# BEYOND THE BASICS: MRI GADOLINIUM BASED CONTRASTS AGENTS UPDATES AND GUIDELINES REVIEW

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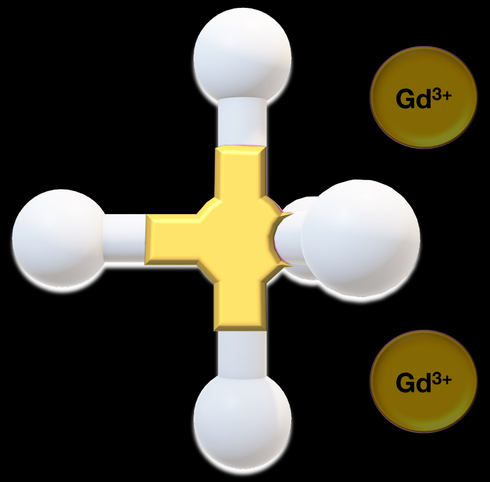

# Abbreviations

- MRI: Magnetic Resonance Imaging
- GBCAs: Gadolinium-based contrast agents
- EMA: European Medicines Agency
- ACR: American College of Radiology
- ESUR: European Society of Urogenital Radiology
- CT: Computed tomography
- NSF:  Nephrogenic systemic fibrosis
- $Gd^{3+}$: Gadolinium ion
- $Mn^{2+}$: Manganase ion
- $Fe^{3+}$: Iron ion
- IONs: Iron oxide nanoparticles
- U-SPION: Ultra-Small Superparamagnetic Iron Oxide nanoparticles
- SPION: Small Superparamagnetic Iron Oxide nanoparticles
- OATP: Organic anion transporting polypeptides
- MRP: Membrane multidrug resistance protein
- FDA: Food and Drug Administration
- eGFR: Estimated glomerular filtration rate
- CKD: Chronic kidney disease
- AKI: Acute Kidney Injury
- GDD:  Gadolinium deposition disease
- SAGE: Symptoms Associated with Gadolinium Exposure
- CNS: Central nervous system

# DISCLOSURES

The authors have no conflict of interest to declare

# TEACHING POINTS

1. To describe the classification of contrast agents in magnetic resonance imaging based on the type and biodistribution.
2. To explain the main characteristics of Gadolinium.
3. To review Gadolinium-based contrast agents (GBCAs), describing their generalities and classifications.
4. To list the early and late adverse reactions GBCAs and explain Gadolinium deposition disease/symptoms associated with Gadolinium exposure, based on the different guidelines of the American College of Radiology (ACR) and European Society of Radiology (ESUR).
5. To define nephrogenic systemic fibrosis.
6. To review current recommendations according to ACR and ESUR guidelines on risk assessment, pregnancy, breastfeeding and waiting time between examinations.
7. To summarize information about the development of new GBCAs.

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# INTRODUCTION

In magnetic resonance imaging (MRI), contrast agents are used to improve the image and contrast of tissues. Gadolinium-based contrast agents (GBCAs) have been widely used since its approval by FDA (Food and Drug Administration) in 1988 and have increased the capacity of pathological findings.

The main component of GBCAs is gadolinium, a heavy metal used in MRI for its paramagnetic effects.
Through over time, different types of GBCAs have been implemented in the clinical setting and others have been withdrawn for safety reasons, additionally new contrast agents are being developed and investigated.

It is important to know and understand GBCAs from their composition to adverse reactions, which allow us to make appropriate use of this agent in clinical practice in MRI.

This presentation aims to provide knowledge on the use of GBCAs, as well as updates and recommendations according to the latest guidelines of the American College of Radiology (ACR) and European Society of Radiology (ESUR).

# CONTRAST AGENTS IN MRI

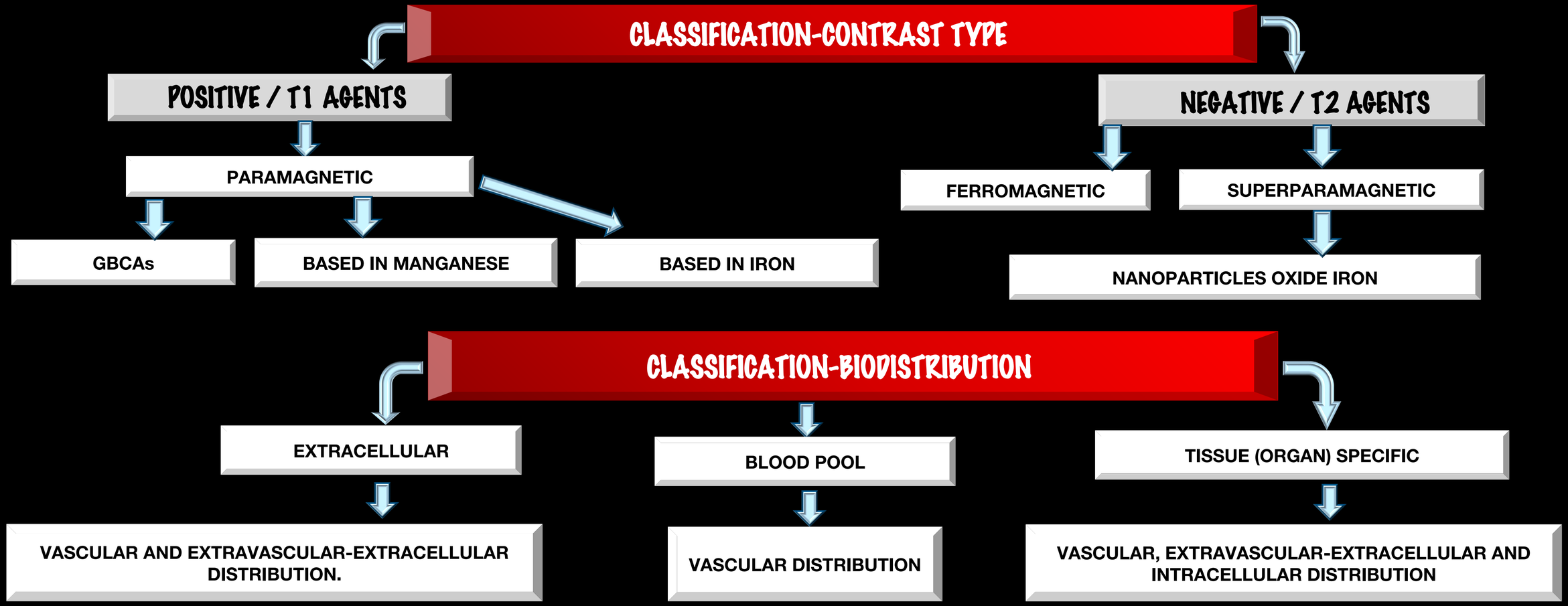
- In MRI the contrast agent is used to generate a strong signal between the tissues and thus increase the contrast of the image.
- Contrast agents reduce relaxation times due to their characteristics and allow the signal of healthy tissue to be differentiated from diseased tissue.

## AN IDEAL MRI CONTRAST AGENT SHOULD HAVE

| STRONG STABILITY | HIGH RELAXIVITY | ADEQUATE SUSCEPTIBILITY | TISSUE SPECIFICITY | LOW TOXICITY | OPTIMAL BIODISTRIBUTION | PROPER ELIMINATION |
|---|---|---|---|---|---|---|
| Based in the thermodynamic constant, which secures that the Gd ion is not released in the body. | Enables the alteration of the hydrogen proton relaxation time | Ability to be magnetized in an external magnetic field | Capacity to target specific tissues or organs | Unlikely to cause harmful effects on organic tissues | Remains for a reasonable time in the blood flow and tissues to ensure adecuate constrat | Facility to be excreted from the target tissue and rapidly released outside the body |

# CONTRAST AGENTS IN MRI

MRI contrast agents can be classified according to different criteria:

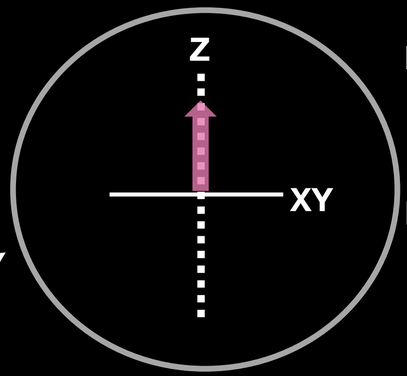


# CONTRAST AGENTS IN MRI

| TYPE OF CONTRAST | MECHANISM | WHAT ARE THEY? | MAGNETIC PROPERTY |
|---|---|---|---|

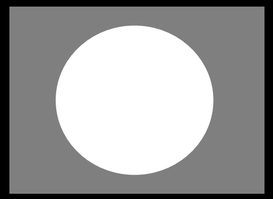
## 1- TYPE OF CONTRAST AND MAGNETIC PROPERTIES

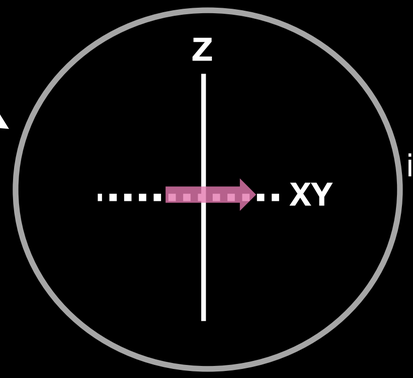
MRI




**T1 Contrast (+)**

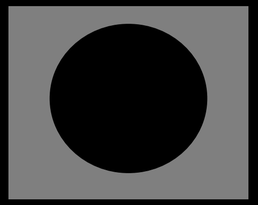
Increases contrast and the signal intensity on the T1-weighted image by shortening the LONGITUDINAL relaxation time of the proton






**T2 Contrast (-)**

Decreases the signal intensity on the T2-weighted image by shortening the proton TRANSVERSE relaxation time.



$Gd^{3+}$: Gadolinium ion
$Mn^{2+}$: Manganase ion
$Fe^{3+}$: Iron ion
IONs: Iron oxide nanoparticles
U-SPION: Ultra-Small Superparamagnetic Iron Oxide nanoparticles
SPION: Small Superparamagnetic Iron Oxide nanoparticles

- $Gd^{3+}$
- $Mn^{2+}$
- $Fe^{3+}$

**PARAMAGNETIC**

Metal ions with unpaired electrons in the outer orbital shells exhibit high magnetic susceptibility and fluctuating magnetic fields that affect nearby protons.

- U-SPION
- IONs
- SPION

**SUPERPARAMAGNETIC**

Are colloidal materials made up of particles (~ 5-200 nm in diameter) and in the presence of an external magnetic field they align with the field and produce high magnetism

# CONTRAST AGENTS IN MRI

MRI contrast agents can be administered: intravenously, orally or inhalation. Intravenous can be classified: extracellular, blood pool and tissue/organ-specific agents

## 2- BIODISTRIBUTION

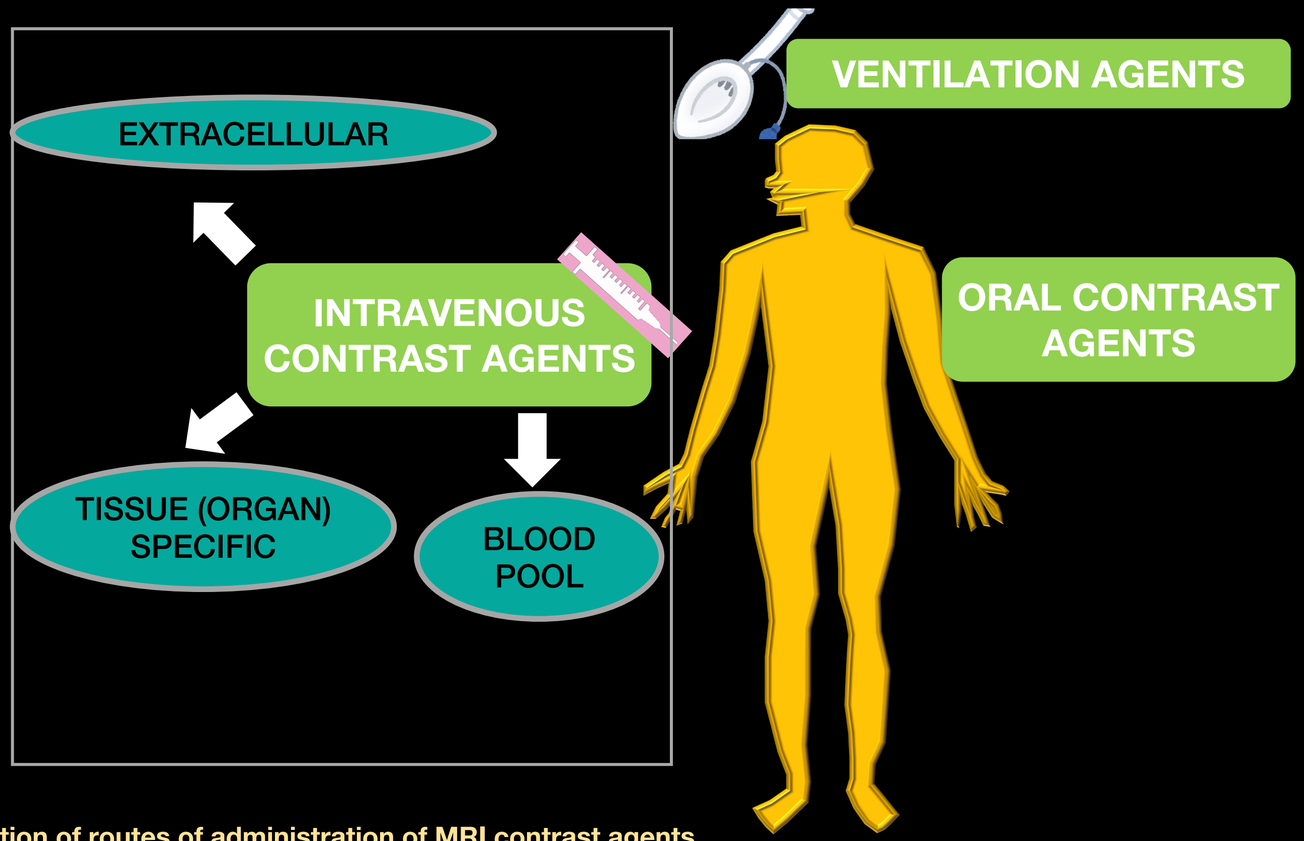



Illustration of routes of administration of MRI contrast agents

## BIODISTRIBUTION AND EXCRETION ROUTES OF CONTRAST AGENTS

- Hepatobiliary
- Renal

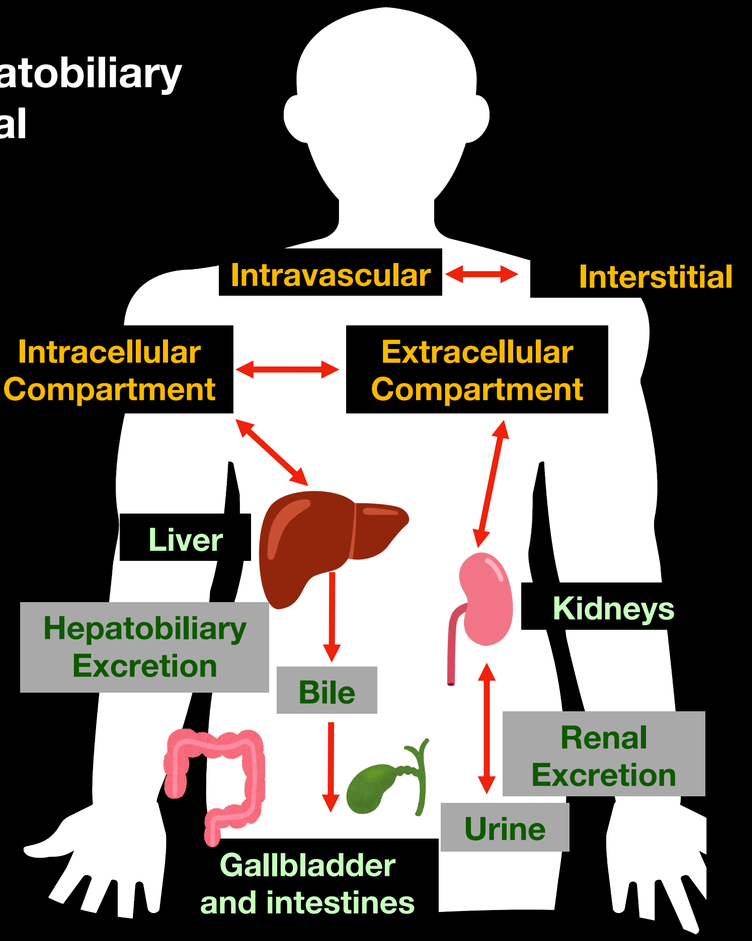



Illustration shows distribution sites and excretion routes of contrast agents administered intravenously

# CONTRAST AGENTS IN MRI

## 2- BIODISTRIBUTION

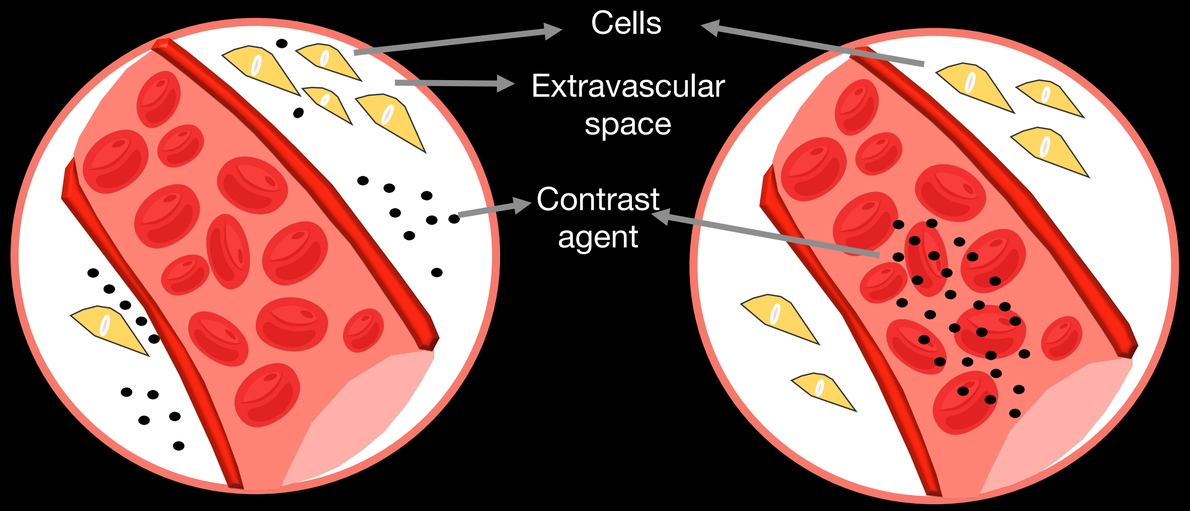
**Three Types:**

### A) EXTRACELLULAR

They accumulate from the bloodstream to the extracellular fluid and are distributed to the extravascular and interstitial fluid, they are excreted mainly through the kidneys.

### B) BLOOD POOL

Agents that remain in the intravascular space, avoid passing into the interstitium and provide high contrast of the vascular system.




Illustrations A) demonstration of the mechanism of extracellular contrast agents B) Blood pool agents

### C) TISSUE (ORGAN) SPECIFIC

Organ-specific contrast agents are capable of targeting the liver, spleen, bones, brain, lymph and other organs. Liver-specific contrast agents have affinity for a cell or receptor, can be divided into two main classes: hepatocyte-targeting agents( Gadolinium based and Manganese based) and reticuloendothelial system targeting agents (SPION).

**Its distribution is vascular, extravascular-extracellular and intracellular.**

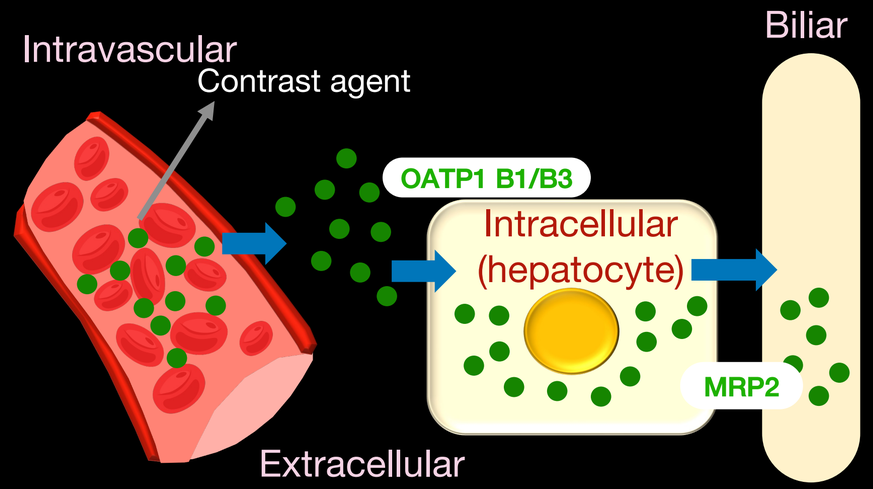


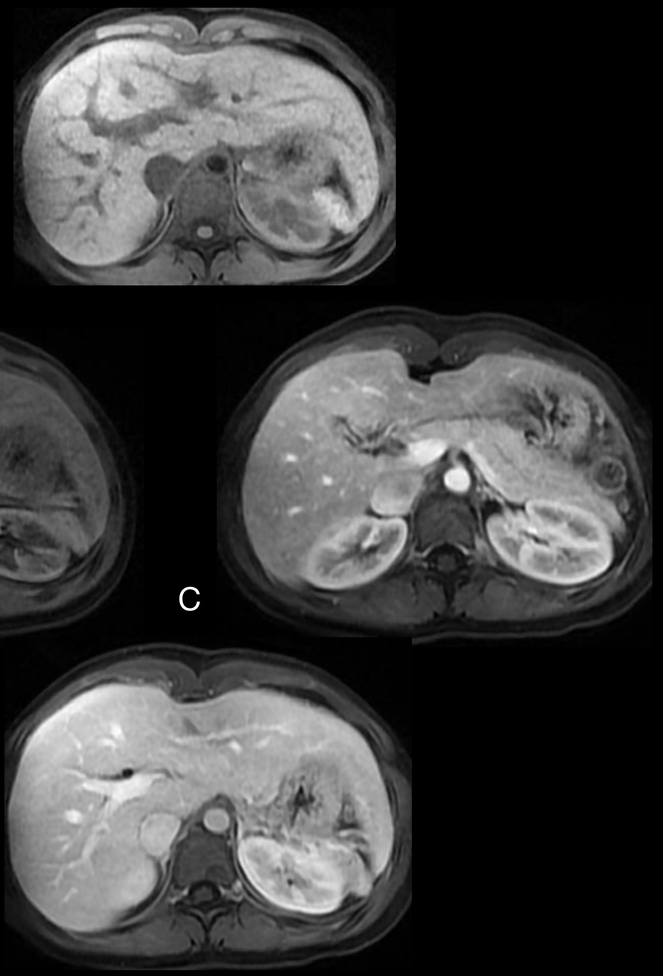

Illustration shows distribution of tissue specific agents (hepatocyte- targeting)

# CONTRAST AGENTS IN MRI

## PROTOCOL MRI

### EXTRACELLULAR AGENTS

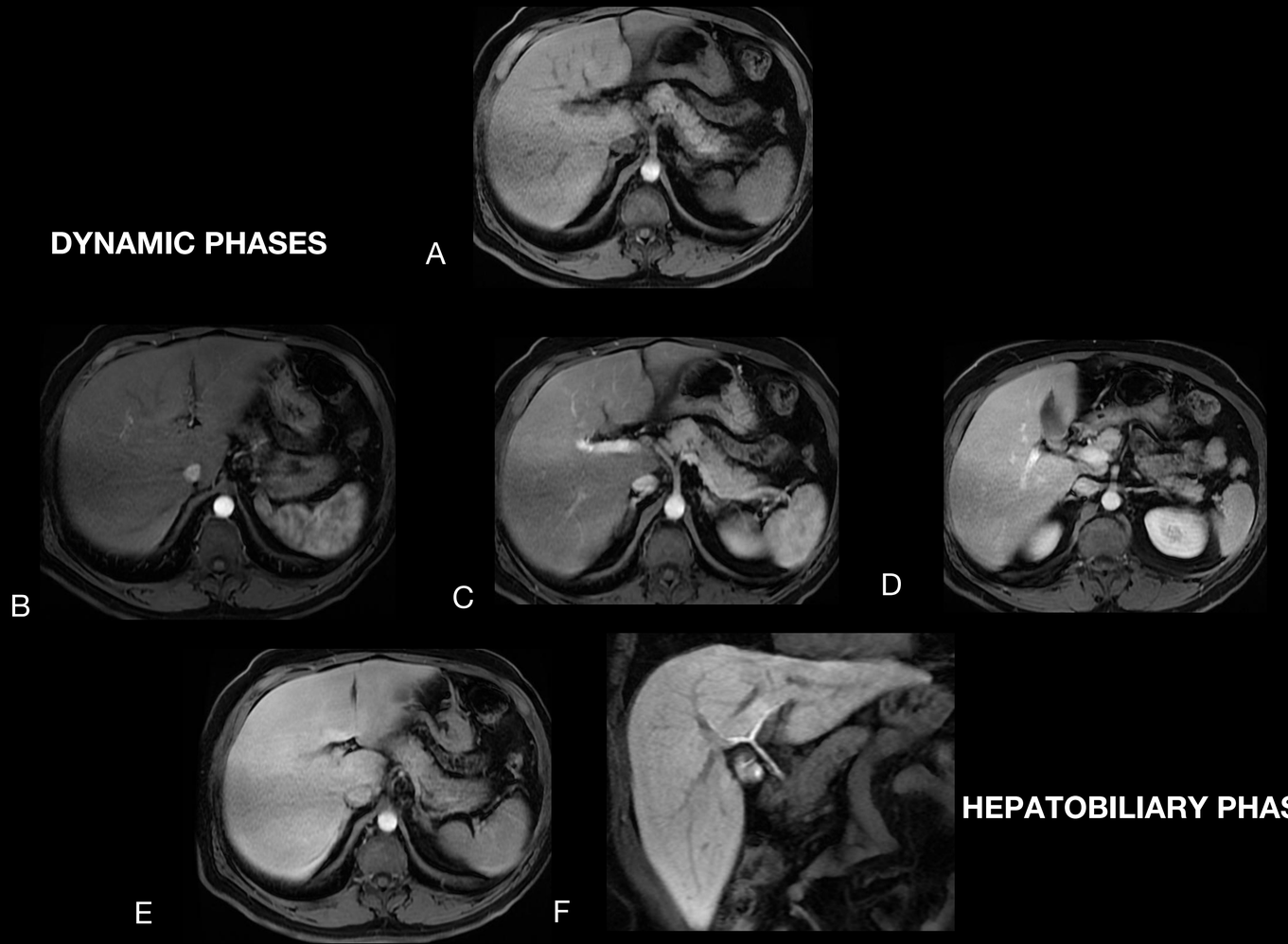
DYNAMIC PHASES




MRI. Dynamic phase contrasted with gadoteric acid A) T1 weighted non-contrast B) T1 + C, early arterial phase C) T1 + C, late arterial phase D) T1+ C, portal venous phase

### TISSUE SPECIFIC AGENTS

DYNAMIC PHASES




HEPATOBILIARY PHASE

MRI. Dynamic contrasted and hepatobiliary phase with gadoxetate disodium A) T1 weighted non-contrast B) T1 + C, early arterial phase C) T1 + C, late arterial phase D) T1+ C, portal venous phase E) transition phase F) hepatobiliary phase (20 minutes)

# GADOLINIUM (Gd) FEATURES

## WHAT IS GADOLINIUM ($Gd^{3+}$)?

**GADOLINIUM ($Gd^{3+}$) :**

-Paramagnetic and heavy metal.

-Silver white color

- 7 unpaired orbital electrons, in layer 4 f internal.
- Atomic number of 64
- The most paramagnetic metal ion used in MRI contrast agents.

## WHAT HAPPEN WITH GADOLINIUM ?

**GADOLINIUM ($Gd^{3+}$) FREE IS TOXIC !!**

-Needs to be bound to an organic ligand (a carrier molecule / chelating agent) forming a chelated compound.

- This decreases the toxic effect of the free Gd ion.

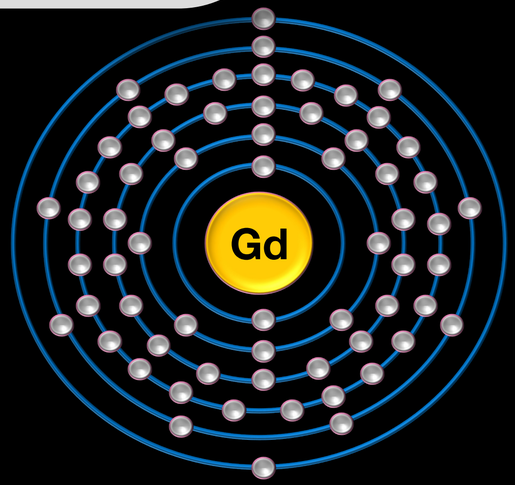
## WHAT DOES THE UNION OF GADOLINIUM WITH ITS CHELATE DEPEND ON?

**THERMODYNAMIC STABILITY**

DETERMINE THEIR OVERALL CHEMICAL STABILITY

**KINETIC STABILITY**

The name gadolinium is from the metal gadolinite, from the lanthanide group, named after the finnish chemist Johan Gadolin (1760-1852).




64 157.25

**Gd**

**Gadolinium**

**Thermodinamic stability**
Afinity between the Gd and the ligand, equilibrium state between chelated and non-chelated gadolinium.

$$Gd + L \approx GdL \qquad K_{GdL} \approx \frac{[GdL]}{[Gd][L]}$$

Gd: Gadolinium
L: Ligand

**Kinetic stability**: Dissociation rate, which explains how quickly resting equilibrium is achieved and how quickly gadolinium is released from a gadolinium complex (Rate of dissociation of gadolinium from its chelate).

# GADOLINIUM-BASED CONTRAST AGENTS (GBCAs)

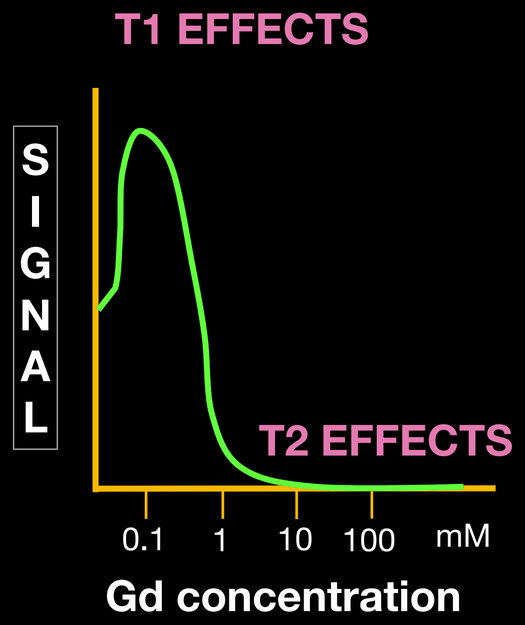
## MECHANISM/EFFECT OF GBCAs IN MRI

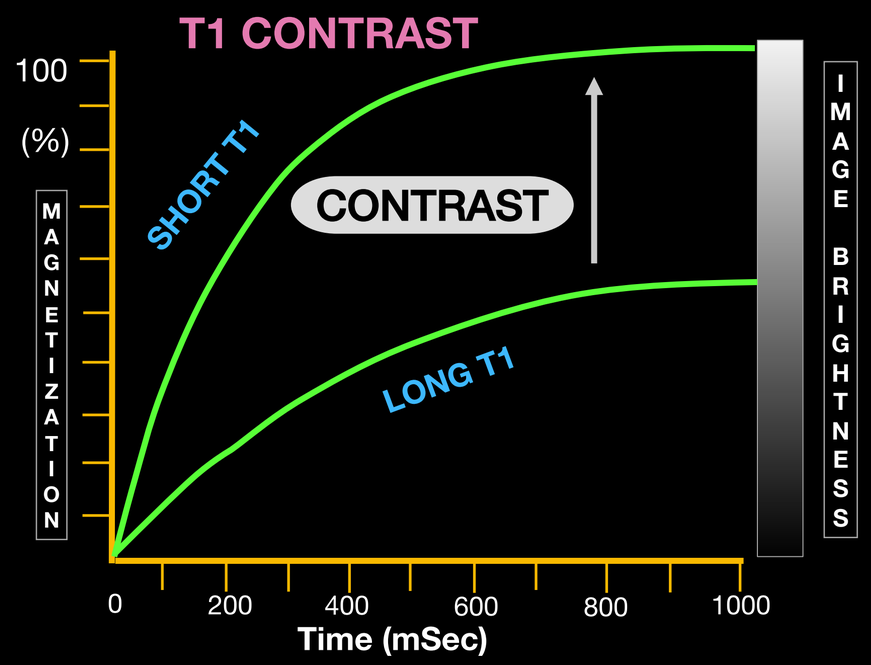
Relaxivity is the ability of an agent to increase relaxation rates of the surrounding protons.

GBCAs create high magnetic moment, modifies protons relaxation times, shortens the T1 and T2 of the tissues.

The relaxation of the nuclear spin is due to the dipole-dipole magnetic interaction between the unpaired electrons of $Gd^{3+}$ and the water molecules

Resulting in an increase in the intensity of the T1-weighted signal and a decrease in the T2-weighted sequences.




Efficiency of GBCAs: **RELAXITIVITY!!**

T1-relaxitivity depends on: the changes and numbers of the water molecules bound to $Gd^{+3}$ of the inner sphere ($q$), the rotation times ($\tau R$) and the mean residence lifetime ($\tau M$)

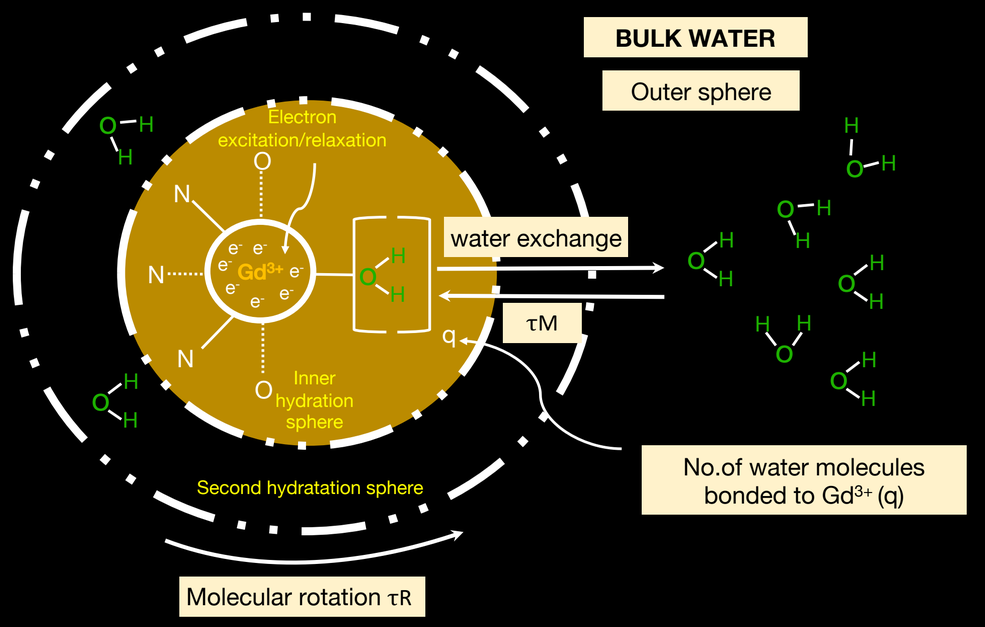
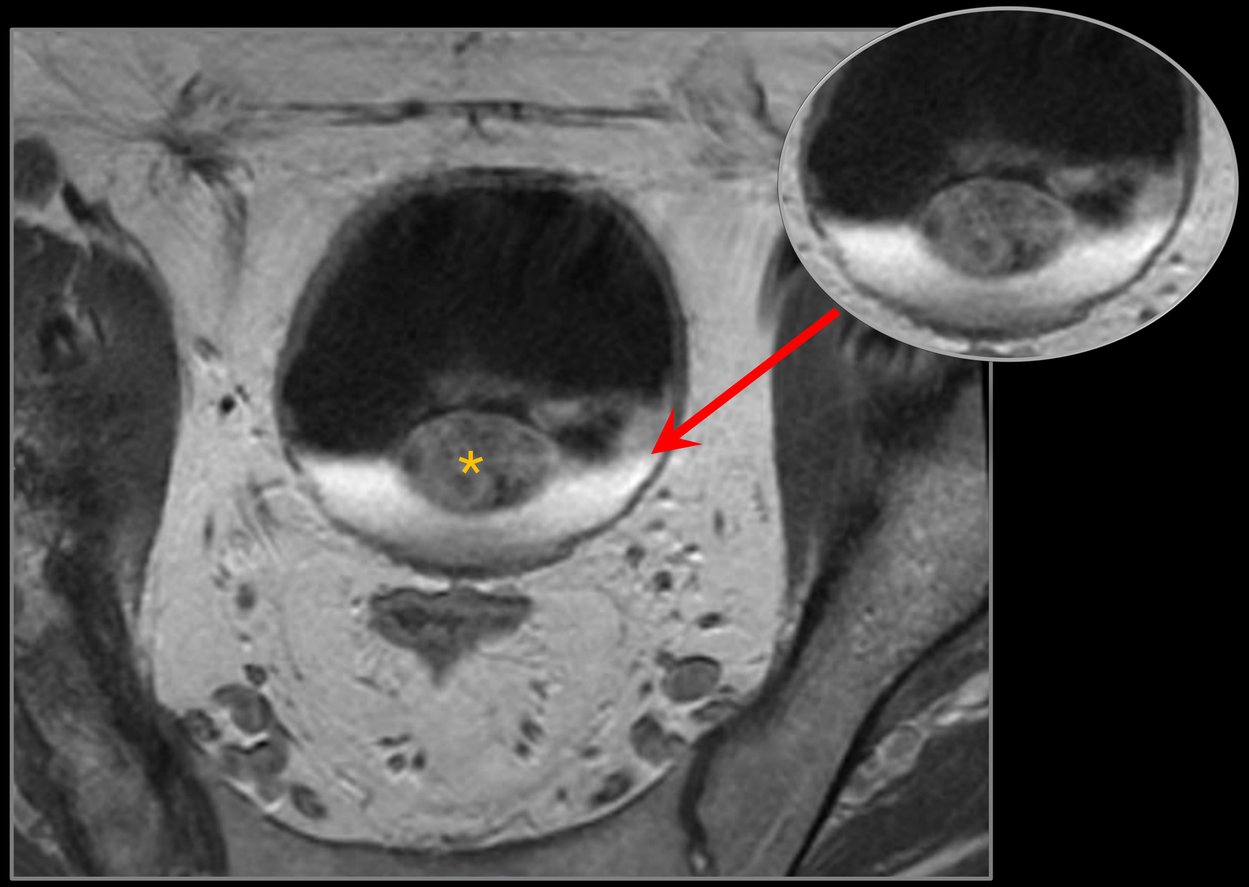


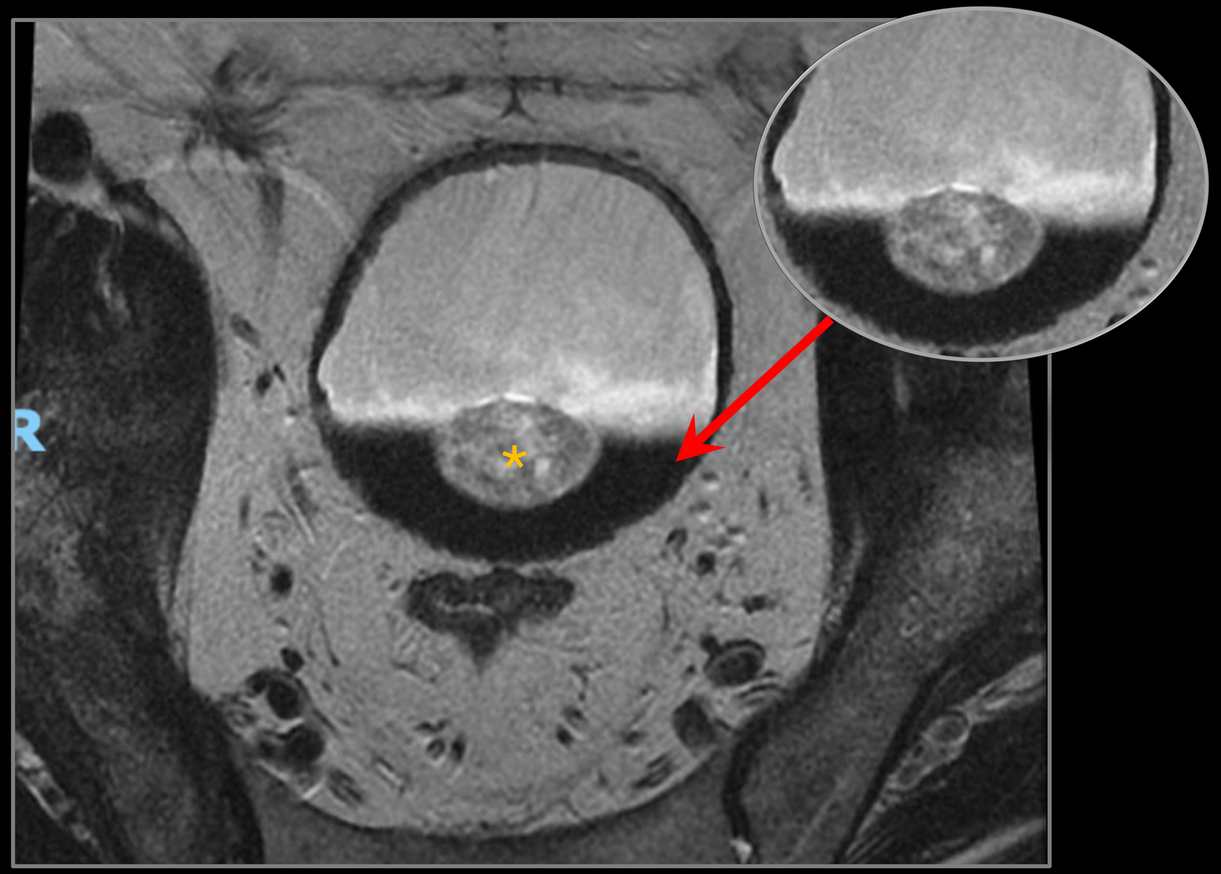

Illustration shows intrinsic factors that affect the T1 relaxation of the $Gd^{3+}$ molecular complex

# GADOLINIUM-BASED CONTRAST AGENTS (GBCAs)

## MECHANISM/EFFECT OF GBCAs IN MRI



MRI. T1-weighted postcontrast (Gadoteric acid). Late phase 4 minutes
Arrow showing the hyperintense contrast in the urinary bladder.
Additionally, intravesical prostate growth is observed (*).




MRI. T2-weighted postcontrast (Gadoteric acid). Late phase 4 minutes
Arrow showing the hypointense contrast in the urinary bladder.
Additionally, intravesical prostate growth is observed (*).

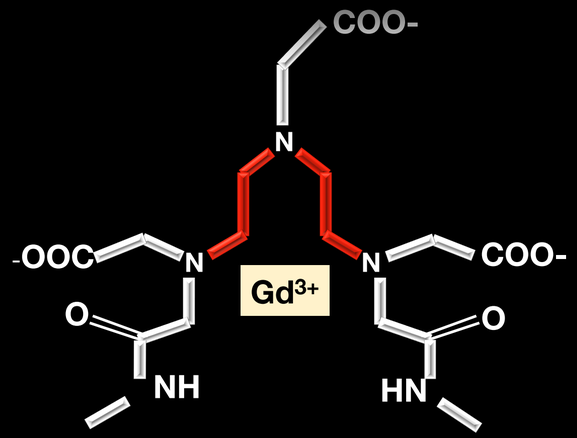
# GADOLINIUM-BASED CONTRAST AGENTS (GBCAs)

## CLASSIFICATION OF GBCAs BASED ON CHELANTING AGENT

**GBCAs are $Gd^{3+}$ cations chelated with organic ligands that can be linear or macrocyclic according to the molecular structure and ionic or non-ionic according ionicity.**

### MOLECULAR STRUCTURE

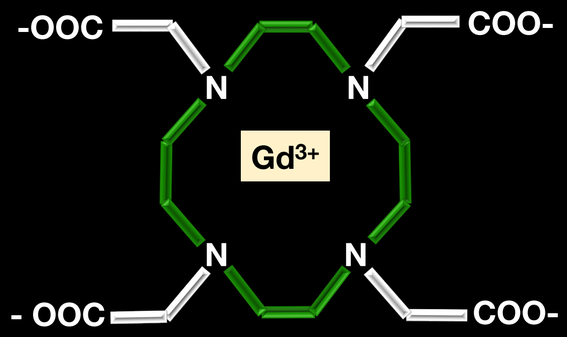
#### LINEAR AGENTS




LINEAR AGENTS ARE CHAIN-SHAPED AND ARE NOT COMPLETELY ENCLOSING THE GADOLINIUM IONS

MORE TENDENCY TO DISSOCIATE THE GADOLINIUM ION AND SUBSEQUENT UNWANTED TOXIC EFFECTS

#### CYCLIC AGENTS




THE GADOLINIUM ION IS CAGED IN A RIGID CAVITY OF THE LIGAND.

HIGH STABILITY AND RELATIVELY FAST WATER EXCHANGE RATE

Ionicity: Ability to dissolve into charged particles when introduced into a solution.

Directly related to osmolality.

### IONICITY

#### IONIC

THE GADOLINIUM ION HAS A STRONG BOND WITH THE CARBOXYL GROUPS

MORE STABLE AND HIGHER OSMOLALITY

#### NON-IONIC

THE GADOLINIUM ION HAS A WEAK BOND WITH THE AMIDE OR ALCOHOL FUNCTIONAL GROUPS

LESS STABLE AND LOWER OSMOLALITY

# GADOLINIUM-BASED CONTRAST AGENTS (GBCAs)

## CLASSIFICATION OF GBCAs

### GBCAs STABILITY FROM THE HIGHEST TO THE LOWEST

1.-MACROCYCLIC IONIC

⇩

Less probability of releasing gadolinium in the body

⇩

More stable
Less toxic

2.-MACROCYCLIC NON-IONIC

3.-LINEAR IONIC

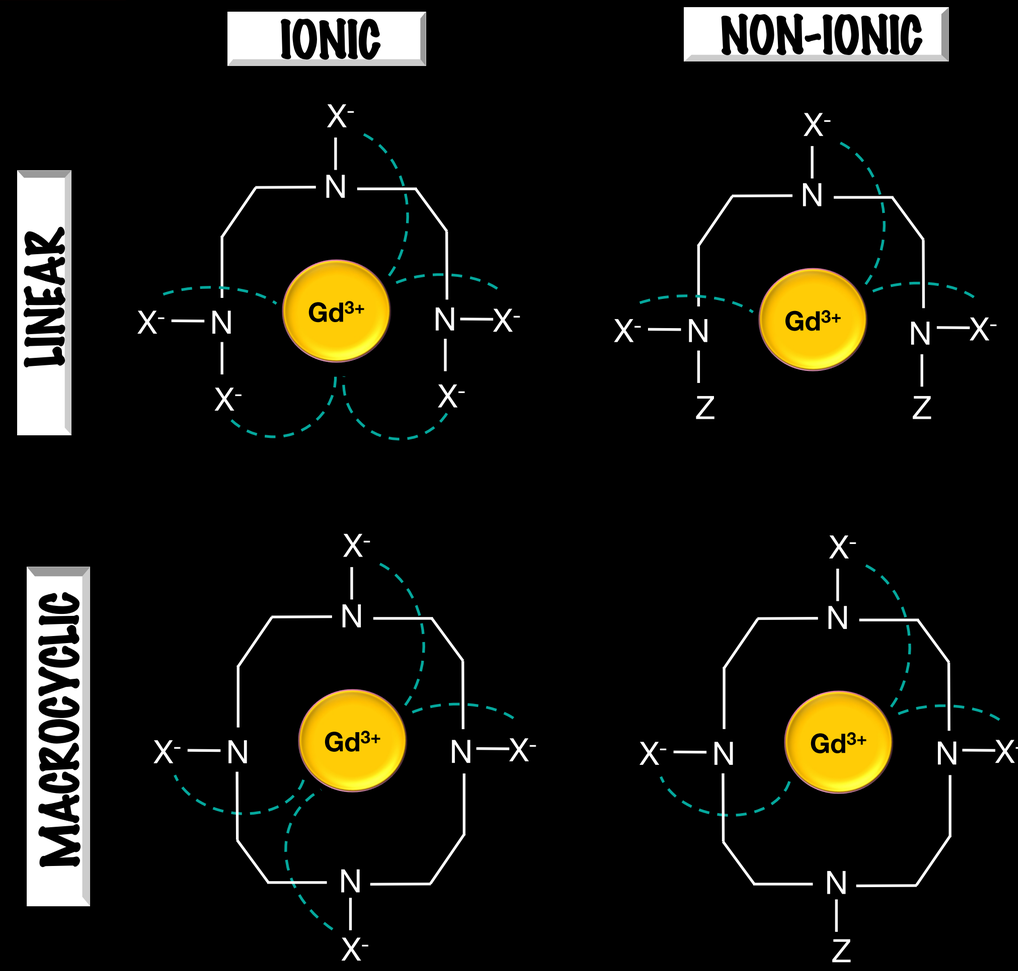
4.-LINEAR NON-IONIC

⇩

More probability of releasing gadolinium in the body

⇩

Less stable
More toxic




Figures of examples of GBCAs structure.
Solid lines: Simple covalent bonds between atoms.
Dashed lines: Ionic bonds due to weaker electrical adhesion

# GADOLINIUM-BASED CONTRAST AGENTS (GBCAs)

**GBCAs approved by FDA, below is the table of its distribution, Kinetic stability, Chelate Chemistry, ionicity, stability, viscosity, and osmolality.**

| Brand name (commercial-manufacturer), [year FDA approved] | Chemical abbreviation | Distribution | Kinetic stability T ½ hours | Chemical Structure | Stability | Osmolality | TD Log Ktherm | Conditional (Log Kcond at pH 7.4) | Viscocity 37°C |
|---|---|---|---|---|---|---|---|---|---|
| Gadoteridol (ProHance – Bracco) [1992] | Gd-HP-DO3A | Extracellular | 3.9 h | Macrocyclic non-ionic | High | 630 | 23.8 | 17.1 | 1.3 |
| Gadodiamide* (Omniscan-GE Healthcare) [1993] | Gd-DTPA-BMA | Extracellular | < 5 s | Linear non-ionic | Low | 789 | 16.9 | 14.9 | 1.4 |
| Gadobenate dimeglumine (MultiHance –Bracco) [2004] | Gd-BOPTA | 95% Extracellular 5%Hepatobiliary (Hepatobiliary phase: 1 hour) | < 5 s | Linear ionic | Intermediate | 1970 | 22.6 | 18.4 | 5.3 |
| Gadoxetic acid (Eovist and Primovist- Bayer Healthcare) [2008] | Gd-EOB-DTPA | 50% Extracellular 50 %Hepatobiliary ( Hepatobiliary phase: 20 min) | < 5 s | Linear ionic | Intermediate | 688 | 23.5 | 18.7 | 12 |
| Gadobutrol (Gadavist - Bayer Healthcare) [2011] | Gd-DO3A-butrol | Extracellular | 43h | Macrocyclic non-ionic | Intermediate | 1603 | 21.8 | 14.7 | 5 |
| Gadoterate meglumine (Dotarem – Guerbet) [2013] and (Clariscan - GE Healthcare) [2019] | Gd-DOTA | Extracellular | 338 h (Dotarem) | Macrocyclic ionic | High | 1350 | 25.6 | 19.3 | 2 |
| Dadopentetate dimeglumine* (Magnevist- Bayer Healthcare) | Gd-DTPA | Extracellular | < 5 s | Linear ionic | Intermediate | 1960 | 22.1 | 17.7 | 2.9 |
| Gadoversetamide* (Optimark-Guerbet) [1999] | Gd-DTPA-BMEA | Extracellular | < 5 s | Linear non-ionic | Low | 1110 | 16.6 | 15 | 2 |
| Gadopiclenol (Elucirem-Guerbet and Vueway –Bracco) [2022] | NA | Extracellular | 480 h | Macrocyclic non-ionic | High | 1350 | 19.7 | 15.5 | 7.6 |

* GBCAs suspended by EMA (European Medicines Agency)

Log Ktherm: Thermodynamic Stability constant.
Conditional (Log Kcond at pH 7.4): Conditional Stability constant
NA: No data available

# GADOLINIUM-BASED CONTRAST AGENTS (GBCAs)

## WHY IS FREE GADOLINIUM TOXIC?

**The unchelated gadolinium ion is very toxic, the transmetalation theory for gadolinium dechelation is the main one.**

Gadolinium is bound to a protein and forms a stable, inert and non-toxic chelate; however, it can be released through a process called transmetalation, which is the replacement of gadolinium by an endogenous cation, mainly zinc.

**TRANSMETALATION REACTION**

There are cations endogenous ($Fe^{2+}$, $Cu^{2+}$, $Zn^{2+}$ , $Ca^{2+}$) that compete to displace $Gd^{3+}$ from its chelate.
Free Gd is associated with endogenous anions like $CO_3^{2-}$ and $PO_4^{3-}$, which causes the formation of insoluble compounds (salts such as gadolinium phosphate or other chemical species)

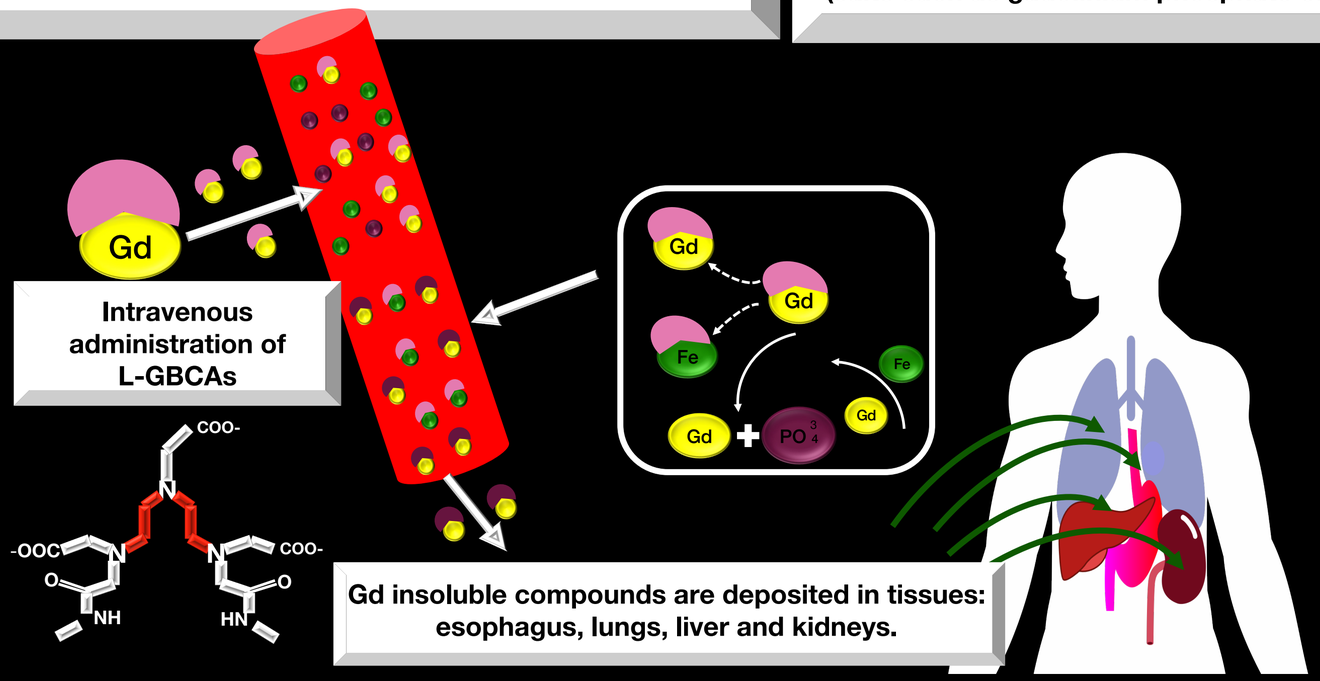



Illustration demonstrating after the administration of linear GBCAs (L-GBCAs), the process of transmetalation and deposition in the different tissues

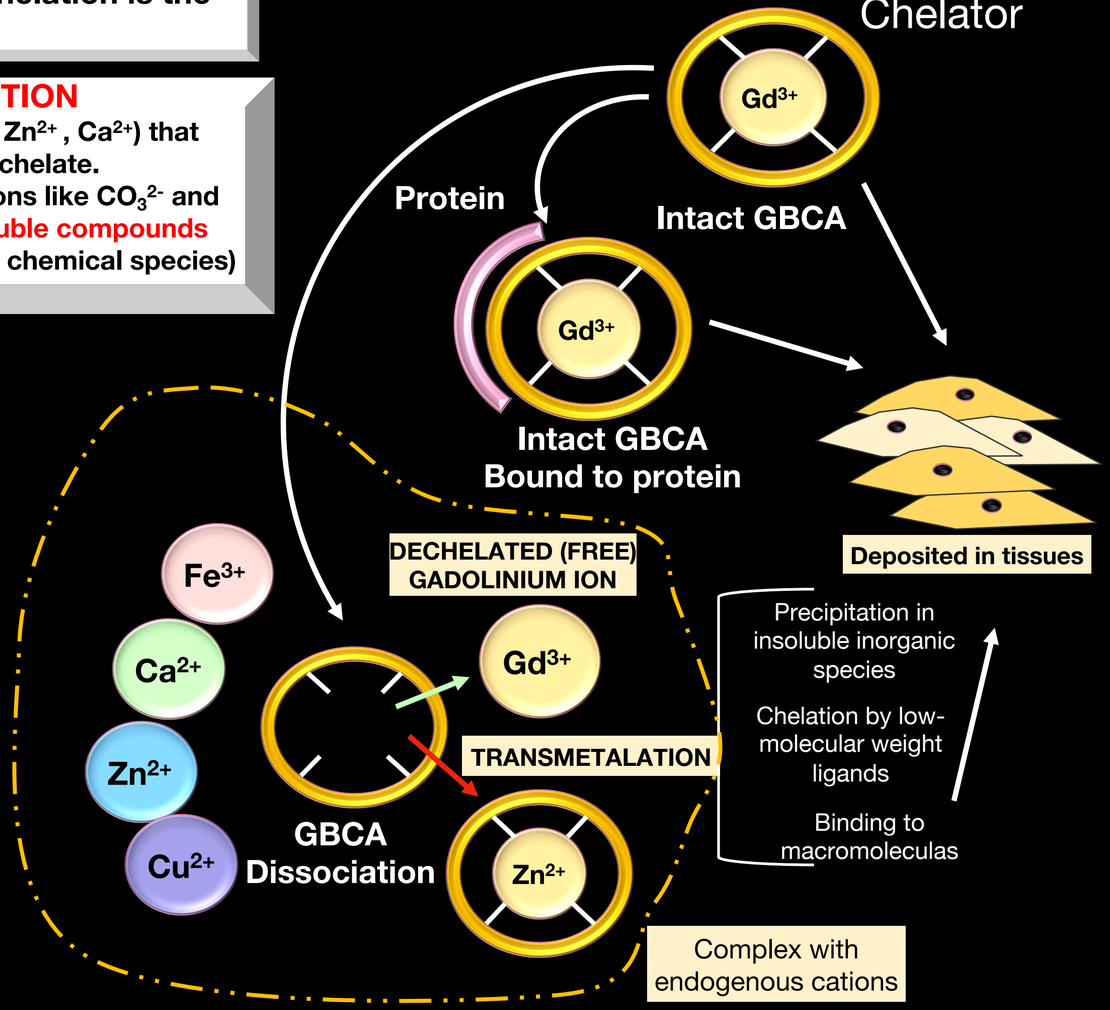



Figure demonstrating the three possible mechanisms of gadolinium deposition in tissues. Dashed lines enclose the main theory.

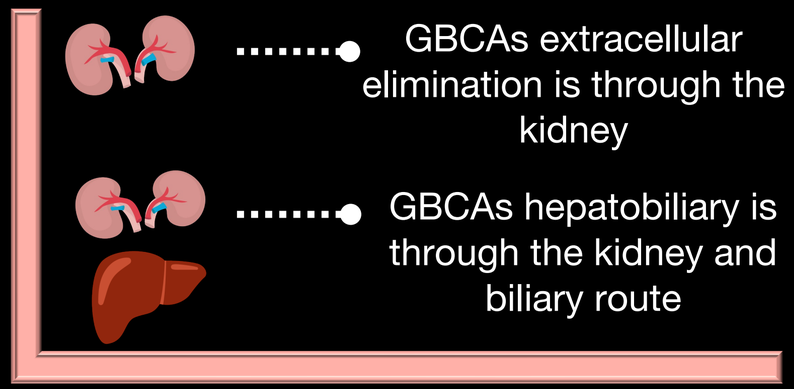
# GADOLINIUM-BASED CONTRAST AGENTS (GBCAs)

## WHAT IS THE PROBABILITY THAT TRANSMETALATION WILL OCCUR?

Depends on the affinity of the endogenous ions for the ligand, this in turn depends on:
-THERMODYNAMIC AND KINETIC STABILITY OF THE METAL ION CHELATE

The extended HALF-LIFE period due to renal dysfunction + certain specific pharmacokinetic properties may favor dissociated GBCAs.

## ELIMINATION (HALF-LIFE) OF GBCAs



GBCAs extracellular elimination is through the kidney

GBCAs hepatobiliary is through the kidney and biliary route

### GBCAs Extracellular

| CONDITION | ELIMINATION (T1/2 HOURS) |
|---|---|
| Normal renal function | 1.5 h |
| Mild renal insufficiency (eGFR 60–90 mL/ min/1.73 m2) | 3.2 h |
| Moderate renal insufficiency(eGFR 30–60 mL/ min/1.73 m2) | 3.8 to 6.9 h |
| Severe renal insufficiency (eGFR <30 mL/ min/1.73 m2), excluding dialysis. | 9.5 to 30 h |

### GBCAs hepatobiliary

| CONDITION | ELIMINATION (T1/2 HOURS) |
|---|---|
| Normal renal function | Young people 1.0 h<br>Older people 1.8 h |
| Severe liver failure (Child-Pugh C cirrhosis) | Gadoxetic acid 2.6 h<br>Gadobenate 2.2 h |
| Moderate renal insufficiency | Gadoxetic acid 2.2 h<br>Gadobenate 5.6 h |
| Severe renal insufficiency | Gadoxetic acid 20 h<br>Gadobenate 9.2 h |

**Important point:** The bile duct can compensate for deterioration in renal function.
Moderate liver failure does not change plasma life.

Tables showing the elimination times of GBCAs according to kidney condition and are based on ESUR Contrast Media Safety Committee.

# GADOLINIUM-BASED CONTRAST AGENTS (GBCAs)

## CURRENT CLASSIFICATION OF GBCAs BY RISK OF NSF-ACR (2024)

**UPDATE (2024): GADOXETATE DISODIUM IS IN GROUP II**
**previously in GROUP III**

| | *CYCLIC* | *LINEAR* |
|---|---|---|
| ***IONIC*** | GADOTERIC ACID (DOTAREM®- GUERBET-CLARISCAN-GE HEALTHCARE) | GADOBENATE DIMEGLUMINE (MULTIHANCE®-BRACCO DIAGNOSTICS)<br>GADOXETATE DISODIUM (EOVIST – BAYER HEALTHCARE PHARMACEUTICALS; PRIMOVIST IN MANY COUNTRIES) |
| ***NON IONIC*** | GADOTERIDOL (PROHANCE®-BRACCO DIAGNOSTICS)<br>GADOBUTROL (GADAVIST- BAYER HEALTHCARE PHARMACEUTICALS, GADOVIST IN MANY COUNTRIES.)<br>GADOPICLENOL (ELUCIREM® – GUERBET, VUEWAY® – BRACCO DIAGNOSTICS) | GADOPENTETATE DIMEGLUMINE (MAGNEVIST®- BAYER HEALTHCARE PHARMACEUTICALS)<br>GADODIAMIDE (OMNISCAN®- GE HEALTHCARE)<br>GADOVERSETAMIDE (OPTIMARK®-GUERBET) |

**Group I (orange): Highest number of NSF cases**
**Group II (green): Few, if any, cases of NSF.**
**GROUP III: Few, if any, cases of NSF but limited data available. Currently there are no agents int this category (since April 2024)**

## ASSESSMENT OF RISK

**Group II:** Patients who are administered standard or lower doses than the standard, the risk of NSF is sufficiently low or possibly non-existent: **Assessment of renal function (eGFR) is optional** either with a questionnaire or laboratory tests before the administration of GBCAs.
Should be administered if deemed necessary by the supervising radiologist and at low doses.

**Group I and III:** If the patient is receiving group I, is at risk of developing NSF if these conditions exist:
1-On hemo or peritoneal dyalisis
2- eGFR < 30 ml/min/1.73 $m^2$ without dialysis
3- Acute kidney injury (AKI)

**Patient who requiere evaluation of eGFR before administrating Group I and III:**
- Inpatients: eGFR within 2 days before MRI
- Outpatients with risk factors without prior eGFR at the time the MRI is scheduled.
- Outpatients with risk factors and previous eGFR of 45-59 and more than 6 weeks prior to the MRI.
- Outpatients with recent previous eGFR <44.

# GADOLINIUM-BASED CONTRAST AGENTS (GBCAs)

## ADVERSE REACTIONS

The classification of adverse reactions according to ACR

ACR

### ACUTE EFFECTS

#### A) Physiologic (the most frequent and mild)

| Mild: | Moderate: | Severe: |
|---|---|---|
| -Limited nausea / vomiting limited<br>- Transient flushing / warmth / chills<br>- Headache / dizziness / anxiety / altered taste<br>- Mild hypertension<br>- Vasovagal reaction that resolves spontaneously | - Protracted nausea / vomiting<br>- Hypertensive urgency<br>- Isolated chest pain<br>- Vasovagal reaction that requires and is responsive to treatment | - Vasovagal reaction resistant to treatment<br>- Arrhythmia<br>- Convulsions, seizures<br>- Hypertensive emergency |

#### B) Allergic- like reactions

-They are similar to allergic-like reactions to iodinated contrast agents.
Severe anaphylactic reactions (rare 0.001% to 0.01% but can endanger the patient's life)

| Mild: | Moderate: | Severe: |
|---|---|---|
| - Limited urticaria / pruritis<br>- Cutaneous edema<br>- Limited “itchy”/“scratchy” throat<br>Nasal congestion.<br>- Sneezing / conjunctivitis / rhinorrhea | - Diffuse urticaria / pruritis<br>- Diffuse erythema, stable vital signs<br>- Facial edema without dyspnea<br>- Throat tightness/ hoarseness without dyspnea<br>- Wheezing / bronchospasm, mild or no hypoxia | - Diffuse edema, or facial edema with dyspnea<br>- Diffuse erythema with hypotension<br>- Laryngeal edema with stridor and/or hypoxia<br>- Wheezing / bronchospasm, significant hypoxia<br>- Anaphylactic shock (hypotension + tachycardia) |

Tables are based on ACR guidelines

### CRONIC EFFECTS

Adverse reactions at approved doses (0.1 to 0.2 mmol/kg most GBCAs) are 0.07% and 2.4% [1].

#### Nephrogenic systemic fibrosis (NSF)

We will discuss this entity in the following slides.

### RISK FACTORS

✓ Previous allergic reaction to GBCAs

✓ Asthma/other allergies: slightly higher risk of presenting an allergic reaction to GBCAs compared to patients who do not have this condition.

# GADOLINIUM-BASED CONTRAST AGENTS (GBCAs)

## ADVERSE REACTIONS

The classification of adverse reactions according to ESUR

ESUR

### ACUTE

Immediate reactions : within 1 hour of administration of GBCAs
0.7-3% of patients receiving non-ionic GBCAs

**A) Chemotoxic**

Depend on the doses and chemical properties

| Mild | Moderate | Severe |
|---|---|---|
| Nausea<br>Vomiting<br>Heat/chills<br>Anxiety<br>Vasovagal reaction that resolves spontaneously | Vasovagal reaction | Arrhythmia<br>Convulsion |

**B) Hypersensitivity / allergy- like reactions (0,003% a 0,008%)**

Dose-independent and unpredictable
Skin manifestations of 75 to 100%, urticaria and erythema are the most frequent.

| Mild | Moderate | Severe |
|---|---|---|
| Mild urticaria/itching<br>Erythema | Marked urticaria<br>Mild bronchospasm<br>Facial/laryngeal edema | Hypotensive shock<br>Respiratory arrest<br>Cardiac arrest |

Tables are based on ESUR guidelines

Delayed hypersensitivity reactions ARE VERY RARE, they are "non-immediate reactions" between 1 hour and 10 days after administration of GBCAs, these can be serious cutaneous adverse reactions.

### VERY LATE ADVERSE REACTIONS

Occur after 1 week after administration of GBCAs

**Nephrogenic systemic fibrosis (NSF)**

**We will discuss this entity in the following slides.**

## RISK FACTORS

- For acute adverse reactions:
  Previous moderate/severe acute reaction
  History of asthma and atopy

- For very late adverse reactions:
  Reduced renal function
  Type of contrast (increases with linear)

# GADOLINIUM-BASED CONTRAST AGENTS (GBCAs)

## NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

### DEFINITION

Multisystem fibrotic disease.
It is a rare disease that was described in 2000 (initially not linked to GBCAs), mainly involves the skin and subcutaneous tissue, but also affects multiple organs, such as the lungs, esophagus, heart, and musculoskeletal system.

Initial symptoms: pruritus, skin thickening erythema, edema, heat of the extremity with pain, this entity can be progressive causing spasms, muscle weakness and disability.

### ASSOCIATIONS

Currently, exposure to GBCA is considered a necessary factor to develop NSF. In 2006 the link between NSF and GBCAs was identified.

Advanced kidney disease is the main risk factor for NSF.

It is now known that the probability of developing NSF varies according to the different types of GBCAs (**see GBCAs classification by risk of NSF)

### TIME LAPSE BETWEEN EXPOSURE AND DEVELOPMENT OF NSF

After the administration of GBCAs, symptoms can appear between days and months in most cases, however there are symptoms that have appeared years later (very rare).

### THE END OF NSF?

Most unstable GBCAs (group I) have been discontinuated and strict recommendations in patients with kidney failure have been applied after 2006, this has dramatically decreased the number of NSF cases.

Since 2008 only seven cases are reported in the literature.
In 2020 three cases were reported and confirmed by pathology [4]

# GADOLINIUM-BASED CONTRAST AGENTS (GBCAs)

## NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

### MECHANISM

NSF

The current hypothesis is the release of gadolinium from its chelates, in patients with advanced renal function and delayed elimination of GBCAs. Then the transmetalation process mentioned above occurs where the free gadolinium binds to anions forming insoluble compounds that are deposited in different tissues. Subsequently, a fibrotic reaction develops due to the activation of fibrocytes.

### RISK FACTORS

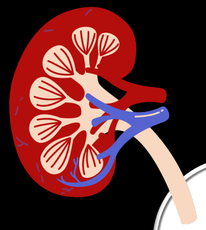
| | |
|---|---|
| Chronic kidney disease (CKD) | Exposure GBCAs I: End-stage CKD5 and severe CKD4, 1% to 7% probability of NSF |
| Acute kidney injury (AKI) | 12% and 20% of NSF cases have developed in patients with AKI with or without CKD. |
| High-dose and multiple exposures | The majority of NSF has been observed with high doses of GBCA in single or cumulative administration, that is, multiple times over months or years. |
| Other POSSIBLE risk factors: | Metabolic acidosis, medications, high levels of iron, calcium and/or phosphate<br>high-dose erythropoietin, therapy<br>Immunosuppression, vasculopathy,<br>Infection. |
| Hepatic insufficiency/hepatorenal syndrome | Liver disease alone, without the presence of AKI or severe CKD, is NOT an independent risk factor for NSF. |

# GADOLINIUM-BASED CONTRAST AGENTS (GBCAs)

## GBCAs AND POSTCONTRAST ACUTE KIDNEY INJURY (AKI)

### GUIDELINES

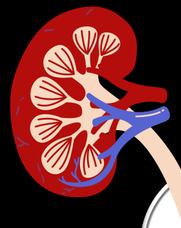
**ACR**



In approved dose:
Not considered nephrotoxic

Nephrotoxicity ?

**ESUR**



In approved dose:
Low risk AKI

But...
what About
the

deposition of gadolinium
in the tissues?

NEXT

# GADOLINIUM-BASED CONTRAST AGENTS (GBCAs)

## GADOLINIUM DEPOSITION DISEASE (GDD)

European Journal of Radiology

IN 2016 SUGGEST A NEW TERM !!

According to literature In USA this disease “GDD” is describe as “SAGE”

GDD

What does it mean?

Symptoms after exposure to GBCAs that are not related to alteration of renal function **(REGARDLESS)** and early and late onset adverse reactions.

Symptoms

To **diagnose GDD** [8], 3 of the following 5 symptoms are needed:

1. Bone pain
2. Peripheral leg and arm pain
3. Central torso pain.
4. Headache and clouded mentation
5. Peripheral leg and arm thickening and discoloration.

# GADOLINIUM-BASED CONTRAST AGENTS (GBCAs)

## SYMPTOMS ASSOCIATED WITH GADOLINIUM EXPOSURE (SAGE)

### ACR

**IN 2022 MEMBERS OF ACR SUGGEST A NEW TERM !!**

↓

**SAGE**

**What does it mean?**

↓

Appearance of symptoms after administration of GBCAs **REGARDLESS** of renal function, which are not related to early and late adverse reactions. This term has been used because **there is currently no known causal relationship between GBCAs and symptoms** and therefore does not diagnose the "disease" early.

**There are authors who mention that there is no sufficient and definitive evidence to confirm the existence of this entity [4]**

**Symptoms**

↓

- ✓ Headache
- ✓ Bone and joint pain
- ✓ Joint Stiffness
- ✓ Muscle spams
- ✓ Fatigue
- ✓ Clouded mentation
- ✓ Skin thickening, discoloration and pain
- ✓ Painful tendons and ligaments
- ✓ Tighness in the hands and feet
- ✓ Peripheral neurophatic pain

**Stratification**

↓

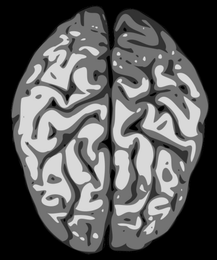
Early onset (<24 hours after GBCA exposure)

Late onset (≥ 24 hours after GBCA exposure).

# GADOLINIUM-BASED CONTRAST AGENTS (GBCAs)

## GADOLINIUM DEPOSITION PHENOMENON (GDP)

**CURRENTLY UNKNOWN SIGNIFICANCE !!**
More research is needed on possible mechanisms and potential toxicity hypotheses.

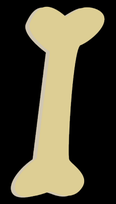


### CNS TISSUES (BRAIN)

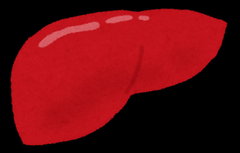
First reported in 2014 by Kandal et al [25] who described $Gd^{3+}$ deposition in the brain in patients with repeated dose of GBCAs and most of them with normal eGFR.

This phenomenon has been described as being dose-dependent and occurring in patients without clinically evident disease (normal liver and kidney function and no alteration of the blood-brain barrier)

Increased signal intensity on unenhanced T1 MRI was observed in the **GLOBUS PALLIDUS AND DENTATE NUCLEUS** in patients who received linear GBCA and also with macrocyclic GBCA but less accentuated.



### NON-CNS TISSUES



Gadolinium deposition has also been reported in other organs such as skin, bones and liver.

Studies report that the deposit of gadolinium is greater in the bones than in other tissues and that it can remain for up to 8 years in a higher concentration than the brain. [13]

**GDP presents regardless of renal function**

# GADOLINIUM-BASED CONTRAST AGENTS (GBCAs)

## GUIDELINES AND UPDATES ON THE USE OF GBCAs

FDA- APPROVED GBCAs

RECOMMENDATIONS

RECOMMENDED DOSE?

GBCAs DOSE (SINGLE IMAGING SESSION): appromately 0.1 mmol/kg OR 0.2 mL/kg.


LIVER- SPECIFIC GADOXETIC ACID DOSE: 0.025 mmol/kg OR 0.1 mL/kg

# GADOLINIUM-BASED CONTRAST AGENTS (GBCAs)

## GUIDELINES AND UPDATES ON THE USE OF GBCAs

## PREGNANCY AND LACTATION

## RECOMMENDATIONS BY ACR

**IS THE ADMINISTRATION OF GBCAs SAFE IN PREGNANT WOMEN AND DURING BREASTFEEDING?**

### PREGNANT OR POTENTIALLY PREGNANT PATIENTS

**IT'S STILL NOT CLEAR**

**CAUTION !!**

**Avoid routine administration**

1. Pregnant + normal renal function: Administer GBCAs, when the benefit is considered greater and justified for the patient or the fetus than the unknown potential risk to the fetus.

If a GBCA is used it must be low risk for NSF and the lowest dose to obtein the diagnosis.

2. Pregnant + severe renal insufficiency: similar recommendations as in non-pregnant patients

Studies on animals reveal that some GBCAs cross the placenta and enter the fetal circulation.

### BREASTFEEDING

**IT IS CONSIDERED SAFE !!**

There is a small percentage of GBCAs that is excreted in breast milk (<0.04% of the administered dose) and absorbed in the infant's intestine (<0.0004%) [1].

**"Do not discontinue breastfeeding after administration of GBCAs to the mother"**

If there is a disagreement between the mother and the radiologist, the final decision to discontinue temporarilly breastfeeding (for a period of 12 to 24 hours) should be left to the mother.

# GADOLINIUM-BASED CONTRAST AGENTS (GBCAs)

## GUIDELINES AND UPDATES ON THE USE OF GBCAs

### PREGNANCY AND LACTATION

**RECOMMENDATIONS BY ESUR/European Journal of radiology**

**IS THE ADMINISTRATION OF GBCAs SAFE IN PREGNANT WOMEN AND DURING BREASTFEEDING?**

### PREGNANT OR POTENTIALLY PREGNANT PATIENTS

**IT'S CONTROVERSIAL !!**

1. Pregnant + normal renal function: Administration GBCAs in extremely necessary cases, when there is a strong clinical indication.
   Administer ONLY the most stable GBCAs (macrocyclic) and smallest quantity dose.

2. Pregnant + impaired renal function: GBCAs contraindicated

GBCAs could cross the placenta and enter the fetal circulation.

### BREASTFEEDING

**Lactation+ normal renal function: No breast-feeding interruption normally when macrocyclic GBCAs are used.**

Lactation + impaired renal function: GBCAs contraindicated

# GADOLINIUM-BASED CONTRAST AGENTS (GBCAs)

## GUIDELINES AND UPDATES ON THE USE OF GBCAs

ACR

RECOMMENDATIONS

## RECOMMENDATIONS FOR CERTAIN GROUPS OF PATIENTS

| GROUP | RECOMMENDATION |
|---|---|
| End-stage renal disease on chronic dialysis | **Use GBCAs group II.**<br>**GBCAs group I: contraindicated.**<br>It is suggested that the MRI study with GBCAs should be optimally performed before and close to regularly scheduled hemodialysis.<br>Do not modify hemodialysis (daily or multiple sessions per day) due to the risk associated with the catheter. |
| CKD 4 or 5 (eGFR<30mL/min/1.73m$^2$) not on chronic dialysis | **Use GBCAs group II.**<br>**GBCAs group I: contraindicated.** |
| CKD 3 (eGFR 30 to 59 mL / min/1.73 m$^2$) | **No special precaution required** |
| CKD 1or 2 (eGFR 60 to119 ml/min/1.73m$^2$) | **Administration of any GBCAs is considered safe** |
| Acute kidney injury (AKI) | **Group II GBCAs can be used**<br>**Avoid Group I GBCAs** |
| Children | **Continue with the recommendations for adult patients.**<br>**However, caution must be taken.**<br>**It is suggested to use group II GBCAs.** |

# GADOLINIUM-BASED CONTRAST AGENTS (GBCAs)

## GUIDELINES AND UPDATES ON THE USE OF GBCAs

ESUR Contrast Media Safety Committee 2023

RECOMMENDATIONS

### WAITING TIMES BETWEEN EXAMINATIONS

1-TIME INTERVALS BETWEEN TWO GBCAs INJECTIONS?

**Important date:** if it is an emergency or “life or death situations”, reduce the waiting time. Don't delay

Depends on the renal function

**Normal and mildly decreased renal function (eGFR >60 ml/min/1.73m2)**

- ✓ Preferably 12 hours
- ✓ Minimum 4 hours, if there is clinical justification

**Moderately decreased renal function (eGFR 30-60 ml/min/1.73m2)**

- ✓ Preferably 48 hours
- ✓ Minimum 16 hours, if there is clinical justification

**Severely decreased renal function (eGFR < 30 ml/min/1.73m2)**

- ✓ Preferably 7 days
- ✓ Minimum 2.5 days, if there is clinical justification

# GADOLINIUM-BASED CONTRAST AGENTS (GBCAs)

## GUIDELINES AND UPDATES ON THE USE OF GBCAs

ESUR Contrast Media Safety Committee

RECOMMENDATIONS

### WAITING TIMES BETWEEN EXAMINATIONS

**2-TIME INTERVALS BETWEEN AN IODINE-BASED CONTRAST MEDIUM AND A GADOLINIUM-BASED CONTRAST AGENT?**

**Importat date:** It is suggested that contrast MRI be performed first, except if the tomography is to evaluate the urinary system (kidneys, ureters and bladder), in which case start with CT.

Depends on the renal function

**Normal and mildly decreased renal function (eGFR >60 ml/min/1.73m2)**

- ✓ Preferably 6 hours
- ✓ Minimum 2 hours, if there is clinical justification

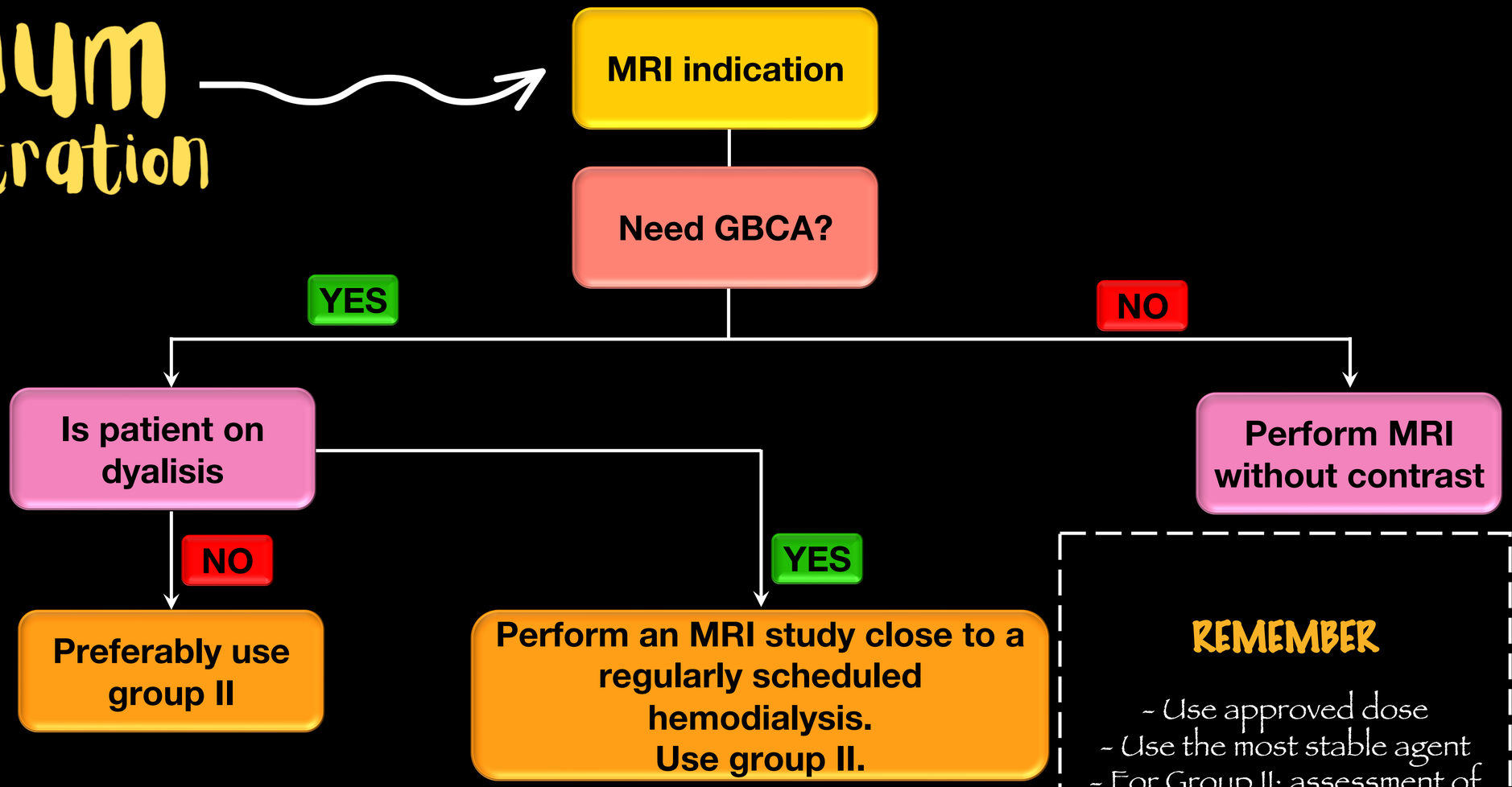
**Moderately decreased renal function (eGFR 30-60 ml/min/1.73m2)**

- ✓ Preferably 48 hours
- ✓ Minimum 16 hours, if there is clinical justification

**Severely decreased renal function (eGFR < 30 ml/min/1.73m2)**

- ✓ Preferably 7 days
- ✓ Minimum 2.5 days, if there is clinical justification

# Gadolinium
## GBCAs administration




### KEY POINTS

Hemodialysis is capable of eliminating GBCAs from the body, however even the reduction in the risk of NSF is theoretical, since it is not completely demonstrated.

Therefore, any type of dialysis is NOT prophylactic for NSF.

Hemodialysis is more effective compared to peritoneal dialysis in eliminating GBCAs [14].

Studies have shown a reduction in $Gd^{3+}$ after one session of hemodialysis (75-98%) and after three sessions (>98%) [15]

### REMEMBER

- Use approved dose
- Use the most stable agent
- For Group II: assessment of eGFR is optional according to ACR

# GADOLINIUM-BASED CONTRAST AGENTS (GBCAs)

## WHAT'S NEW? Contrast agents MRI in development

### GBCAs

#### GADOQUATRANE

This novel agent is in clinical research by Bayer.

Extracellular and macrocyclic GBCAs for MRI.

It has tetrameric structure, high stability, relaxation and allows a lower clinical dose of gadolinium.

Hofmann et al. evaluated 49 healthy participants, they concluded that Gadoquatrane is a promising next generation agent, presenting high relaxivity and tolerability [5]

**Currently in Phase III trial.**

### MANGANESE-BASED CONTRAST AGENT

Considered a probable alternative to gadolinium.
The first of its kind.

It is currently in research by GE HealthCare.

Extracellular and macrocyclic agent, has comparable relaxivity.

In a clinical trial, at the Oslo University Hospital, Rikshospitalet, concluded that the contrast has good tolerability and no serious adverse reactions. McDonald J. R. comments that "this agent may have benefits: reduced risk of tissue deposition and increased safety for certain at-risk patient populations compared to GBCAs and offers similar imaging potential and lower environmental impact" [7]

**Currently in Phase I trial.**

### SPION

#### FERUMOXYTOL

Iron oxide nanoparticles have been investigated.

Also as a promising alternative to GBCAs.

High relaxivity, absence of renal metabolism, reduced doses of contrast agents.

Longer half-life in blood (>14 hours) and offers high-resolution angioresonance.

Allows applicability in certain groups of patients such as children [6] [8]

# CONCLUSIONS

Recommendations and guidelines are constantly updated and should be followed to guarantee the security of the GBCAs in different populations.

GBCAs are the most used agents in magnetic resonance imaging and currently have a great impact on the diagnosis and follow-up of millions of patients around the world. Radiologists must have the necessary knowledge of GBCAs to appropiately use them when necessary.

Always consider the risks and benefits before using GBCAs. The use of group II has increased over the last years, as they are considered the safest and have the lowest risk of NSF.

The deposition of gadolinium in the organs is still undergoing investigation, it primarely affects the brain currently with no clinical significance and presents even in patiens with normal kidney function.

Promising next-generation GBCAs and other alternative MRI agents to gadolinium are currently in research with added benefits like lower dose and lower environmental impact.

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