Safety First: Considerations for Emerging Modalities and Adjunct Therapies

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Disclosures

• Guofan Xu, MD, PhD has no financial or other conflicts of interest to disclose
CPE Information

• Target Audience: Pharmacists
• ACPE#: 0202-0000-19-017-L05-P
• Activity Type: Knowledge-based
Learning Objectives

At the completion of this knowledge-based activity, participants will be able to:

• Describe the emerging modality of PETMR and how it compares to the current PET/CT imaging process.

• Discuss patient and provider safety of the emerging modality of PETMR.

• Explain the patient safety considerations of adjunct therapies (gadolinium, morphine, diphenhydramine, adenosine, Lexiscan and DATScan).

• Identify other drug interactions with emerging modality of PET/MRI.
1. Which of the following diagnostic imaging modality provides the best radiation safety profile?
   A. Magnetic resonance imaging (MRI)
   B. Positron emission tomography (PET)
   C. Computer tomography (CT)
   D. Single photon emission tomography (SPECT)
2. Which of the following patients will have the most benefit of PET/MRI exam from radiation exposure reduction as compared with PET/CT exam?

A. A 67 year old male with acute myeloid leukemia.
B. A 39 year old female with metastatic breast cancer.
C. A 52 year old male with adenocarcinoma of the left upper lobe of lung.
D. A 18 year old female with Hodgkin’s Lymphoma.
3. Which of the following patient is most safe to have a PET/MRI exam instead of PET/CT exam?

A. A 43 year old female with newly diagnosed breast cancer who has hearing aid implant.
B. A 65 year old male with prostate cancer and chronic renal failure on dialysis.
C. A 74 year old male with lung cancer and remote history of knee replacements.
D. A 30 year old male with mantle cell lymphoma and acute onset of renal failure (GFR < 25).
4. Which of the following medication will likely interfere PET/MRI evaluation of multiple myeloma?

A. Metformin  
B. Diazepam (Valium)  
C. Lasix (Furosemide)  
D. Neupogen (Filgrastin)
Content

• Understand the basic concept of PET/MRI and how it compares to the current PET/CT

• Patient safety issues of emerging modality PET/MRI

• Patient safety considerations of adjunct therapies (gadolinium)

• Identify other drug interactions with merging modality of PET/MRI
• What is PET/CT? Positron emission tomography (PET) and computed tomography (CT)

A 64 year old male with Mantle Cell Lymphoma, diagnosis confirmed with lymph node biopsy.
MRI

• What is MRI? Magnetic Resonance Imaging
PET/MRI

Feature of imaging modalities

Table 1. Features of available and emerging imaging modalities

<table>
<thead>
<tr>
<th>Modality</th>
<th>Temporal Resolution</th>
<th>Spatial Resolution</th>
<th>Depth of Penetration</th>
<th>Sensitivity</th>
<th>Multiplexing Capability</th>
<th>Cost</th>
<th>Safety Profile</th>
<th>Used Clinically</th>
</tr>
</thead>
<tbody>
<tr>
<td>Computed tomography (CT)</td>
<td>Minutes</td>
<td>50-200 μm (preclinical) 0.5-1 mm (clinical)</td>
<td>Limitless</td>
<td>ND</td>
<td>Could be possible</td>
<td>$$$</td>
<td>Ionizing radiation</td>
<td>Yes</td>
</tr>
<tr>
<td>Magnetic resonance imaging (MRI)</td>
<td>Minutes-hours</td>
<td>25-100 μm (preclinical) ~1 mm (clinical)</td>
<td>Limitless</td>
<td>$10^{-3}$ to $10^{-5}$ M</td>
<td>No</td>
<td>$$$</td>
<td>No ionizing radiation</td>
<td>Yes</td>
</tr>
<tr>
<td>Positron emission tomography (PET)</td>
<td>Seconds-minutes</td>
<td>1-2 mm (preclinical) 5-7 mm (clinical)</td>
<td>Limitless</td>
<td>$10^{-11}$ to $10^{-12}$ M</td>
<td>No</td>
<td>$$$</td>
<td>Ionizing radiation</td>
<td>Yes</td>
</tr>
<tr>
<td>Single photon emission tomography (SPECT)</td>
<td>Minutes</td>
<td>1-2 mm (preclinical) 8-10 mm (clinical)</td>
<td>Limitless</td>
<td>$10^{-10}$ to $10^{-11}$ M</td>
<td>Yes</td>
<td>$$</td>
<td>Ionizing radiation</td>
<td>Yes</td>
</tr>
<tr>
<td>Ultrasound (US)</td>
<td>Seconds-minutes</td>
<td>0.01-0.1 mm for superficial (few mm depth) 1-2 mm for deeper (few cm depth) applications</td>
<td>mm-cm</td>
<td>Excellent when microbubbles are used (~10-12 M)</td>
<td>Not yet</td>
<td>$$</td>
<td>Good safety profile</td>
<td>Yes</td>
</tr>
<tr>
<td>Optical fluorescence imaging</td>
<td>Seconds-minutes</td>
<td>2-3 mm</td>
<td>&lt;1 cm</td>
<td>$10^{-9}$ to $10^{-12}$ M</td>
<td>Yes</td>
<td>$$</td>
<td>Good safety profile but depends on fluorophore used and mass needed</td>
<td>Emerging clinical utility (see text)</td>
</tr>
<tr>
<td>Optical bioluminescence imaging</td>
<td>Seconds-minutes</td>
<td>3-5 mm</td>
<td>1-2 cm</td>
<td>$10^{-13}$ to $10^{-17}$ M</td>
<td>Yes</td>
<td>$$</td>
<td>Good safety profile</td>
<td>Low potential for clinical translation (see text)</td>
</tr>
<tr>
<td>Surface-enhanced raman scattering (SERS) imaging</td>
<td>Minutes-days</td>
<td>mm</td>
<td>~5 mm</td>
<td>$10^{-12}$ to $10^{-15}$ M</td>
<td>Yes</td>
<td>ND</td>
<td>ND</td>
<td>Limited clinical applications (see text)</td>
</tr>
<tr>
<td>Photocoustic imaging (PAI)</td>
<td>Seconds-minutes</td>
<td>~10 μm to 1 mm</td>
<td>6 mm to 5 cm</td>
<td>ND</td>
<td>Yes</td>
<td>$$</td>
<td>Good safety profile but depends on imaging agent used and mass needed</td>
<td>Clinically Translatable</td>
</tr>
<tr>
<td>Intravital microscopy (IVM)</td>
<td>Seconds-days</td>
<td>1-10 μm</td>
<td>~700 μm</td>
<td>$10^{-10}$ to $10^{-17}$ M</td>
<td>Yes</td>
<td>$$$</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND, Not determined.
Clinical application of PET/MRI

• MRI has better soft tissue contrast than CT.

• Perspective clinical application of PET/MRI including: *Simultaneous*
  • Oncology
  • Neurology
  • Cardiology
Uptake of FDG from the blood into the cells is facilitated by the glucose transporters (GLUT). Since the blood glucose concentration is typically higher than the intracellular concentration, the inward rate is higher than diffusion out of the cells. Hexokinase converts FDG to FDG-6-phosphate (FDG-6-P). Most cells with the notable exception of the liver have little phosphatase. FDG-6-P is not a substrate for further metabolism.

2-fluoro-2-deoxy-D-glucose (FDG) is an analog of D-glucose where the hydroxyl in the 2 position is replace by fluorine-18.
FDG PET mechanism for cancer detection

- Normal cells primarily rely on mitochondrial oxidative phosphorylation to generate the energy needed for the cellular processes.
- Most cancer cells are switched to aerobic glycolysis, even in the presence of oxygen, the Warburg effect. Accordingly in cancer cells most glucose when metabolized to pyruvate will be further converted into lactate even in the presence of oxygen.
- Much higher amounts of glucose is utilized in cancer cells (10-20 fold) even if these cells do not have a higher energy need. Glucose metabolism in normal non-hypoxic cells through oxidative phosphorylation is much more effective than aerobic glycolysis.

PET/CT image vs. PET/MRI image

20min PET/CT (45 min Post Injection)

30min PET/MRI (80 min Post Injection)

4.8 mCi FDG
Emerging modality of PET/MRI (Pros)

- MR soft tissue contrast superior to that of CT. Wider variety of tissue contrasts.
- Flexible choice of MR techniques – morphological imaging, molecular imaging agents, perfusion imaging, diffusion imaging, and MR spectroscopy.
- No ionizing (CT) radiation dose.
- Potential for simultaneous MR/PET imaging.
- Good registration of structural and molecular imaging data.
- Anatomic priors for PET reconstruction and data modeling.
- PET and MR Spectroscopy can measure spatially matched biochemical content and physiological status.
- Possible correction for positron range issues.
Emerging modality of PET/MRI (Cons)

- Expensive
- Attenuation information not directly measured as in CT
- Uncertainty regarding throughput, cost effectiveness and ultimate clinical role
- No Particular clinical application
- Technically difficult to develop
Emerging modality of PET/MRI (Cons)

- Potential advantages of PET/CT over PET/MRI
- Lower scanner costs and generally shorter acquisition times
- Not contraindicated in patients with pacemakers, aneurysm coils, etc.
- Superior anatomic evaluation of the lung parenchyma, including greater sensitivity for pulmonary nodules that are too small to resolve by PET or MRI.
- Less susceptible to attenuation correction artifacts, such as those arising from tissue classification errors in MRI-based segmentation algorithms
- Better conspicuity of benign bone lesions
## PET/CT vs. PET/MRI

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PET/CT</strong></td>
<td><strong>Limited soft tissue contrast</strong>&lt;br&gt;• Fast CT exam does not provide extra time for PET acquisition&lt;br&gt;• IV contrast not routinely used&lt;br&gt;• If focused MRI needed, must be additional exam&lt;br&gt;• Ionizing radiation from CT component</td>
</tr>
<tr>
<td>• Widely available&lt;br&gt;• Established imaging protocols&lt;br&gt;• Evidence proven indications&lt;br&gt;• Familiarity among ordering providers&lt;br&gt;• Quantitative accuracy well established&lt;br&gt;• Imaging of small pulmonary nodules&lt;br&gt;• Exams performed in as little as 30 minutes</td>
<td>&lt;br&gt;<strong>PET/MRI</strong>&lt;br&gt;• Improved soft tissue contrast&lt;br&gt;• Added value of DWI&lt;br&gt;• Increased available time to collect PET data&lt;br&gt;• Better motion correction&lt;br&gt;• Convenience and time savings with combined exams&lt;br&gt;• Use of MRI specific contrast agents&lt;br&gt;• No ionizing radiation from MRI component</td>
</tr>
<tr>
<td><strong>PET/MRI</strong></td>
<td><strong>Limited availability</strong>&lt;br&gt;• Protocols and indications still in development&lt;br&gt;• Require technologist knowledgeable in both NM and MRI&lt;br&gt;• Quantitative accuracy still being determined&lt;br&gt;• Exams may take 1 hour or longer&lt;br&gt;• Limited evaluation of pulmonary parenchyma</td>
</tr>
</tbody>
</table>
Evolvement of PET/MRI configurations
Current state of art PET/MRI - Siemens PET/MR system

**MRI:** 3-T (length, 163 cm; bore, 60 cm), an actively shielded gradient coil system (length, 159 cm; amplitude, 45 mT/m; and slew rate, 200 T/m/s), The MR FOV of 0.5–50 cm, with a 2-D slice thickness from 0.1 to 200 mm, 3D thickness from 5 to 500 mm

**PET:** 8 rings of 56 blocks each - 8x8 detector elements/block of LSO crystals (4 x 4 x 20 mm), coupled to 3x3 APDs, Axial FOV: 25.8 cm, Transverse FOV: 59.4 cm
Current state of art PET/MRI - GE PET/MR system

PET: LYSO, TOF capable, ~ 400 ps (6 cm positioning error), 25 cm axial FOV, 60 cm transverse FOV

MRI: 3T Magnet, (MR750W), 60 cm bore w/ 50cm FOV, Multi-drive XMIT with 32 ch + 33 T/m & 120 T/m/s gradient strength
New GE Signa PET/MR
Outperform with higher sensitivity

PET/MR
21 cps/KBq

Conventional PET
7 cps/KBq
PET/MRI in Alzheimer’s disease (Neurology Application)

Simultaneous delineate amyloid deposition, gray matter atrophy, white matter disease
Attenuation Correction in PET/MRI

Attenuation correction accounts for the fact that photons arising from structures deeper in the body are more likely to be attenuated than those arising from the surface.

-- CT provides patient-specific attenuation correction maps using the calculated reconstruction of internal density inherent to the process of CT imaging.

-- MRI, cannot directly assess tissue density and in particular has difficulty imaging the lung and bones.
PET/MRI Attenuation correction approach -1
PET/MRI Attenuation correction approach - 2

- MR Images by bed position
- Segmentation Parameters
- Body contour and lung segmentation
- Fat/tissue classification
- Truncation completion
- MR whole-body attenuation
PET/MR from status Quo to Status Go – updates from recent Tubingen 2016 meeting (5th meeting)

- About 100 systems installed
- Prostate cancer imaging with Ga-68 PSMA as a new key application
- PET/MR is not to replace PET/CT but rather to improve MR in areas of opportunity

Bailey et al, Mol. Imaging and Biology 2016
• Describe the emerging modality of PETMR and how it compares to the current PET/CT imaging process.

• Discuss patient and provider safety of the emerging modality of PETMR.

• Explain the patient safety considerations of adjunct therapies (gadolinium, morphine, diphenhydramine, adenosine, Lexiscan and DATScan).

• Identify other drug interactions with emerging modality of PET/MRI.
Radiation Reduction

- FDG-PET/MRI can provide diagnostic PET images with an equivalent dose of administered PET tracer compared to PET/CT.

- The CT component of FDG-PET/CT typically contributes up to 54% to 81% of the combined radiation dose. FDG-PET/MRI has the potential to significantly reduce radiation exposure without sacrificing the quality of anatomic images.

- Members of radiation-vulnerable populations, such as children, adolescents, and young adults with potentially curable cancers, stand to derive the most benefit from PET/MRI radiation dose reduction, especially if frequent restaging with PET is needed for optimal management.

- FDG-PET/MRI potentially improves characterization of certain incidental lesions initially detected on FDG-PET/CT but deemed indeterminate. This potential could reduce costs and risks to the patient from the invasive procedures and/or additional or imaging studies.
Radiation dose in diagnostic imaging modalities in pediatric patients with neuroblastoma

<table>
<thead>
<tr>
<th></th>
<th>Conventional X-ray</th>
<th>CT of CT</th>
<th>PET/CT</th>
<th>PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>DoseTrack group (n=31)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of exams</td>
<td>1090</td>
<td>81</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Estimated total effective dose (mSv)</td>
<td>90.44</td>
<td>107.13</td>
<td>138.79</td>
<td></td>
</tr>
<tr>
<td>Mean effective dose per exam (mSv)</td>
<td>0.04±0.19</td>
<td>1.09±1.11</td>
<td>8.35±7.45</td>
<td></td>
</tr>
</tbody>
</table>

|                      |        |         |        |         |
| Pre-DoseTrack group (n=32) |       |         |        |         |
| Total number of exams | 4269   | 332     | 65     |         |
| Adopted mean effective dose per exam (mSv) | 0.04±0.19          | 1.09±1.11 | 8.35±7.45 |       |
| Estimated total effective dose (mSv) | 170.76           | 361.88  | 542.75 |         |

|                      |        |         |        |         |        |         |        |         |
| Total group (n=63)   |        |         |        |         |        |         |        |         |
| Total number of exams | 5359      | 413     | 82     | 180     |
| Estimated total effective dose (mSv) | 214.36           | 450.17  | 684.70 | 620.54  |
| Estimated cumulative dose per person (mSv) | 3.43±2.86     | 7.66±6.09 | 18.35±13.52 | 10.71±10.05 |
| Relative dose (%)   | 8.5     | 19.1    | 45.7   | 26.7    |

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• Explain the patient safety considerations of adjunct therapies (gadolinium, morphine, diphenhydramine, adenosine, Lexiscan and DATScan).
• Identify other drug interactions with emerging modality of PET/MRI
PET Safety

• Workflow for radioactivity
• Isotope Parameters
• Radiation Protection Goals (100mrem/year for general public), as low as reasonably achievable (ALARA)
• Shielding material and shielding calculations
• Radiation Safety Issues
<table>
<thead>
<tr>
<th>Isotope</th>
<th>Half-life</th>
<th>$\beta^+$ Energy (MeV)</th>
<th>$\gamma$ Energy (MeV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-11</td>
<td>20.4 m</td>
<td>0.385 (99.8%)</td>
<td></td>
</tr>
<tr>
<td>N-13</td>
<td>9.97 m</td>
<td>0.492 (99.8%)</td>
<td></td>
</tr>
<tr>
<td>O-15</td>
<td>122 s</td>
<td>0.735 (99.9%)</td>
<td></td>
</tr>
<tr>
<td>F-18</td>
<td>110 m</td>
<td>0.250 (100%)</td>
<td></td>
</tr>
<tr>
<td>K-38</td>
<td>7.64 m</td>
<td>1.216 (99.3%)</td>
<td>2.167 (99.8%)</td>
</tr>
<tr>
<td>Cu-62</td>
<td>9.74 m</td>
<td>1.315 (97.6%)</td>
<td></td>
</tr>
<tr>
<td>Cu-64</td>
<td>12.7 h</td>
<td>0.278 (17.9%)</td>
<td></td>
</tr>
<tr>
<td>Ga-68</td>
<td>68.1 h</td>
<td>0.836 (8.79%), 1.077 (3.0%)</td>
<td>0.352 (1.12%)</td>
</tr>
<tr>
<td>Rb-82</td>
<td>75 s</td>
<td>1.523 (83.3%), 0.776 (13.4%)</td>
<td>1.157 (10.2%)</td>
</tr>
<tr>
<td>I-124</td>
<td>4.18 d</td>
<td>0.686 (11.3%), 1.691(10.4%), 7.228(10.0%), 0.974(11.3%)</td>
<td>1.509 (3.0%), 1.376(1.7%),1.325</td>
</tr>
</tbody>
</table>

(1.43%)
MRI safety issues

• MRI safety issue: *projectiles, thermal burns, and hearing loss in poorly protected patients*

• The powerful magnetic field of the MR system will attract iron-containing (ferromagnetic) objects and may cause them to move suddenly and with great force, which imposes risk to the patient or anyone in the object's "flight path."

• The powerful magnetic field of the MR system will pull on any iron-containing object in the body, such as certain aneurysm clips or certain medication pumps. Every MRI facility has a comprehensive screening procedure and protocol. Due to the presence of an unacceptable implant or device, the exam may have to be canceled.

• The magnetic field of the MR system may damage an external hearing aid or cause a heart pacemaker, electrical stimulator, or neurostimulator to malfunction or cause injury.

• In addition, a metallic implant or other object may cause signal loss or distort the MR images. This may be unavoidable.
FDA MRI safety guideline

https://www.fda.gov/Radiation-EmittingProducts
Patient safety consideration of PET/MRI with contrast

Gadolinium-based contrast agents (GBCAs) increase the risk for Nephrogenic systemic fibrosis (NSF) among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.
• Describe the emerging modality of PETMR and how it compares to the current PET/CT imaging process.
• Discuss patient and provider safety of the emerging modality of PETMR
• Explain the patient safety considerations of adjunct therapies (gadolinium, morphine, diphenhydramine, adenosine, Lexiscan and DATScan).
• Identify other drug interactions with emerging modality of PET/MRI
Brown fat activities

- Brown fat can be confused with neck muscle uptake, or small lymph nodes.
- Brown fat uptake can also be abolished by low does of diazepam (Valium).
- Muscle relaxants reinforced this confusion.
- In children, uptake of meta-iodo-benzyl-guanidine (MIBG) and tetrofosmin in brown fat has also been recognized.
Colonic Stimulating Factor, such as filgrastim and pegfilgrastim, are frequently prescribed to patients with non-myeloid malignancies. These agents act on hematopoetic cells to stimulate proliferation, differentiation, and end-cell functional activation. This augmentation of hematopoetic function increases the metabolism of the spleen and bone marrow, which may confound
Metformin effect
• Laxatives. The use of a laxative that stimulates peristalsis and may produce irritation of the tissues runs the risk of increasing FDG uptake rather than reducing it, posing a potential interference with abdominal imaging.

• Metformin.

• Corticosteroids - Corticosteroids are frequently used in combination with antineoplastic agents in the treatment of cancer, which would increase hepatic glycogen stores and insulin resistance.

• Other agents that pose a risk for Hyperglycemia - Any drug or therapy that alters or may alter blood glucose and/or insulin levels poses the risk for “pharmacological” interactions with FDG.
MRI intravenous Gadolinium contrast agent nephrotoxicity

• Free Gd ion is a known heavy metal toxin, the intravenous Gd agents that have been approved for human use in the United States have been shown to be remarkably stable and safe pharmaceutical agents. The potential nephrotoxicity of standard doses intravenous Gd for MRI does not appear to be clinically significant.

• Applications with higher doses, particularly in high-risk patients with underlying renal insufficiency, one must be aware of the potential to induce ARF.

• A reasonable preventative measure would be to ensure adequate hydration. (Alkalinization of the urine with sodium bicarbonate could be considered.)

• Substituting Gd for iodinated contrast in X-ray studies in the setting of renal insufficiency appears to be unwarranted.

• Contraindication to iodinated contrast such as a history of severe allergy, the patient should be premedicated for a potential cross-reaction.
Current FDA approved Gadolinium-based contrast agents

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Other</th>
<th>Label Dose</th>
<th>FDA labeling age</th>
<th>FDA approved indication* (see label for precise labeling information)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadavist</td>
<td>Gd-BT-DO3A (gadobutrol)</td>
<td>0.1 mmol/Kg (0.1 mL/Kg)</td>
<td>Any Age</td>
<td>Central Nervous System, Pediatrics and adult, Breast disease</td>
</tr>
<tr>
<td>Dotarem</td>
<td>Gd-DOTA (gadoterate meglumine)</td>
<td>0.1 mmol/Kg (0.2 mL/Kg)</td>
<td>≥2 years</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>Prohance</td>
<td>Gd-HP-DO3A (gadoteridol)</td>
<td>0.1 mmol/Kg (0.2 mL/Kg)</td>
<td>2 – 18 years and adults</td>
<td>Central Nervous System, Extracranial/Extraspinal Tissues</td>
</tr>
<tr>
<td>Magnevist VL</td>
<td>Gd-DTPA (gadopentetate dimeglumine)</td>
<td>0.1 mmol/Kg (0.2 mL/Kg)</td>
<td>≥2 years</td>
<td>Central Nervous System, Extracranial/Extraspinal Tissues, Body (excluding the heart)</td>
</tr>
<tr>
<td>Mriportance</td>
<td>Gd-BOPTA (gadobrazone dimeglumine)</td>
<td>0.1 mmol/Kg (0.2 mL/Kg)</td>
<td>≥2 years</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>Eovist</td>
<td>Gd-EOB-DTPA (gadoxetic acid disodium)</td>
<td>0.025 mmol/Kg (0.1 mL/Kg)</td>
<td>Adults</td>
<td>Liver lesions</td>
</tr>
<tr>
<td>Ablavar (previously Vasevist)</td>
<td>Gd-DTPA (gadofosveset trisodium, MS-325)</td>
<td>0.03 mmol/Kg (0.12 mL/Kg)</td>
<td>Adults</td>
<td>Aortoiliac occlusive disease</td>
</tr>
<tr>
<td>Optimark Omniscan</td>
<td>Gd-DTPA-BMEA (gadoversetamide) ionic &amp; Gd-DTPA-BMA (gadodiamide)</td>
<td>0.1 mmol/Kg (0.2 mL/Kg), 0.1 mmol/Kg (0.2 mL/Kg)</td>
<td>18–76 years, 2–16 years and adults</td>
<td>Central Nervous System, Liver, Central Nervous System, Body (noncardiac)</td>
</tr>
</tbody>
</table>

MR contrast agents are detected indirectly through their effects on the nuclear magnetic relaxation time constants (T1, T2, and T2*) of water in tissues. The intravenous Gd agents shorten all three of these time constants; however, typical applications of contrast-enhanced MRI specifically rely on shortening of T1.
Drug interaction with merging modality of PET/MRI

• Gadolinium-based contrast agents (GBCAs) increase the risk for Nephrogenic systemic fibrosis (NSF) among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.
Drug interaction with merging modality of PET/MRI

• Patients with kidney disease:

  Do not administer OMNISCAN to patients with:
  • chronic, severe kidney disease (GFR < 30 mL/min/1.73m²), or
  • acute kidney injury, commonly in the setting of surgery, severe infection, injury or drug-induced kidney toxicity.

• Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g., age > 60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.
### Drugs Associated with Nephrotoxicity

<table>
<thead>
<tr>
<th>Drug class/drug(s)</th>
<th>Pathophysiologic mechanism of renal injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesics</td>
<td></td>
</tr>
<tr>
<td>Acetaminophen, aspirin</td>
<td>Chronic interstitial nephritis</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>Acute interstitial nephritis, altered</td>
</tr>
<tr>
<td></td>
<td>intraglomerular hemodynamics, chronic</td>
</tr>
<tr>
<td></td>
<td>interstitial nephritis, glomerulonephritis</td>
</tr>
<tr>
<td>Antidepressants/mood stabilizers</td>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td>Amitriptyline (Elavil®), doxepin</td>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td>(Zonalon), fluoxetine (Prozac)</td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td>Chronic interstitial nephritis, glomerulonephritis, rhabdomyolysis</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td>Diphenhydramine (Benadryl),</td>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td>doxylamine (Unisom)</td>
<td></td>
</tr>
<tr>
<td>Antimicrobials</td>
<td></td>
</tr>
<tr>
<td>Acyclovir (Zovirax)</td>
<td>Acute interstitial nephritis, crystal</td>
</tr>
<tr>
<td></td>
<td>nephropathy</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Tubular cell toxicity</td>
</tr>
<tr>
<td>Amphotericin B (Fungizone®;</td>
<td>Tubular cell toxicity</td>
</tr>
<tr>
<td>deoxycholic acid formulation more</td>
<td></td>
</tr>
<tr>
<td>so than the lipid formulation)</td>
<td></td>
</tr>
<tr>
<td>Beta lactams (penicillins,</td>
<td>Acute interstitial nephritis, giome-</td>
</tr>
<tr>
<td>cephalosporins)</td>
<td>rulonephritis (ampicillin, penicillin)</td>
</tr>
<tr>
<td>Forsomocet (Foscarit)</td>
<td>Crystal nephropathy, tubular cell toxicity</td>
</tr>
<tr>
<td>Ganciclovir (Cytovene)</td>
<td>Crystal nephropathy</td>
</tr>
<tr>
<td>Pantamidine (Pantam)</td>
<td>Tubular cell toxicity</td>
</tr>
<tr>
<td>Quinolones</td>
<td>Acute interstitial nephritis, crystal</td>
</tr>
<tr>
<td></td>
<td>nephropathy (ciprofloxacin [Cipro])</td>
</tr>
<tr>
<td>Rifampin (Rifadin)</td>
<td>Acute interstitial nephritis</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Acute interstitial nephritis, crystal</td>
</tr>
<tr>
<td></td>
<td>nephropathy</td>
</tr>
<tr>
<td>Vancomycin (Vancocin)</td>
<td>Acute interstitial nephritis</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>(continued)</td>
<td></td>
</tr>
</tbody>
</table>

### Antiretrovirals
- Adenosine (Videx), didanosine (Videx), stavudine (Zidovudine), tenofovir (Viread)
- Indinavir (Crixivan)

### Benzodiazepines
- Calcineurin inhibitors
- Cyclosporine (Neoral)

### Tacrolimus (Prograf)

### Cardiovascular agents
- Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers
- Clopigrogl (Plavix), ticlopidine (Ticlid)

### Statins
- Rhabdomyolysis

### Chemotherapeutics
- Carmustine (Gliadel), semustine (investigational)
- Cisplatin (Platinol)

### Interferon-alpha (Intron A)

### Methotrexate

### Mitoctymic C (Mutamycin)

### Contrast dye

### Diuretics
- Loop diuretics, thiazides
- Triamterene (Dyrenium)

### Drugs of abuse
- Cocaine, heroin, ketamine (Ketalar), methadone, methamphetaminine

### Herbs
- Chinese herbs with aristolochic acid
- Chronic interstitial nephritis
- Proton pump inhibitors
- Lansoprazole (Prevacid), omeprazole (Prilosec), pantoprazole (Protonix)
- Acute interstitial nephritis
- Others
- Allopurinol (Zyloprim)
- Gold therapy
- Haloperidol (Haldol)
- Promazone (Areda)
- Phenytoin (Dilantin)
- Quinine (Quinaldine)
- Ranitidine (Zantac)
- Zoledronate (Zomet)

### Tubular cell toxicity

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Closing remarks/conclusion

- Many potential scenarios in which PET/MRI can provide added value compared to PET/CT or MRI alone.
- Reduction in radiation dose to vulnerable populations (e.g., children, pregnant women, young adults) of 54% to 81%.
- PET/CT still confers certain diagnostic advantages over PET/MRI, especially in the context of osseous or pulmonary lesions.
- The long-term economic viability of clinical PET/MRI will depend on scanning efficiency, perceived clinical utility, and reimbursement.
1. Which of the following diagnostic imaging modality provides the best radiation safety profile?
   A. Magnetic resonance imaging (MRI)
   B. Positron emission tomography (PET)
   C. Computer tomography (CT)
   D. Single photon emission tomography (SPECT)

Your questions need to reflect each learning objectives approved for your program. Please avoid True/False questions. Also avoid questions with “all of the above,” “none of the above,” “more than one correct answer” for an answer choice.
2. Which of the following patients will have the most benefit of PET/MRI exam from radiation exposure reduction as compared with PET/CT exam?

A. A 67 year old male with acute myeloid leukemia.
B. A 39 year old female with metastatic breast cancer.
C. A 52 year old male with adenocarcinoma of the left upper lobe of lung.
D. A 18 year old female with Hodgkin’s Lymphoma.
3. Which of the following patient is most safe to have a PET/MRI exam instead of PET/CT exam?

A. A 43 year old female with newly diagnosed breast cancer who has hearing aid implant.

B. A 65 year old male with prostate cancer and chronic renal failure on dialysis.

C. A 74 year old male with lung cancer and remote history of knee replacements.

D. A 30 year old male with mantle cell lymphoma and acute onset of renal failure (GFR < 25 ).
4. Which of the following medication will likely interfere PET/MRI evaluation of multiple myeloma?

A. Metformin  
B. Diazepam (Valium)  
C. Lasix (Furosemide)  
D. Neupogen (Filgrastin)
Safety Considerations
Drug Interactions in PET and Nuclear Medicine

Eric Smith, PharmD, MS, BCNP
Associate Professor of Radiology and Pharmacy
University of North Carolina
Disclosures

• Nothing to disclose
Learning Objectives

• Describe the emerging modality of PETMR and how it compares to the current PET/CT imaging process.

• Discuss patient and provider safety of the emerging modality of PETMR

• Explain the patient safety considerations of adjunct therapies (gadolinium, morphine, diphenhydramine, adenosine, Lexiscan and DATScan).

• Identify other drug interactions with emerging modality of PET/MRI
Learning Objectives

• Identify common safety requirements for PET-MR
  • Review magnet hazards
  • Understand equipment factors that may jeopardize safety

• Recognize the patient considerations of adjunct therapies.
  • Understand safety of contrast agents
  • Review commonly used agents (Lexiscan, morphine, etc.)
  • Assess interactions which may interfere with procedures
1. Which of the following is most critical when considering patient safety during a PET-MR scan?

A. MRI scans consist of large doses of ionizing radiation; therefore the dose of the radiopharmaceutical should be reduced.
B. Gadolinium contrast agents have little interaction with PET radiopharmaceuticals’ therefore, no precautions are needed.
C. Syringe shields should be tested prior to patient injection to ensure there are minimal interactions with the magnet.
D. Because of the bore diameter of the MR, all patients must be given a mild sedative.
2. The most serious complication resulting from the administration of MR contrast agents is

A. Itching and swelling at the site of administration
B. Nausea and vomiting after administration
C. Nephrogenic systemic fibrosis of tissue
D. Hypotension during administration
3. Patient ZM presents to the nuclear medicine department for a bone scan. During his interview, the technologist learns he uses OTC antacids daily. What potential issue may arise in ZM’s scan?

A. The radiopharmaceutical will not be absorbed from the GI into systemic circulation; therefore, the uptake in the bone will be minimal.

B. The radiopharmaceutical will have an increased clearance rate, but the bone should demonstrate normal uptake.

C. The radiopharmaceutical may be taken up by liver, resulting in decreased uptake in the bone.

D. The radiopharmaceutical will be retained in the blood pool indefinitely, and the scan will show enhanced bone uptake.
4. What is the likely outcome of using a long-acting somatostatin analog shortly before administering NETSpot?

A. Long-acting somatostatin analogs will enhance the image by increasing uptake of the radiopharmaceutical.

B. Long-acting somatostatin analogs will enhance the image by decreasing the excretion rate of the radiopharmaceutical.

C. Long acting somatostatin analogs will decrease the resolution by increasing the excretion rate of the radiopharmaceutical.

D. Long acting somatostatin analogs will decrease the resolution by decreasing the uptake of the radiopharmaceutical.
• Application of magnetic field
• Alignment of proton spin
• Radio frequency
• Proton spin flipped
• Field terminated
• Protons return to natural spin at various rates
• This return releases measurable energy as a radio signal and is translated into an image
MR Overview

Image modified from KhanAcademy.org

MR Images provided by UNC BRIC
PET-MR Considerations

• Positives
  • Anatomical clarity of MR
  • Physiologic data of PET
  • Reduced radiation exposure

• “Negatives”
  • Tech training
  • MR safety
PET-MR Image
MR Safety

- Magnetic field of MR is over 30,000 times that of the earth
  - MR = 1.5, 3, 7, etc. tesla
  - Earth = ~45 microtesla

- Field Containment

- Big No No’s in MR Suite
  - Metal!!! No gurneys, Texas-sized belt buckles, watches
  - Implants – pacemaker, insulin pump, plates, joint replacement, etc.
http://www.refindia.net/rindia/cartoons/images/mri%20final_b.jpg
That’s gonna leave a mark!!
MR Contrast

- Paramagnetic elements
  - (Gd, Fe, Ni, Co)

- Gadolinium based agents
  - Element 64
  - Intended to affect the recoil of hydrogen atoms
  - T1 vs T2 weighting
MR Contrast

• Types of Contrast Agents
  • Linear versus Marcocyclic
  • Ionic versus Non-ionic

• Properties of Agents
  • Hydrophilic
  • Renal clearance
  • Retention in bone and brain
Approved MRI Contrast Agents

- Multihance (gadobenate)
- Eovist (gadoxetate)
- Magnevist (gadopentate)
- Omniscan (gadodiamide)
- Prohance (gadoteridol)
- Dotarem (gadoterate)
- Vasovist (gadofosveset)
- Gadovist (gadobutrol)
Precautions for Contrast

• Reactions
  • Mild (Nonallergic)
    • Happens most frequently
    • Injection site disturbance, N/V,
  • Mild (Likely Allergic)
    • Itching, swelling (hives), erythema
  • Moderate (Likely Allergic)
    • Respiratory issues,
  • Severe or life-threatening
    • Respiratory distress, anaphylaxis, chest tightness

• “Black Box” Warning on all agents for NSF
Contrast Drug Interactions

• Very few studies to show drug-drug interactions
• Renal insufficiency (and subsequently any drugs that alter renal function) leads to decreased excretion
Drugs in Imaging

- Radiopharmaceutical Tracer Principle
- Known/Presumed Drug Interactions with Radiopharmaceuticals
- Ancillary Drugs for Imaging
- Interactions with Ancillary Drugs
Tracer Principle

• Radiopharmaceuticals do their best work in trace amounts
  • No expected/desired pharmacologic effect
  • No toxic effect
  • Nano to microgram amounts

• High specific activity
  • Large amount of radioactivity per gram of material
  • Allows for administration of needed activity without administering mass

• These principles minimize “traditional” drug-drug interactions
# “New” Radiopharmaceuticals

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Generic Name</th>
<th>Date Approved</th>
<th>Sponsor</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyvid</td>
<td>Florbetapir</td>
<td>April 2012</td>
<td>Lilly (Avid)</td>
<td>Dementia</td>
</tr>
<tr>
<td>Choline</td>
<td>Choline</td>
<td>September 2012</td>
<td>Mayo Clinic</td>
<td>Prostate Cancer</td>
</tr>
<tr>
<td>Lymphoseek</td>
<td>Tilmanocept</td>
<td>March 2013</td>
<td>Navidea</td>
<td>Lymphoscintigraphy</td>
</tr>
<tr>
<td>Xofigo</td>
<td>Radium dichloride</td>
<td>May 2013</td>
<td>Bayer</td>
<td>CRPC</td>
</tr>
<tr>
<td>Vizamyl</td>
<td>Flutatmetamol</td>
<td>October 2013</td>
<td>GE</td>
<td>Dementia</td>
</tr>
<tr>
<td>Neuraceq</td>
<td>Florbetaben</td>
<td>March 2014</td>
<td>Piramal</td>
<td>Dementia</td>
</tr>
<tr>
<td>Axumin</td>
<td>Fluciclovine</td>
<td>May 2016</td>
<td>Blue Earth</td>
<td>Prostate Cancer</td>
</tr>
<tr>
<td>NETSpot</td>
<td>Ga-DOTATATE</td>
<td>June 2016</td>
<td>Norvartis (AAA)</td>
<td>Neuroendocrine tumors</td>
</tr>
<tr>
<td>RUBY FILL</td>
<td>Rubidium chloride</td>
<td>September 2016</td>
<td>Jubilant DraxImage</td>
<td>Myocardial perfusion</td>
</tr>
<tr>
<td>Lutathera</td>
<td>Lu-DOTATATE</td>
<td>January 2018</td>
<td>Novartis (AAA)</td>
<td>Neuroendocrine tumors</td>
</tr>
<tr>
<td>Azedra</td>
<td>Iobenguane</td>
<td>July 2018</td>
<td>Progenics</td>
<td>Neural crest tumors</td>
</tr>
</tbody>
</table>
Amyvid/Vizamyl/Neuraceq

- Donezepil, galantamine, memantine used during clinical trials with no changes in SUVs noted
- Polysorbate in Vizamyl may cause reactions in patients with sensitivities
- Ethanol content of Neuraceq may result in reactions in patients taking disulfram

Vizamyl PI, GE Healthcare, Arlington Heights, IL; Revised February 2017
Choline

- Drugs that may cause reduced uptake:
  - Colchicine
  - Anti-androgen therapy

Lymphoseek

• Local anesthetics
  • May alter distribution by reducing lymphatic flow

Images accessed from:
Xofigo

- Calcium Channel Blockers and Bisphosphonates
  - No interaction detected during clinical trial
- Clozapine
  - Increased risk of agranulocytosis and myelosuppression
- Abiraterone with prednisone
  - Increase in mortality and fractures
- Antineoplastics
  - Increased risks of myelosuppression
Axumin

• Amino acid (leucine) analog
• No exercise 24hrs prior to scan
• No food or drink 4hrs prior to scan
  • High protein diet → decrease in uptake
• Scan starts within 5 minutes of injection
• Somatostatin analogs
  • Lanreotide
  • Octreotide
  • Pasireotide

• Compete with uptake and should not be administered before NETSpot or Lutathera
  • Carcinoid syndrome may dictate injection of short acting somatostatin to treat symptoms

• Long acting analogs may be administered 4-24hrs post infusion
Azedra (I-131 mIBG)

- Norepinephrine analog
- Uses: Tx of paraganglioma and pheochromocytoma
- Precautions:
  - Thyroid blockade
  - Hydration
- Interactions:
  - Reduction in uptake:
    - Cocaine, methylphenidate, dextroamphetamine, phentermine, tramadol, MAOIs, reserpine, phenylephrine, ephedrine, TCAs, herbal supplements
    - D/C at least 5 half-lives before tx
- Renal function is important for clearance
Bone Studies

• Tc-99m HDP/MDP
  • Decreased bone uptake: corticosteroids, estrogen, bisphosphonates, ferrous sulfate
  • Shift in uptake: vincristine, bleomycin, doxorubicin, methotrexate

• Quadramet/Metastron
  • Increased likelihood of bone marrow suppression – avoid other agents that lower blood counts
• DaTScan (I-123 Ioflupane)
  • Drugs that decrease binding: amphetamines, ephedrine, fentanyl
  • Drugs that increase binding: phenylephrine, norepinephrine

Thyroid Uptake Studies

• Reduction of uptake:
  • Adrenocorticosteroids, tapazole, nitrates, perchlorate, sulfonamides (d/c 1 week before study)
  • Contrast media (wait 2-4wks), expectorants, vitamins/minerals, antihistamines, PTU, anticoagulants, benzodiazepines
  • Thyroid meds – d/c T4 2-4d; d/c T3 4-6wk
  • Amiodarone – d/c 6mo.

• Reduction of absorption:
  • Limit food intake 2 hours prior and 2 hours post administration

• Confounding Meds:
  • TKIs, interferons, lithium can cause hypo or hyperthyroidism
# Agents for Cardiac Stress Studies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Effect/MOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>Run, Forrest, Run!</td>
<td>Increase cardiac output and vasodilation (target &gt;85% max heart rate for stress studies)</td>
</tr>
<tr>
<td>Regadenoson</td>
<td>Bolus injection of 0.4mg in 5mL</td>
<td>Coronary vasodilation via the A2A receptors</td>
</tr>
<tr>
<td>Adenosine</td>
<td>140mcg/kg/min over 6 minutes</td>
<td>Nonspecific vasodilation</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>0.56mg/kg over 4 minutes</td>
<td>Inhibits reuptake and deamination of endogenous adenosine leading to vasodilation</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>Incremental dosing starting at 5-10mcg/kg/min increasing by 10mcg/kg/min every 3 minutes until 40mcg/kg/min</td>
<td>Interaction with B1 and B2 receptors to cause increase in heart rate, contractility, and blood pressure similar to exercise</td>
</tr>
</tbody>
</table>

## Drug Interactions in Myocardial Perfusion Studies

- **Exercise-Induced Stress**
  - Betablockers
- **Drug-Induced Stress**

<table>
<thead>
<tr>
<th>Stress Agent</th>
<th>Interacting Drug(s)</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regadenoson</td>
<td>Methylxanthines</td>
<td>Decrease vasodilation through competitive binding</td>
</tr>
<tr>
<td>Adenosine</td>
<td>Methylxanthines</td>
<td>Decrease vasodilation through competitive binding</td>
</tr>
<tr>
<td></td>
<td>Digoxin, SSRIs, amiodarone, fluoroquinolones,</td>
<td>Increase risk of VF or arrhythmias</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>Enoxaparin, LMWH, warfarin, factor Xa inhibitors</td>
<td>Increase risk for hemorrhage</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>Beta-blockers, PDE5 inhibitors</td>
<td>Prevent increase in heart rate</td>
</tr>
</tbody>
</table>
Other Cardiac Studies

• I-123 mIBG for assessment of sympathetic innervation in heart failure patients

• Food interactions: chocolate and blue cheese

• Drug interactions
  • Uptake Inhibition: opioids, tramadol, cocaine, TCAs, antipsychotics (e.g., trazadone, haloperidol, promethazine), lebatalol
  • Depletion of granule storage: reserpine, sympathomimetics (e.g., pseudoephedrine, phenylpropanolamine, ephedrine)
  • Increased uptake and retention: calcium channel blockers

Adreview PI; GE Healthcare, Arlington Heights, IL Revised March 2013
Other Cardiac Studies

• $^{99m}$Tc labeled RBCs for LVEF assessment
• Decreased labelling efficiency
  • Dextran
  • Penicillin
  • Heparin
  • Contrast media
  • HCTZ
• Interference with output
  • Beta-blockers
  • Nitrates
  • Calcium channel blockers
Liver Studies

• Biliary
  • Narcotics
  • Diet
  • Sincalide
  • Phenobarbital

• Liver/Spleen
  • Aluminum and magnesium compounds – lung activity due to flocculation
Gastric Studies

• Gastric Emptying
  • Drugs that slow GI motility (anticholinergics, sucralfate)
  • Drugs that speed GI motility (metoclopramide)

• Meckel’s
  • H₂ blockers
  • PPIs
  • Glucagon
  • Dextran
• Reduction of GFR (DTPA)
  • Aluminum containing compounds, nephrotoxic drugs, ACE inhibitors
• Reduction in uptake (DMSA)
  • Aluminum chloride, sodium bicarbonate (may lead to liver activity)
  • ACE inhibitors
  • Also remember DMSA is dependent on pH for proper complexation!
• Adjuvant pharmaceuticals
  • Furosemide (20mg IV)
  • Captopril
• Distribution changes
  • Patient cold during uptake leads to brown fat uptake
  • Glucose levels too high leads to diminished tracer uptake
  • Insulin pushes FDG to muscles
  • Metformin shows intense gut activity
  • Colony stimulating factors result in uptake in the bone marrow
• PET-MR offers lower radiation exposure with few risks aside from magnet safety

• MR contrast is relatively safe
  • Must consider underlying diseases
  • Few drug-drug interactions

• Prescribed and elicit drugs can cause altered biodistribution of diagnostic radiopharmaceuticals and may also interfere with adjuvant pharmaceuticals used in imaging procedures

• Diet may alter biodistribution or interfere with tracer localization
1. Which of the following is most critical when considering patient safety during a PET-MR scan?

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B. Nausea and vomiting after administration
C. Nephrogenic systemic fibrosis of tissue
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