Università
degli Studi
di Padova

I Mezzi di contrasto in RM cardiaca

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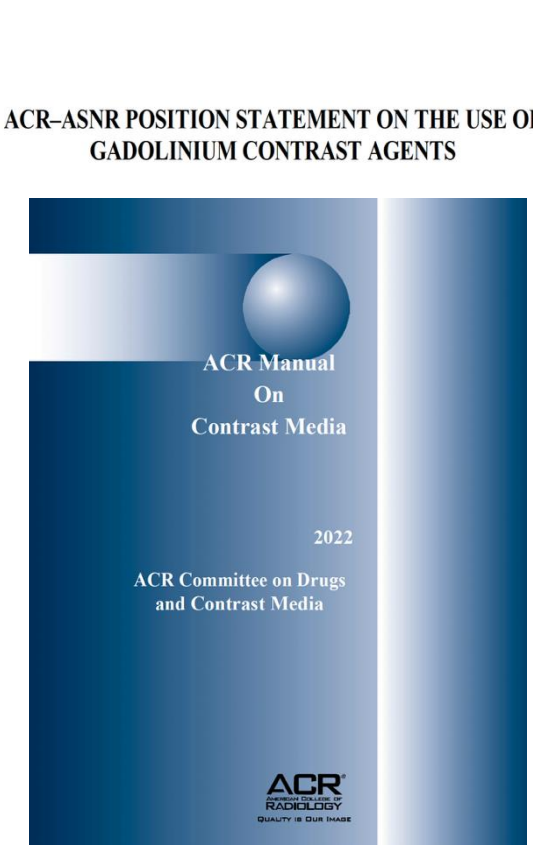
GBCA IN CARDIAC MRI

Overview → How and why? → Adverse effects → SNF → Brain deposition → THM

GBCA for Cardiac MRI



Kramer *et al. Journal of Cardiovascular Magnetic Resonance* (2020) 22:17
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Journal of Cardiovascular Magnetic Resonance

RESEARCH Open Access

Standardized cardiovascular magnetic resonance imaging (CMR) protocols: 2020 update

Christopher M. Kramer[1*], Jörg Barkhausen[2], Chiara Bucciarelli-Ducci[3], Scott D. Flamm[4], Raymond J. Kim[5] and Eike Nagel[6]

Radiology: Cardiothoracic Imaging

ORIGINAL RESEARCH

Gadolinium-based Contrast Agents for Cardiac MRI: Use of Linear and Macrocyclic Agents with Associated Safety Profile from 154 779 European Patients

Johannes Uhlig, MD, MPH • Omar Al-Bourini, MD • Rodrigo Salgado, MD • Marco Francone, MD, PhD • Rozemarijn Vliegenthart, MD, PhD • Jens Bremerich, MD • Joachim Lotz, MD • Matthias Gutberlet, MD, PhD

Radiology: Cardiothoracic Imaging 2020; 2(5):e200102 • https://doi.org/10.1148/ryct.2020200102 •

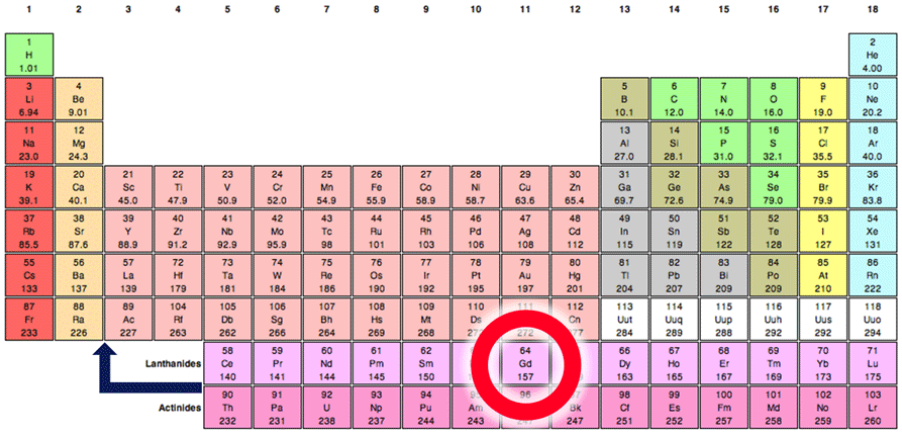
Gadolinium-based contrast agents - GBCA

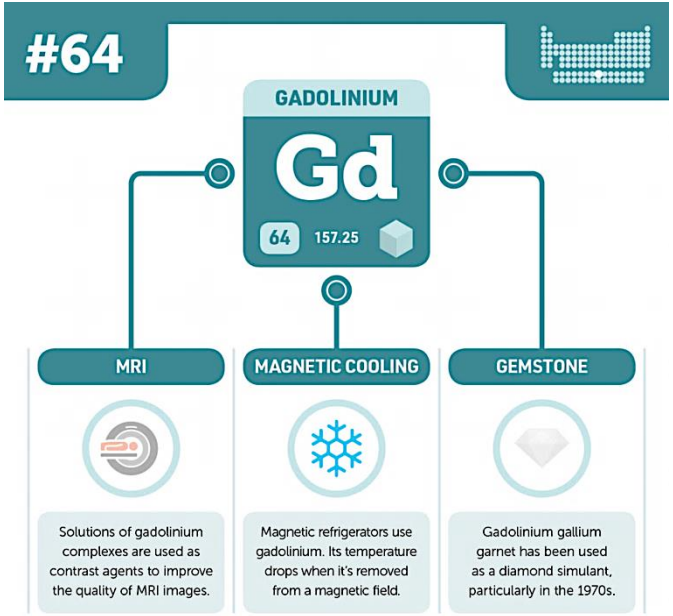
* **More than 300 million GBCA doses** worldwide since 1988: crucial medical information and excellent safety profile.
* **Nephrogenic systemic sclerosis (NSF)** and **long-term gadolinium retention in the brain:** regulatory actions.
* In 2017 the **EMA** suspended the marketing authorizations of multipurpose **linear** GBCAs.
* Healthcare professionals should consider the characteristics of each agent when choosing a GBCA.
* The **dose** of GBCA should be **as low as possible.**
* **Noncontrast techniques** should be considered whenever possible.

Overview

Types of Contrast Agents

- **Why Gadolinium?**
  - A paramagnetic substance
  - Atomic number of 64
  - 7 unpaired electrons
  - **TOXIC**
  - To reduce their toxicity they have to be bound in **chelates.**



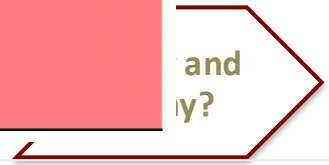


How and why?

Types of Contrast Agents

* Based on the type of ligand, GBCAs can be categorized as **ionic versus nonionic** and **linear versus macrocyclic** compounds.
* All GBCAs share a common structure of an organic ligand that tightly binds to and improves the stability, solubility, and safety of the central gadolinium heavy metal ion.
* **Cyclic** GBCAs are more stable than linear one, and have a higher stability constant and substantially lower dissociation rate.

	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)



Types of Contrast Agents

Table 2: GBCA Subtypes with Commercial Names, Molecular Properties, and EMA Approval Evaluated in this Study

GBCA Subtype	Exemplary Commercial Name	No. of Examinations Evaluated	Molecular Structure	Molarity (mmol/mL)	EMA Approval in Body Scans*
Gadobutrol	Gadovist (Leverkusen, Germany)	85 883	Macrocyclic	1.0	Maintain
Gadoteric acid	Dotarem (Guerbet, Princeton, NJ), Artirem (Guerbet)	29 919	Macrocyclic	0.5	Maintain
Gadoteridol	ProHance (Bracco Diagnostics, Singen, Germany)	11 161	Macrocyclic	0.5	Maintain
Gadobenate dimeglumine	MultiHance (Bracco Diagnostics)	9237	Linear	0.5	Restrict to liver scans
Gadopentetate dimeglumine	Magnevist (Bayer HealthCare)	6585	Linear	0.5	Suspend
Gadodiamide	Omniscan (GE Healthcare, Chicago, Ill)	3070	Linear	0.5	Suspend

Note.—EMA = European Medicines Agency, GBCA = gadolinium-based contrast agent.
* As of July 20, 2017.

GBCA IN CARDIAC MRI

Table I. Commonly administered contrast agents for cardiovascular magnetic resonance imaging[a]

Generic name	Product name	Chemical abbreviation	Manufacturer	Type	Approved	Molarity	Osmolality (osmol/kg)	Viscosity (centipoise)
~~Gadopentetate~~	~~Magnevist~~	~~Gd-DTPA~~	~~Berlex~~	~~Extracellular, paramagnetic~~	~~US FDA~~	~~0.500~~	~~1.96~~	~~2.90~~
~~Gadodiamide~~	~~Omniscan~~	~~Gd-DTPA-BMA~~	~~Nycomed, Amersham~~	~~Extracellular, paramagnetic~~	~~US FDA~~	~~0.500~~	~~0.79~~	~~1.40~~
~~Gadoversetamide~~	~~OptiMARK~~	~~Gd-DTPA-BMEA~~	~~Mallinckrodt~~	~~Extracellular, paramagnetic~~	~~US FDA~~	~~0.500~~	~~1.11~~	~~2.00~~
Gadoteridol	ProHance	Gd-HPDO3A	Bracco	Extracellular, paramagnetic	US FDA	0.500	0.63	1.30
Gadobenate	MultiHance	Gd-BOPTA	Bracco	Extracellular, paramagnetic	US FDA	0.500	1.97	5.30
Gadoterate	Dotarem	Gd-DOTA	Guerbet	Extracellular, paramagnetic	EU	0.500	1.35	2.00
Gadobutrol	Gadovist	Gd-DO3A-butrol	Schering	Extracellular, paramagnetic	EU	1.000	1.39	3.70

a Most of the contrast agents listed here have been approved by the FDA and have already been in use for more than two decades.

EXTRACELLULAR
(NON BLOOD-POOL)

Overview | How and why? | Adverse effects | SNF | Brain deposition | THM

GBCA IN CARDIAC MRI

* **Gadolinium based contrast agent (GBCA) dosing and safety in cardiac MRI:**

1. Volumes and injection rates vary depending on the contrast agent and scan protocol.
2. Injection rates are different for **1 mmol/ml** contrast agents (gadobutrol) and **0.5 mmol/ml** agents. As a guideline, divide the given injection rates by a factor of 2 for the 1 mmol/ml formulation.
3. GBCA contrast agents with higher relaxivity require smaller doses.

Table 1 Contrast and chasing bolus doses and injection rates

Indication	Contrast dose (mmol/kg body weight)	Injection rate	Saline chasing bolus	Injection rate
Perfusion	0.05–0.1	3–7 ml/s	30 ml	3–7 ml/s
Late gadolinium enhancement	0.1–0.2		20 ml	
Angiography (carotids, renals, aorta)	0.1–0.2	2–3 ml/s	20 ml	2–3 ml/s
Time-resolved angiography	0.05	3–5 ml/s	30 ml	3–5 ml/s
Peripheral angiography	0.2	first 10 ml @ 1.5 ml/s, rest @ 0.4–0.8 ml/s	20 ml	0.4–0.8 ml/s

GBCA IN CARDIAC MRI

* **Gadolinium based contrast agent (GBCA) dosing and safety in cardiac MRI:**

4. Approved clinical doses range from **0.1 and 0.3 mmol/kg** body weight.

5. **The document on standardized cardiac MR protocols of the Society for Cardiovascular Magnetic Resonance (SCMR)** provides a practical overview of the recommended contrast and chasing bolus doses and injections rates (**0.05-0.1 mmol/kg** for perfusion imaging and **0.1-0.2 mmol/kg** for LGE imaging).

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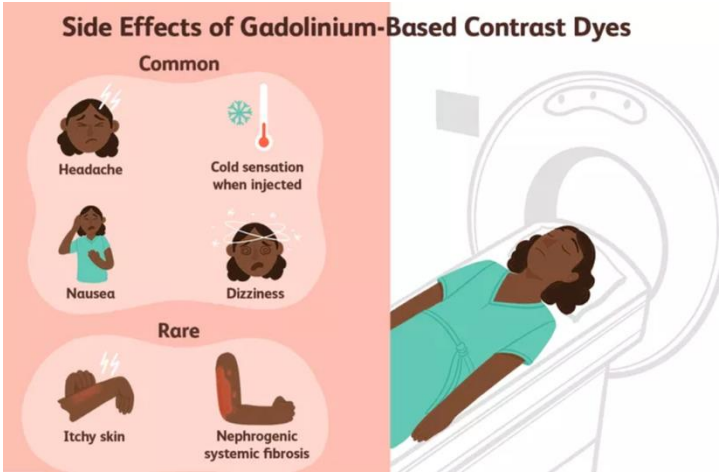
GBCA: ACUTE ADVERSE EVENTS

* GBCAs can be considered **safe** for the referred population in general and the cardiac MRI population in particular, with reported **acute adverse event (AAE)** rates **0.04%-3%** in recent reports, at clinical doses (0.1–0.2 mmol/kg)

* Most reactions are mild and physiologic, including coldness, warmth, or pain at the injection site; nausea with or without vomiting; headache; paresthesias; dizziness.



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* Allergic-like reactions are uncommon (**0.004% to 0.7%**). **Severe** life-threatening anaphylactic reactions occur but are exceedingly rare (**0.001% to 0.01%**). Fatal reactions to gadolinium chelate agents occur but are extremely rare.

* **No deaths due to contrast administration in cardiac MRI were reported.**

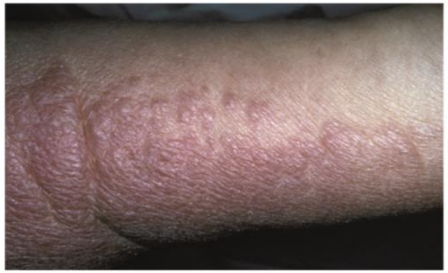
* AAEs are reported to be more common after administration of any **pharmacologic stressor** (dobutamine and regadenoson > adenosine).

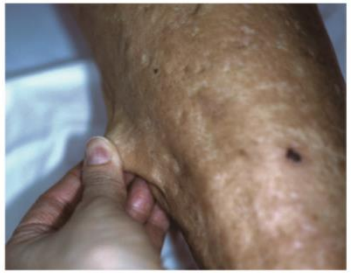
GBCA: ACUTE ADVERSE EVENTS

* The frequency of AAEs to GBCM is about **8 times higher** in patients with a **previous reaction to GBCM**.
* A **prior reaction to iodinated contrast media** increases the risk of reactions to GBCAs.
* **Treatment** of acute adverse reactions to GBCM is similar to that for acute reactions to iodinated contrast media.
* At many institutions, a prior allergic-like reaction to GBCM is often an indication for **corticosteroid prophy**laxis prior to subsequent exposures.

GBCA & NSF

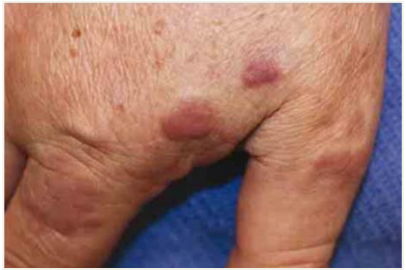
* Rare fibrosing condition
* Patches of skin become thickened and tethered to the underlying tissue
* The fibrosing process can also involve internal organs
* 5% of cases have a fulminant course, resulting in death





Prince et al. RadioGraphics 2009; 29:1565–1574

- In 2000 the first report on nephrogenic systemic fibrosis (NSF), observed in patients with endstage chronic kidney disease.
- In 2006 Grobner associated Gd with NSF
- High et al. and Wiginton et al. found Gd in the biopsy of NSF patients



GBCA & NSF

- The exact mechanism of NSF causation is unknown. The pathogenesis of NSF most likely involves the **dissociation of free and toxic Gd3+** through transmetallation by endogenous metal ions such as Zn2+ or Cu2+.

- It is now known that there are differences in the likelihood of a patient developing NSF after exposure to different formulations of GBCAs.

TABLE I. Gadolinium … osis

	Cyclic	
Ionic	Gadoteric a… (Dotarem, … Clariscan, …	racco Diagnostics Inc.)
		Pharmaceuticals Inc.)
		Bayer HealthCare
Nonionic	Gadoterido…	
	Gadobutrol … Pharmaceu…	

Classification of GBCAs Based on NSF Risk

Generic Name	Trade Name	EMA*	FDA†	ACR‡
Gadodiamide	Omniscan®	High	+	Group I
Gadoversetamide	OptiMark®	High	+	Group I
Gadopentetate dimeglumine	Magnevist®	High	+	Group I
Gadobenate dimeglumine	MultiHance®	Intermed	–	Group II
Gadoteridol	ProHance®	Low	–	Group II
Gadobutrol	Gadavist®	Low	–	Group II
Gadoteric acid	Dotarem®	Low	NA	Group II
Gadoxetic acid	Eovist®/Primovist®	Intermed	–	Group III
Gadofosveset	Ablavar®	Intermed	–	Group III

In 2009, the FDA determined that moderate renal impairment (eGFR of 30-60 mL/min/1.73 m²) was NOT a risk factor for NSF.

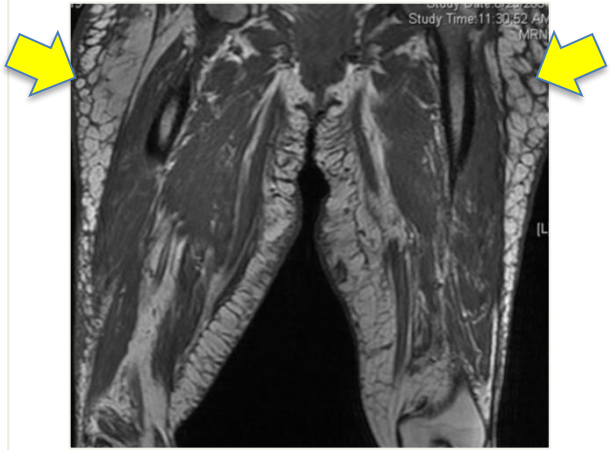
NSF risk
Contraindicated in patients with AKI or severe CKD (GFR <30 mL/min/1.73 m²)
Associated with NSF

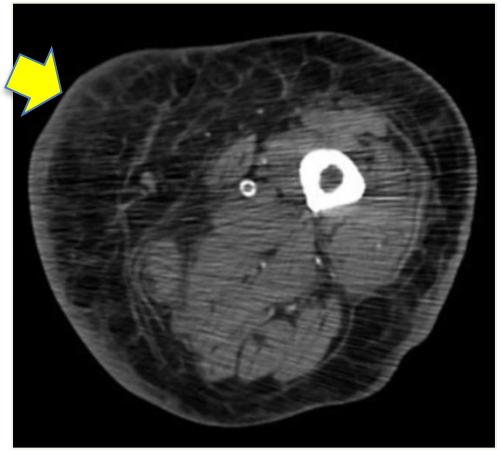
GBCA & NSF

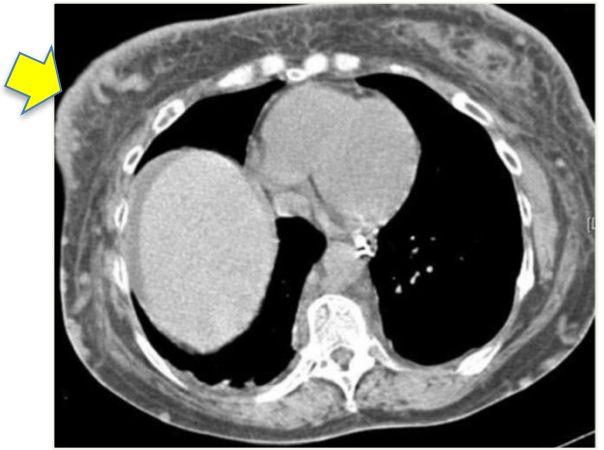
- Among patients with severe CKD (CKD4) that developed NSF, most had an eGFR between 15-30 ml/min/1.73 m2. There have been rare published case reports of patients with eGFR values **> 30 ml/min/1.73 m2**.

- As studies found an association between high dosage of gadolinium chelates (0.2–0.3 mmol/kg) and increased incidence of NSF, **double or triple dosing is no longer common practice**.

- GBCM are not considered nephrotoxic at dosages approved for MR imaging (0.1–0.2 mmol/kg).







GBCA & NSF

- In **2017**, the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency **suspended the use of high-risk linear Group III GBCAs** (gadodiamide, gadopentetate dimeglumine, and gadoversetamide) and **limited the use of gadobenate dimeglumine and gadoxetic acid (Group II) to hepatobiliary imaging only.**

Table 7. Classification of gadolinium-based contrast agents with risk of nephrogenic systemic fibrosis.

Risk of NSF	ACR (USA)	EMA (Europe)
High risk	Gadodiamide (Omniscan®) Gadopentetate dimeglumine (Magnevist®) Gadoversetamide (OptiMark™)	~~Gadodiamide (Omniscan®)~~ ~~Gadopentetate dimeglumine (Magnevist®)~~ ~~Gadoversetamide (OptiMARK™)~~
Medium risk	–	Gadoxetic acid (Primovist®) ~~Gadofosveset (Vasovist®)~~ Gadobenate dimeglumine (Multihance®)
Low risk	Gadoteric acid (Dotarem®)† Gadoteridol (ProHance®) Gadobenate dimeglumine (Multihance®) Gadobutrol (Gadovist®)†	Gadoteric acid (Dotarem®) Gadoteridol (ProHance®) Gadobutrol (Gadovist®)

†Not approved by the US FDA.
ACR: American College of Radiology; NSF: Nephrogenic systemic fibrosis.
Data taken from [104,106].

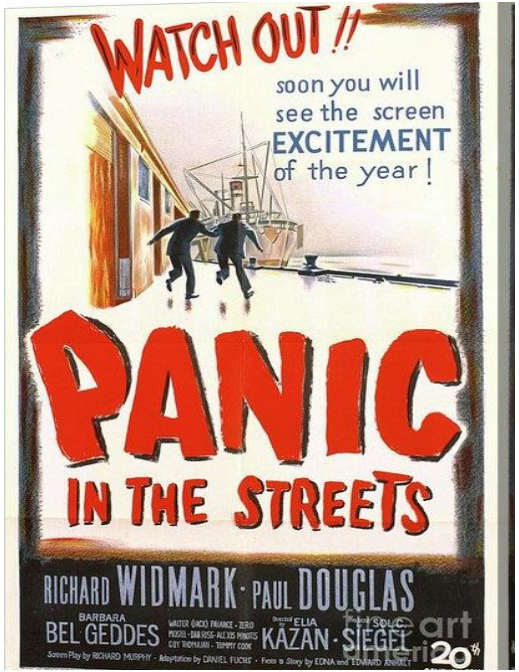
- Patients receiving **group I GBCAs** should be considered at risk of developing NSF if any of the following conditions apply to the patient:
  - On dialysis (of any form)
  - Severe or end-stage CKD (CKD 4 or 5, eGFR < 30 mL / min/1.73 m2)
  - AKI
- No special precautions are typically necessary for patients with stage 1, 2, or 3 CKD.

GBCA & BRAIN DEPOSITION

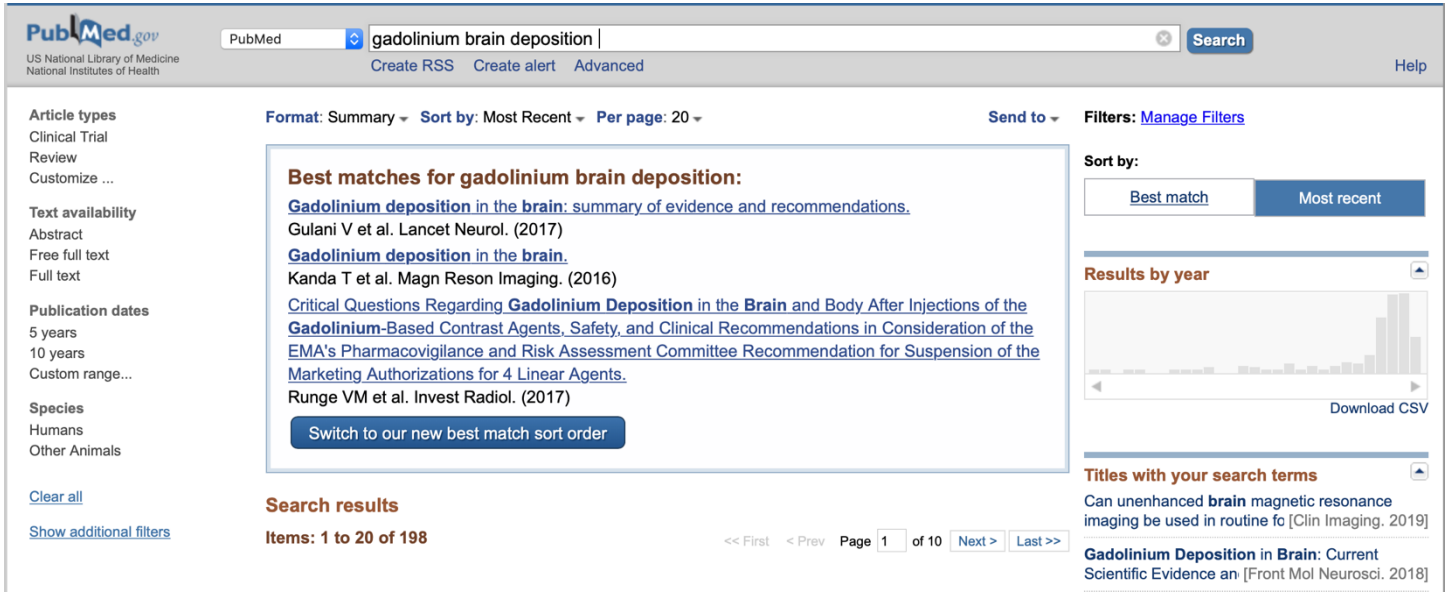
ORIGINAL RESEARCH ■ NEURORADIOLOGY

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[1]

Radiology



GBCA & BRAIN DEPOSITION



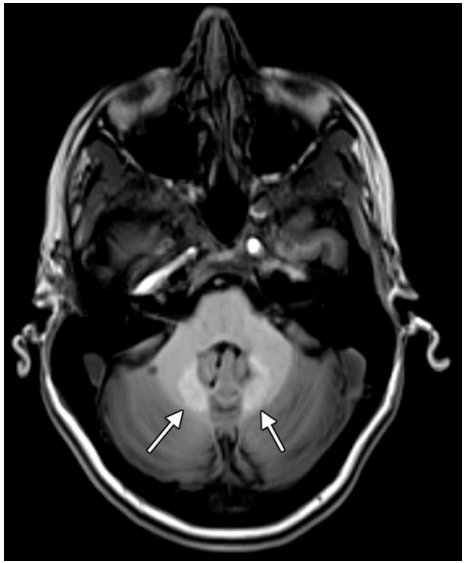
GBCA & BRAIN DEPOSITION

- Less stable compounds (**linear agents**) are more strongly linked to brain deposition than more stable compounds (macrocyclic agents).
- GBCA brain deposition depend on the **cumulative dose** and **administered class.**
- Not clear if the accumulated gadolinium is free Gd3+ or chelated
- Up until now, the clinical relevance of the gadolinium brain deposition is unknown.
  It has not been associated with neurologic or biological adverse effects.

RSNA Statement on Gadolinium-Based MR Contrast Agents
Updated: 4/15/2018

The Radiological Society of North America (RSNA) is committed to excellence in patient care through education and research.

- Several preliminary studies have demonstrated the presence of residual gadolinium concentrations in the brains of patients with no history of kidney disease. The clinical significance of this observation is unknown at this time, but warrants attention.



RadioGraphics

GBCA IN CARDIAC MRI

* **Noncontrast techniques** should be considered whenever possible

* For all patients at risk of chronically reduced renal function (including age >60 years, hypertension, or diabetes), **GFR** should be estimated through laboratory sampling.

* GBCAs should be carefully administered when **GFR<30ml/min/1.73m2.**

* The use of a lower-than-recommended GBCA **dose** for NSF prevention is not supported by evidence and may compromise image quality.

* Need of **further research** about other sites of GBCAs' deposits.

GBCA IN CARDIAC MRI

GBCA IN CARDIAC MRI

Thank you for your attention!