Gadolinium Contrast-Enhanced Neuro MRI Protocols
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Outline / Objectives
✓ Overview: gadolinium-based contrast agents
✓ Clinical crossover trials: tumors
✓ CNS protocol strategies: efficiency & timing
  - Post Gd T2 FLAIR, PWI, 3D / 4D options

Indiana University Seminar 10.15.11

Rethinking Your MR Protocols

• Contrast
  - Which agent
  - What dose
  - Rate / flush
  - Safety – acute & chronic

• Pulse sequences
  - Which ones
  - What order
  - Timing during / after Gd
  - Consistency across sites

Background Physics: Relax!

• Relaxation times
  - T1 – longitudinal relaxation time (ms)
  - T2 – transverse relaxation time (ms)

• Relaxation rates
  - R1 – longitudinal relaxation rate (s⁻¹) = 1/T1
  - R2 – transverse relaxation rate (s⁻¹) = 1/T2

• Relaxivity
  - r1 and r2 (L x mmol⁻¹ x s⁻¹)
  - A measure of how effectively a contrast agent enhances relaxation rate (R1 or R2)

Gadolinium-based Contrast Agents

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Generic Name</th>
<th>Approved in US</th>
<th>Conditional Stability</th>
<th>r1 (1.5 T)</th>
<th>r2 (1.5 T)</th>
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</thead>
<tbody>
<tr>
<td>Magnevist</td>
<td>Gd-DTPA</td>
<td>1988</td>
<td>10</td>
<td>18.4</td>
<td>3.9</td>
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<tr>
<td>ProHance</td>
<td>Gadopentetate dimethylamine</td>
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<td>10</td>
<td>17.2</td>
<td>3.7</td>
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<td>Omniscan</td>
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<td>10</td>
<td>14.9</td>
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<tr>
<td>Optimark</td>
<td>Gadoversetamide</td>
<td>1999</td>
<td>10</td>
<td>15.0</td>
<td>~ 4</td>
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<tr>
<td>MultiHance</td>
<td>Gadobenate dimethylamine</td>
<td>2004</td>
<td>10</td>
<td>18.4</td>
<td>7.9</td>
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<tr>
<td>Gadavist</td>
<td>Gadobutrol</td>
<td>2011</td>
<td>10</td>
<td>15.5</td>
<td>4.7</td>
</tr>
</tbody>
</table>

Pintaske Invest Radiol 2006; 41:213-221
Frenzel Invest Radiol 2006; 43:817-828 erratum: Invest Radiol 2006; 41:859

Contrast Comparisons: Study Design

• Intra-individual crossover design
  - Baseline
  - Randomization
  - Contrast A
  - MR #1
  - Contrast A
  - Blinded readings
  - 3-14 days

• Randomized, controlled comparison
  - Same patient, same lesion, same protocol
  - Blinded readings – quantitative & qualitative
**Intraindividual Crossover Comparison**

**Gadopentetate vs Gadobenate: Timecourse**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Gadobenate (MultiHance)</th>
<th>Gadopentetate (Magnevist)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>2-4</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>4-6</td>
<td></td>
<td>6</td>
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<tr>
<td>6-8</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>8-10</td>
<td></td>
<td>10</td>
</tr>
</tbody>
</table>

*Lesion contrast significantly higher after MultiHance administration (N = 24)*

Data from Essig M. Appl Radiol 2003; April (suppl):92-100

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**Microvascular Permeability → Contrast Enhancement**

- Normal capillary
- Tumor capillary
- No leakage
- Leakage

Courtesy Tim Roberts, PhD

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**Crossover Comparison: Lung Mets**

**Gadopentetate vs Gadobenate**

- 0.1 mmol/kg Magnevist
- 0.1 mmol/kg MultiHance

Maravilla KR Radiology 2006; 240:389-400 (151 pts brain & spine lesions)

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**The ENHANCE Study**

Contrast-Enhanced MR Imaging of Brain Lesions: A Large-Scale Intraindividual Crossover Comparison of Gadobenate Dimeglumine versus Gadodiamide

- **ORIGINAL RESEARCH**
- **METHODS**
- **RESULTS**
- **CONCLUSION**

Rowley et al AJNR 2008; 29:1684-91
Results: Study Population

- N = 138 → 113 patients evaluable
- Age range: 18-84 years
- Diagnoses
  - Primary glial tumor 46 (41%)
  - Metastatic disease 29 (26%)
  - Extra-axial lesions 19 (17%)
  - Other / unspecified 19 (17%)
- Safety / adverse events
  - Mild / no difference between agents

Rowley et al AJNR 2008; 29:1684-91

Results – Blinded Reader Analysis
Quantitative Assessments: CNR ~30-40%
(p<0.0001; paired t-tests)

Gadodiamide vs Gadobenate (Omniscan® vs MultiHance®)

Single dose MultiHance ~ Double dose traditional

Rowley et al AJNR 2008

Primary Glial Tumor
55 year old woman with glioblastoma
Gadodiamide (Omniscan®)
Gadobenate Dimeglumine (MultiHance®)

Greater enhancement seen with MultiHance®

0708

Metastatic Disease
46-year old male anaplastic carcinoma of the small bowel
Gadodiamide (Omniscan®)
Gadobenate Dimeglumine (MultiHance®)

Single metastasis seen only with MultiHance®

0504

Results – Blinded Reader Global Preference
Qualitative Assessments: N=113
(p<0.0001; Wilcoxon signed rank test)

Gadodiamide vs Gadobenate (Omniscan® vs MultiHance®)

Rowley et al AJNR 2008

Relaxivity Effects at 3T
Gadopentetate Dimeglumine (Magnevist®) r1=3.9
Gadobenate Dimeglumine (MultiHance®) r1=5.9

Z. Rumboldt et al JMRI 2009; 29:760-767
Gadobenate: Low Dose Application at 3T

Huang, B et al    Acta Radiologica 2010 (1): 79-84

1.5T Gd-DPTA 0.1 mmol/kg
3T Gd-DPTA 0.025 mmol/kg
3T Gd-BOPTA 0.05 mmol/kg
3T Gd-BOPTA 0.75 mmol/kg
3T Gd-BOPTA 1.0 mmol/kg

High Relaxivity: Clinical Implications

Kuhn et al    J Neurosurg 2007; 106: 557-566

Gadobenate in Adult CNS Tumors

- Intra-individual crossover studies show
  - Significantly better lesion-to-brain contrast enhancement than non-protein binding agents
  - Significantly better conspicuity of CNS lesions
  - More enhancement → ↑ diagnostic information
  - Relevant to clinical decisions & planning
  - Similar safety profile all agents

Essig M. et al    Appl Radiol 2003; (suppl):92-100
Knopp et al    Radiology 2004; 230: 55-64
Maravilla et al    Radiology 2006; 240: 389-400
Rowley et al    AJNR 2008; 29: 1684-91
Rumboldt et al    JMRI 2009; 29:760-767

High Concentration Contrast - Mets

27 patients
10/27: 1M better
2/27: more mets

Gadobutrol (Gadavist – 1.0 M; r1 = 4.7) → 67 mets
Gadopentetate (Magnevist; r1 = 3.9) → 65 mets

Anzalone et al    Acta Radiol 2009; 50: 933-940

High Relaxivity Agents - Breast MRI

Multicenter, Double-Blind, Randomized, Intra-individual Crossover Comparison of Gadobenate Dimeglumine and Gadopentetate Dimeglumine for Breast MR Imaging (DETECT Trial)

- 151 women
- Intra-individual crossover
- 3 blinded readers
- Mean 11.7% more cancers detected with Gadobenate (MultiHance)

Martincich, L et al    Radiology 2011; 258: 396-408

Breast MRI Enhancement – DETECT Trial

Martincich, L et al    Radiology 2011; 258: 396-408
High Relaxivity Agents - Peripheral MRA

- 92 patients
- Intra-individual crossover
- 3 blinded readers
- MultiHance > Magnevist
  - Enhancement (p ≤ 0.0001)
  - Disease detection (p ≤ 0.0028)
  - All evaluations (p ≤ 0.0001)

Gerretsen, SC et al Radiology 2010; 255: 988-1000

Contrast-Enhanced MR Protocols

- Overall goal: diagnostic protocol efficiency
  - Most information
  - Shortest time
  - Lowest dose

- Post-contrast imaging
  - Traditional T1
    - Be patient: wait 5 min
  - Consider T2 FLAIR

- ‘Free’ information: capture the bolus
  - Dynamic T2* → Perfusion
  - Dynamic T1 → Time-resolved MRA, permeability

11 Minute Screening Brain MR

- Overall goal: diagnostic protocol efficiency
  - Most information
  - Shortest time
  - Lowest dose

Post-Gad T2 FLAIR: Literature

Neuroradiology

Brain: Gadolinium-enhanced Fast Fluid-attenuated Inversion-Recovery MR Imaging

PURPOSE: To determine the clinical utility of gadolinium-enhanced fast fluid-attenuated inversion-recovery (FLAIR) magnetic resonance (MR) imaging of the brain by comparing results with those at gadolinium-enhanced T1-weighted MR imaging with magnetization transfer (MT) saturation.

MATERIALS AND METHODS: In 105 consecutive patients referred for gadolinium-enhanced brain imaging, FLAIR and T1-weighted MR imaging with MT saturation were performed before and after administration of gadopentetate dimeglumine (0.1 mmol per kilogram of body weight). The postcontrast images were evaluated to determine the presence of abnormal contrast enhancement and whether enhancement was more compatible with the FLAIR or T1-weighted sequences.

RESULTS: Thirty-nine studies showed intracranial contrast enhancement. Postcontrast T1-weighted images with MT saturation showed superior enhancement in 14.

Mathews et al Radiology 1999; 211:257-263

Strep aerogenes abscesses

Utility of DWI and post Gad T2 FLAIR Imaging

Meningitis: T1 vs T2 FLAIR + Gd
**Post Gadolinium T2 FLAIR**

- **Advantages**
  - Protocol efficiency
  - Optimized T1 Gd timing
  - Most sensitive for leptomeningeal disease
  - ‘One stop shopping’ for intra-axial lesions

- **Pointers & Caveats**
  - No need for pre-contrast T2 FLAIR
  - T2 effects → ‘dark through’ competition
    - Meningiomas, schwannomas, etc
  - Always use in conjunction with T1 + Gd
  - Use 3D / volumetric if available

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**Advantages of 3D:**
- Scan once → recon many
- Volumetric measurements
- Treatment plans / navigation
- Multi-modality / temporal fusion
- Tissue segmentation
- Future: CAD

**Protocol Note:** Add SE T1’s in: orbit, CN, head & neck, and pituitary (do first)
**Treatment Planning: Imaging Options**

- **2D FLAIR**
  - 1.5 mm 10:41

- **3D FLAIR**
  - 1.6-0.8 mm 3:09

- **3D FLAIR + Gd**
  - 2-3 mm 2:45

**Intra-operative MRI**

**Pre-op Images:**
- T2 FLAIR + Gd
- T1 + Gd
- DTI
- CBV

**Active contrast leakage into surgical bed**

**Brain Tumor Protocols: Contrast Biopsy Site, Tumor Grade and Follow-up**

- **T1 + Gd**
- **T2 FLAIR + Gd**
- CBV

**New additions to consider**

**Brain Perfusion Techniques**

<table>
<thead>
<tr>
<th>Basis</th>
<th>DSC Dynamic Susceptibility Contrast</th>
<th>DCE Dynamic Contrast Enhancement</th>
<th>ASL Arterial Spin Labeling</th>
<th>CTP CT Perfusion</th>
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<tbody>
<tr>
<td>SNR</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Flow</td>
<td>+</td>
<td>-</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Volume</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Transit</td>
<td>++</td>
<td>++ Permeability</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Coverage</td>
<td>+++</td>
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</table>
### Overview: CT and MR Perfusion Methods

<table>
<thead>
<tr>
<th>Inject</th>
<th>Scan</th>
<th>Model</th>
<th>Parameter Maps</th>
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<tbody>
<tr>
<td>CT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MR</td>
<td>Gd</td>
<td></td>
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</table>

**CT**

- **Overview:** CT and MR Perfusion Methods
- **Inject:**
- **Scan:**
- **Model:**
- **Parameter Maps:**

**MR**

- **Overview:** CT and MR Perfusion Methods
- **Inject:**
- **Scan:**
- **Model:**
- **Parameter Maps:**

### Glioma: Perfusion Shows ↑CBV

- **T2**<sup>+</sup> Effect
- **ROI**
- **T2**<sup>+</sup> vs time
- **T1** Effect
- **CBV**

### CBV & Permeability Predict Tumor Grade

- **Grade 2**
- **Fibrillary astrocytoma**
- **K<sub>e</sub>p**
- **T1** based

- **Grade 3**
- **Anaplastic astrocytoma**
- **Grade 4**
- **Glioblastoma multiforme**

**Patankar et al AJNR 2005; 26: 2455-2465**

### ↑ CBV Predicts Glioma Transformation

- **Baseline**
- **6 months**
- **18 months**

**Danchaiwijitr et al Radiology 2008; 247: 170-178**

### Evidence-Based Imaging Recommendations in Acute Ischemic Stroke

**Schellinger, P et al Neurology 2010; 75: 177-185**

**Abstract**

Objectives: To assess the evidence for the use of diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) in the diagnosis of acute ischemic stroke.


Results and Recommendations: PWI is readily available and should be considered in all cases of ischemic stroke to guide imaging and treatment. DWI is more sensitive than PWI for detecting acute ischemic stroke, but PWI is more specific. The accuracy of DWI in predicting cerebral infarction and the role of PWI in predicting reperfusion are still under investigation.

Evidence-based recommendations are based on the American Academy of Neurology's guidelines for the diagnosis and treatment of acute ischemic stroke.
10 Minute Acute Stroke Protocol

Physiologic stroke triage: occlusion site, PWI-DWI mismatch

Ischemic Penumbra

TRICKS MRA 0:54

Time Resolved Imaging of Contrast Kinetics

PWI 1:12 (auto recon at console)

DWI 0:40

FSPGR 0:36

FMT

CBV

CBF

Split Dose Gadobenate ‘Stroke Deluxe’

Single vial - 2 boluses:

T1 – TRICKS – 7 ml

CBF

T2 FLAIR + Gd

FMT

T1 + Gd

T2 * – Perfusion – 13 ml

AVM: First Pass HYPR Flow MRA

Anatomy-Isotropic

Time-resolved

Velocity-resolved

10 frames / sec

100 cm / sec

320x320x320

Summary: Neuro Protocol Update

• Gadolinium – newer agents
  – Gadobenate (MultiHance): ↑ relaxivity
  – Gadobutrol (Gadavist): ↑ concentration
  – Crossover studies: value of high relaxivity
     • CNS tumors, Breast MRI, Peripheral MRA

• Tumor and stroke protocols
  – Post contrast sequences: wait ~ 5 minutes
  – Consider post-Gad T2 FLAIR, 3D sequences
  – Capture the bolus! → Perfusion, 4D MRA

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