Northwestern Medicine

Gadolinium Toxicity and Non-contrast MRI

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Disclosure

- No real or apparent relationships to report.

Outline

- Describe the types of Gadolinium contrast agents (GBCAs)
- Understand their known side effects
- Review public policy regarding GBCAs and how toxicities may differ between types
- Review reasons to pursue DWI / non-contrast MRI methods
- Review technical aspects of DWI / non-contrast methods
- Review current and potential future uses of DWI methods

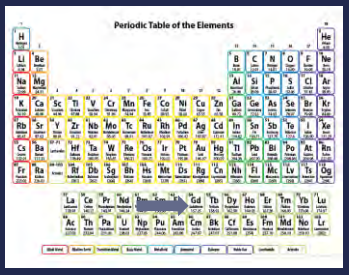
Why GBCAs?

- Essential to many clinical MRI protocols, including DCE MRI
- Enhanced MRI images obtain information not obtainable through other imaging modalities, or non-contrast MRI

Why GBCAs?

- Overall favorable safety profile
  - >450 million doses given worldwide
- Breast MRI without contrast currently not standard of care for most indications (exception: implants)
  - High (enough) relaxivity needed from a contrast agent to make lesions conspicuous

What is Gadolinium?



- A rare earth lanthanide metal
- Is cytotoxic and genotoxic when free

Differences between GBCAs:

- Well publicized:
  - Linear vs. Macrocylic
  - Neutral vs. Ionic (perhaps not as important as w I-, due to small dose volume)
- Degree of protein binding, cellular interactions, kinetic and thermodynamic stability:

Chemical Name	Structure	Ionicity	Protein Binding	k_{on} (sec^{-1}); T1/2	Log K_{cond}	Log K_{cond}	Elimination Half Life (min)	Injected Dose Eliminated within 24 Hours (%)
Gadodiamide	Linear	Nonionic	No	$12.7; <5$ sec	16.9	14.9	77.8 ± 16	95.4 ± 5.5
Gadoversetamide*	Linear	Nonionic	No	$8.6; <1$ sec	16.6	15.0	NA	NA
Gadopentetate dimeglumine	Linear	Ionic	No	$0.58; <5$ sec	22.5	18.4	96 ± 7.8	91 ± 11
Gadoterate dimeglumine	Linear	Ionic	Yes	$0.16; <5$ sec	23.5	18.7	54.6–57	Amount remaining was too small to be detected
Gadobenate dimeglumine	Linear	Ionic	Yes	$0.41; <5$ sec	22.6	18.4	70 ± 16 to 121 ± 36	80–98
Gadoxetate disodium†	Linear	Ionic	Yes	2.9×10^{-3}; 24 sec	22.1	18.9	NA	NA
Gadoteridol	Macrocyclic	Nonionic	No	2.6×10^{-4}; 5.9 hr	23.8	17.1	94.2 ± 4.8	94.4 ± 4.8
Gadobutrol	Macrocyclic	Nonionic	No	2.8×10^{-4}; 4.3 hr	21.8	14.7	108 (72–395)	>90
Gadoterate meglumine	Macrocyclic	Ionic	No	$2–8 \times 10^{-4}$; 3.38 hr	25.6	19.3	84 ± 12 (F); 120 ± 42 (M)	72.9 ± 17.0 (F), 84.4 ± 9.7 (M)

https://doi.org/10.1148/radiol.2018181151

Differences between GBCAs:

- Well publicized:
  - Linear vs. Macrocylic
  - Neutral vs. Ionic
- Degree of protein binding, cellular interactions, kinetic and thermodynamic stability
- Combination of these differences leads to differences in ADME
  - Absorption
  - Distribution
  - Metabolism
  - Excretion
- Class differences and individual chemical differences exist

Differences between GBCAs: Relaxivity

- Differences have a critical effect on imaging efficacy
- Relaxivity plus tissue concentration determine degree of signal change
- Relaxivity varies between categories and across individual agents

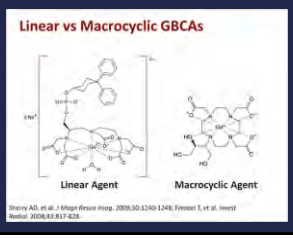
Brand Name	0.47T	1.5T	3.0T	4.7T
Magnevist®	3.8	4.1	3.7	3.8
MultiHance®	9.2	6.3	5.5	5.2
Omniscan™	4.4	4.3	4.0	3.9
Dotarem®	4.3	3.6	3.5	
ProHance®	4.8	4.1	3.7	3.7
Gadavist®	6.1	5.2	5.0	4.7
Eovist®	8.7	6.9		5.9

Rohrer M, Bauer H, Mintorovitch J et al. Comparison of magnetic ... at different magnetic field strengths. Invest Radiol 2005; 40:715-72...

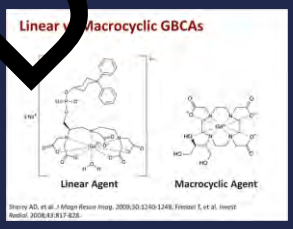
Differences between GBCAs:

Gd bound to an organic ligand to minimize Free Gd toxicity

- These ligands are either linear or macrocyclic:



Differences between GBCAs:



- Macrocyclic:
  - Gd caged within ligand
- Linear:
  - Solutions contain "extra" ligand to keep Gd bound
- Highest dissociation of Gd occurs with linear nonionic

GBCAs: Side effects

- Acute Contrast Reactions
- Nephrogenic Systemic Fibrosis (NSF)
- Tissue Deposition (esp GP and DN)

GBCAs: Side effects

- Acute Contrast Reactions:
  - Very rare for GBCAs
  - Estimates of overall likelihood are in the range of 1:10,000 to 1:40,000

Prince MR, Zhang H, Zou Z, Staron RB, Brill PW. Incidence of immediate gadolinium contrast media reactions. AJR Am J Roentgenol. 2011;196:W138-W143.
Jung JW, Kang HR, Kim MH, et al. Immediate hypersensitivity reaction to gadolinium-based MR contrast media. Radiology. 2012;264:414-422.
Dillman JR, Ellis JH, Cohan RH, Strouse PJ, Jan SC. Frequency and severity of acute allergic-like reactions to gadolinium-containing i.v. contrast media in children and adults. AJR Am J Roentgenol. 2007;189:1533-1538.

GBCAs: Side effects

- Acute Contrast Reactions: "Safer than I-"
  - Hunt compared side effects of CT contrast and Gd based agents
    - ~300K Iodinated, ~150K Gd
    - 522 Total adverse events
      - 458 I-, 64 Gd
      - Only death occurred with I-
    - Of Gad reactions:
      - 15 necessitated treatment of any kind (~0 %)
  - Jung found a single death related Gd administration of >140K doses

Hunt CH, Hartman RP, Hesley GK. [illegible] nol. 2009;193:1124-1.
Jung et al, Radiology 2012: 264: [illegible] 22.

GBCAs: NSF

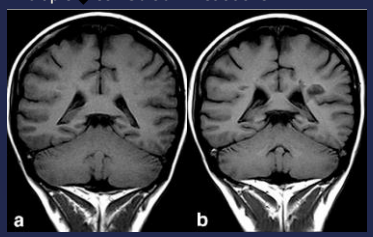
- Nephrogenic Systemic Fibrosis
- Fibrosing disease of the skin and connective tissues of internal organs

GBCAs: NSF

- Associated with lower stability agents (most reported cases w/ two of the linear agents)
- Associated with renal dysfunction, though still a rare occurrence in this patient population
- Near elimination of new NSF cases since practices have recognized risk and moved away from linear agents in patients with kidney disease
- From perspective of breast MRI, may be less critical to our breast screening patient population than deposition concerns

GBCAs: Tissue Retention

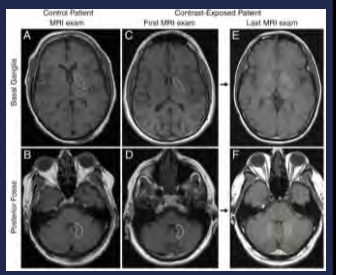
- Tissue Retention and Deposition
  - Gd in [illegible] pallidus and dentate nucleus after multiple linear Gd administrations



Tedeschi, E., Caranci, F., Giordano, F. et al. Radiol med (2017) 122: 589.

GBCAs: Side effects

- Repeat administration of contrast
- Dose dependency of effect



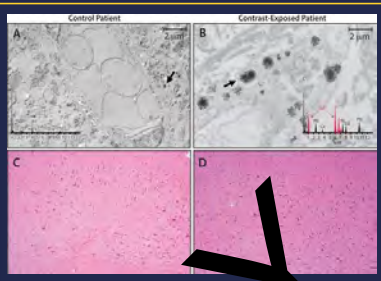
McDonald RJ, McDonald JS, Kallmes DF, et al. Intracranial gadolinium deposition after contrast-enhanced MR imaging. Radiology. 2015;275:772-782.

GBCAs: Side effects

- Study of autopsy specimens:
- Examine specimens from patients exposed to Gd and controls who were not
- "Relatively" normal renal function
- Results:
  - Confirms dose dependency of effect
  - Tissue deposition correlates with degree of increased T1 signal on MRI
  - Gd deposition in primarily capillary endothelium and interstitium, but also in neurons

McDonald RJ, McDonald JS, Kallmes DF, et al. Intracranial gadolinium deposition after contrast-enhanced MR imaging. Radiology. 2015;275:772-782.

GBCAs: Autopsy specimens



- Gd deposition in DN only in exposed patients (A vs B)
- No evidence of cellular injury on H&E (C and D)

McDonald RJ, McDonald JS, Kallmes DF, et al. Intracranial gadolinium deposition after contrast-enhanced MR imaging. Radiology. 2015;275:772-782.

Linear vs. Macrocyclics

- Class differences in retention and deposition:
  - Retention found after administration with the linear agents
  - Linear binding: No "cage" like macrocyclics could relate to this class difference
- Radbruch (2015): Comparison study of linear vs macrocyclic
  - 50 patients with exposure to each agent
  - SI effects in the GP and DN nucleus compared
    - Significant effects seen with linear, but not macrocyc
- Less significant effect with macrocyclics seen in other small studies (small T1 changes reported in some studies)

GBCAs: Policies and Restrictions

- U.S.
  - FDA in 2015: Common sense recommendations
    - Limit use unless truly clinically necessary
    - Carefully assess need for repeat administrations
    - Report possible side effects
    - No change in labeling
  - FDA update (2017):
    - More retention with linear, but no adverse outcomes due to CNS accumulation
    - Continue to evaluate possible NSF risk including in patients with normal renal function
  - FDA update (2018): New patient medication guide on 1st administration, warning on all GBCA labels
- Europe: Most linear agents restricted and/or removed from markets as of July 2017

GBCAs: Side effects

- Tissue Deposition:
- DOES IT MATTER? We don't entirely know yet
- HOW CAN WE ABSOLUTELY TELL?
  - It will continue to be very difficult to study
- Overall safety profile is very strong,yet…

Why study non-contrast methods

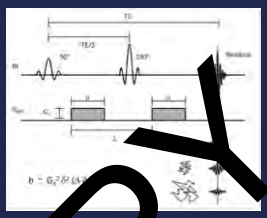
- "At first, do no harm"
  - Screening MRI is a common test, and will likely only become more common (Breast density, Risk assessment recommendations)
  - Women at high risk are likely to have multiple exposures to Gd during a lifetime of screening (recall the dose dependence of the Gd effect)
  - Can we avoid the (potentially harmful) GBCAs altogether?

Why study non-contrast methods

- Improved patient experience
  - No need for IV (or obviously the contrast)
- Potential cost savings without GBCAs (↑ cost effectiveness of MRI)
- Avoid side effect potential

DWI: Technical aspects

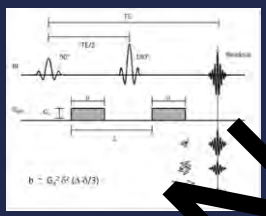
- Widespread use in other areas
- Restricted motion of water = Restricted diffusion



Courtesy of Newstead

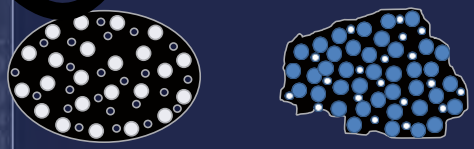
DWI: Technical aspects

- DWI signal: Brownian motion of water
  - Can include degree of cellularity and cell membrane integrity
- For oncology imaging, mostly a study of cellularity
  - High cellularity, less room for water to diffuse



Courtesy Newstead

DWI: Cellularity measured by water movement



Comstock and Schacht, 2019

DWI: Technical Aspects

- ADC map quantifies DWI
  - Can calculate by using b=0 and b=something else (ex. 800) to avoid microperfusion effects
- B value (=strength of diffusion weighting)
  - Low B values show increased microperfusion effects which cause incoherent motion and signal loss
  - Higher B means more signal but also more T2 Shine through
- Standardization has been lacking, leading to difficulty with optimizing or comparing results from different protocols

DWI: Clinical uses

- Given high cellularity of malignant lesions, high DWI and low ADC are expected (exceptions exist eg. Mucinous tumors)
- Shown in multiple studies to be true, with various different thresholds applied:
  - Ex. ADC value of less than 1.1 x 10^{-3} mm2/s
- Much initial interest as an added trait for lesion characterization

Habuuchi et al. J. Magn. Reson. Imaging 2008;28:1157–1165

DWI: Clinical uses

- Combination of findings from DCE MRI and DWI produced a highly accurate test result
  - Sensitivity 92%
  - Specificity 86%
  - PPV 97%
  - NPV 71%

Habuuchi et al. J. Magn. Reson. Imaging 2008;28:1157–1165

DWI: Clinical uses: Adjunct to DCE

- Partridge study compared DCE alone and DCE plus DWI
  - PPV of both protocols was assessed
  - ↑ PPV when DWI is added to the protocol
    - True for mass, NME and may be particularly helpful for small lesions
  - However, considerable overlap e[illegible]sts between ADC maps of benign and malignant les[illegible]ns

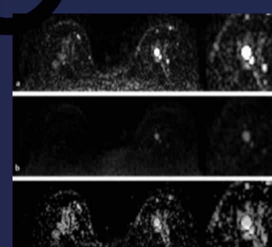
Quantitative Diffusion-Weighted Imaging as [illegible] Conventional Breast [illegible] Improved Positive Predictive Value Savannah C. Partridge, [illegible]dy B. De[illegible]i, Brenda F. Kurland, [illegible] R. Eby, Steven W. White, and Constance D. Lehman. Am[illegible]n Journal of [illegible]ntgenology 2009 193:6, 1716-1722

DWI: Clinical uses

Pathologic Condition	Signal Intensity at Diffusion-weighted Imaging*	Signal Intensity at T2-weighted Imaging	ADC Value	Interpretation of Findings
Cancer, intraductal papilloma, abscess	High	Intermediate	Decreased	High-cellularity tumor, fibrous tissue with high water content
Bloody cyst, abscess	High	Intermediate to high	Decreased	Hemorrhage, high-viscosity fluid
Fibroadenoma, cyst, fibrocystic disease	Intermediate	Intermediate to high	Intermediate to high	Medium cellularit[illegible] ter content, p[illegible]aceous fluid
Cyst, fibroadenoma, mucinous carcinoma	Low	High	Increased	High water c[illegible]nt, low cellularity
Fibroadenoma, central necrosis of cancer, calcification, chronic hemorrhage	Low	Low	Decreased	Calcification[illegible]ous tissue with low w[illegible]ontent, [illegible]alinization[illegible]siderin

Woodhams et al. DWI of the Breast: Principles and Clinical Ap[illegible]
Radiographics 2011;31(4):1059-1084

DWI: Fibroadenoma



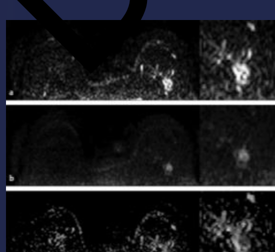
a. DWI b = 0

b. DWI b = 800

c. ADC

Courtesy of Newstead

DW[illegible] IDC



a. DWI b = 0

b. DWI b = 800

c. ADC

Courtesy of Newstead

DWI: Clinical uses: Can it stand alone?

- Maybe so!
- Kazama: DWI as an adjunct to mammo:
  - Performed AUC analysis of ROC curves and compared AUC of mammo, DWI and combo
  - Not a comparison on DWI to DCE however
  - Small reader study (~50 patients)

Kazama, T.et al. (2012), Diffusion-weighted MRI as an adjunct to mammography in women under 50 years of age: An initial study. J. Magn. Reson. Imaging, 36: 139-144. doi:10.1002/jmri.23626

DWI: Clinical uses: Can it stand alone?

- Kazama results: DWI plus mammo outperformed mammo alone (best result), DWI alone also outperformed mammo alone

	Sensitivity (false-negatives by each reader)	Specificity (false-positives by each reader)
Mammography	64% (12, 11, 5, 8)	92% (4, 4, 9, 4)
DW Imaging **	74% (7, 6, 7, 6)	93% (4, 6, 5, 5)
DWI/Cal ***	88% (3, 3, 3, 3)	91% (5, 6, 7, 6)
DWI/MMG ***	93% (2, 3, 0, 2)	85% (8, 9, 13, 9)

Kazama, T et al. (2012), Diffusion-weighted MRI as an adjunct to mammography in women under 50 years of age: An initial study. J. Magn. Reson. Imaging, 36: 139-144. doi:10.1002/jmri.23626

DWI: Clinical uses: Can it stand alone?

- Maybe not! Here we add DCE to the comparison…
- Yabuuchi reader study included 42 cancers, 8 benign lesions and 13 normal studies
- AUC values:
  - Mammo = 0.64 (sens = 40%)
  - DWI/T2 = 0.73 (sens = 50%)
  - DCE = 0.93 (sens = 86%)
- Combo Mammo + DWI/T2 > Mammo
- Combo sensitivity 69% (still < DCE)

Yabuuchi H, Matsuo Y, Sunami S, et al. Detection of non-palpable breast cancer in asymptomatic women by using unenhanced diffusion-weighted and T2-weighted MR imaging: comparison with mammography and dynamic contrast-enhanced MR imaging. Eur Radiol. 2011;21(1):11–17

DWI: Clinical uses: Can it stand alone?

- Why does DWI struggle?
  - DCIS: Variable appearance, low sensitivity
  - Papillomas/High risk lesions: Low ADC, confounders/false positives
  - ILC: Discohesive cells, may lead to underestimation on DWI
  - Fibrocystic change/fibroadenomas: Variable appearance, false positives
  - Mucinous tumors: Mimics a cyst, false negatives

DWI: Clinical uses: Neoadjuvant setting

DWI changes may pre-date DCE changes

- Theory: Apoptosis, cellular membrane breakdown may be induced before tumor size changes
- Low initial ADC and increased ADC during treatment potential biomarkers

DWI: Clinical uses: Neoadjuvant setting

- Often these patients will get repeat MRI.
- Consideration could be given to a non-con comparison study when an initial DCE+DWI study was performed and/or to monitor early or inter-regimen progress.

Other non-contrast methods:

- HiSS: High spectral and spatial imaging
- ASL: Arterial spin labeling
- EPT: Electrical properties tomography

Conclusions:

- GBCAs have an overall strong safety record
- There are differences in side effect profiles of the different contrast agents
- Continued research is needed to ensure that we are able to identify rare side effects
- Non-contrast MRI techniques are a potential option for screening MRI that would avoid IV contrast altogether
- DWI and other techniques are promising options for which continued study is warranted

Thank you!

Special thanks to Gillian Newstead!

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