinium deposition in the brain: current updates. Korean J Radiol 2019;20(1):134-47.