PET/MR: Current State and *Future Directions*

Victor J. Seghers, MD, PhD
Chief, Nuclear Radiology
Edward B. Singleton Dept. of Pediatric Radiology
Texas Children’s Hospital
Houston, TX
Limitations of FDG-PET

Not reliable for lesion detection below 8-10 mm

Physiologic uptake: Thymus, GI tract, Normal Lymphoid Tissue, Brain, Myocardium, Brown Fat, Renal Excretion, Endometrium

Bone Marrow Uptake after Chemo/G-CSF treatment

Flare response after acute Chemo and Radiation tx
### Novel PET Imaging Biomarkers

#### Table 4 PET Radiopharmaceuticals: Mechanisms of Uptake and Localization

<table>
<thead>
<tr>
<th>Biochemical Process</th>
<th>Radiotracer</th>
<th>Mechanism of Uptake or Localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood flow/perfusion</td>
<td>$[^{15}O]$Water</td>
<td>Freely diffusible across membranes</td>
</tr>
<tr>
<td>Glucose metabolism</td>
<td>$[^{18}F]$FDG</td>
<td>Facilitated diffusion via glucose transporters. Substrate for hexokinase in glucose metabolism</td>
</tr>
<tr>
<td>Bone metabolism</td>
<td>$[^{18}F]$Fluoride</td>
<td>Incorporation in the hydroxyapatite crystals in bone</td>
</tr>
<tr>
<td>Membrane synthesis</td>
<td>$[^{11}C]$Choline, $[^{18}F]$Fluorocholine (FCH)</td>
<td>Substrates for choline kinase in choline metabolism</td>
</tr>
<tr>
<td>Lipid synthesis</td>
<td>$[^{18}F]$Fluoroacetate</td>
<td>Acetate is activated to acetyl-CoA in both the cytosol and mitochondria by acetyl-CoA synthetase</td>
</tr>
<tr>
<td>DNA synthesis</td>
<td>$[^{11}C]$Thymidine, $[^{18}F]$Fluorothymidine (FLT)</td>
<td>Substrates for thymidine kinase (TK-1) in DNA synthesis and reflects tumor cell proliferation rate</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>$[^{18}F]$FMISO</td>
<td>Intracellular reduction and binding</td>
</tr>
<tr>
<td>Receptor Binding</td>
<td>$[^{18}F]$FES</td>
<td>Specific binding to estrogen receptors in breast cancer</td>
</tr>
<tr>
<td></td>
<td>$[^{68}Ga]$-DOTATOC</td>
<td>Specific binding to somatostatin receptor (SSTR-II)</td>
</tr>
<tr>
<td></td>
<td>$[^{68}Ga]$-DOTANOC</td>
<td>Specific binding to somatostatin receptor (SSTR-II, III, V)</td>
</tr>
<tr>
<td>AA transport and protein synthesis</td>
<td>$[^{18}F]$FDOPA</td>
<td>Precursor for the synthesis of dopamine</td>
</tr>
<tr>
<td></td>
<td>$[^{11}C]$L-methionine, $[^{18}F]$FMT, $[^{19}F]$FCCA</td>
<td>Transport into the cells involves amino acid carrier protein. Intracellular trapping involves protein synthesis or transmethylation</td>
</tr>
<tr>
<td>Binding to tumor antigens</td>
<td>$[^{124}I}$, $[^{64}Cu}$, $[^{86}Y]$-Labeled Antibodies</td>
<td>Specific binding to tumor associated antigenic binding sites (such as CEA, PSMA, CD20 and CD22)</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>$[^{12}I}$-Annexin V, $[^{64}Cu}$-Annexin V</td>
<td>Specific binding to Phosphatidylserine (PS) on cell membrane</td>
</tr>
<tr>
<td>Angiogenesis</td>
<td>RGD peptide, $[^{18}$F]-FB-Etc(RGDyK)2</td>
<td>Integrin receptors ($\alpha_v\beta_3$) on endothelial cells of neovasculature</td>
</tr>
<tr>
<td>Gene expression</td>
<td>$[^{18}F]$Oligonucleotide, $[^{18}F]$FBG</td>
<td>In vivo hybridization with mRNA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Substrate to herpes virus thymidine kinase</td>
</tr>
</tbody>
</table>
**FDA-approved PET tracers, 1972-2013**

<table>
<thead>
<tr>
<th>PET tracer</th>
<th>Year</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>[F-18] NaF</td>
<td>1972</td>
<td>Osteogenic activity</td>
</tr>
<tr>
<td>[Rb-82] Cl</td>
<td>1989</td>
<td>Myocardial Perfusion</td>
</tr>
<tr>
<td>[F-18] FDG</td>
<td>1994, 1999</td>
<td>Epilepsy, Myocardial hibernation, Oncology</td>
</tr>
<tr>
<td>[F-18] Florbetapir</td>
<td>2012</td>
<td>Amyloid Plaque</td>
</tr>
<tr>
<td>[F-18] Flutemetamol</td>
<td>2013</td>
<td>Amyloid Plaque</td>
</tr>
</tbody>
</table>
PET Tumor Imaging Paradigm

Initial study at diagnosis; confirm uptake in tumor, measure tumor SUV, locate metastases (staging), locate best site for biopsy

Follow-up studies at appropriate intervals; monitor response to therapy

End-of-therapy exam to locate residual tumor that may require additional therapy

After completion of therapy, monitor for recurrence
Only modest gains in survival for the majority of pediatric malignancies since the 1990s, emphasizing the need for novel approaches to treating pediatric cancer.

Voss, Pediatric Radiology 2011
The discovery that [F-18] FDG accumulates in metabolically active tumor cells has revolutionized oncological imaging, particularly for agents that inhibit tumor metabolism and proliferation but without immediate effects on tumor size.

The development of hybrid imaging technologies (SPECT/CT and PET/CT) allows synergistic use of functional and anatomic information to indicate response to therapy.

But it’s not enough....
Past risk-adapted treatment regimens have improved event-free and overall survival in pediatric cancers

**We need new response-based approaches** to identify pts w/ high likelihood of cure, treating them less aggressively, while identifying those not responding to therapy early enough to redirect into more aggressive therapeutic regimens

**WHO staging criteria often insufficient**, relying heavily on tumor size and location (physical exam vs multiplanar cross-sectional imaging techniques) and not accounting for residual post-treatment scar tissue
Future is Now: PET/MRI

1st in Children’s Hospital in North America!!
May 2013
PET/MRI

Concep not new; have been able to fuse indpt. PET and MR images for some time

MR can provide anatomic correlation to PET like CT, but w/ superior tissue characterization

Ability of MR to derive its own metabolic/functional info re. tissues (edema, perfusion, restricted diffusion) and pair with PET attractive

MR has no ionizing radiation
# Vendor Comparison - Hardware

<table>
<thead>
<tr>
<th></th>
<th>Philips</th>
<th>Siemens</th>
<th>GE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td>Ingenuity TF</td>
<td>Biograph mMR</td>
<td>SIGNA</td>
</tr>
<tr>
<td>Field Strength</td>
<td>3 T</td>
<td>3 T</td>
<td>3 T</td>
</tr>
<tr>
<td>Integration</td>
<td>Sequential</td>
<td>Simultaneous</td>
<td>Simultaneous</td>
</tr>
<tr>
<td>Time-of-Flight</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Photon Detection</td>
<td>Photomultiplier tube</td>
<td>Solid-state photodiode</td>
<td>Silicon photomultiplier</td>
</tr>
<tr>
<td>MRAC</td>
<td>3-segment 3D GRE</td>
<td>4-segment 3D Dixon</td>
<td>4-segment 3D Dixon</td>
</tr>
</tbody>
</table>
Requirements for Success: PET/MRI

- Decreased Radiation
- One Stop Shopping
- Fewer Studies
- Fewer sedation events
- Greater convenience
- Cost Effective
- Added Value over PET/CT
PET/MRI
The 5 Million Dollar Question

- Definition of PET/MR
- Scheduling
- Staffing
- Attenuation Correction
- Image Interpretation
- Billing
- Workflow & Protocols
PET/MR or MR/PET or PET/CT + MRI

PET

PET/CT

PET/MRI
PET/MRI Scheduling

Schedulers don’t understand PET/MR
- Knee MR performed on the PET/MR
- PET/MR physically in MRI Dept
- No billing code for PET/MRI
- Schedule PET on PET/MR or PET and MR?

Scheduling workflows need to notify both Nucs and MRI Dept of the exam

Complex/lengthy MR on PET/MR can delay subsequent PET/MR 2/2 radioactive decay
PET/MRI Staffing

Nucs tech runs PET/CT but not PET/MR

Nucs tech performs QC on PET/MR, orders PET tracer, places IV, checks blood glucose, injects PET tracer, performs wipes/surveys of radiation areas, manipulates PET tracer dose (weight-based Protocols and radioactive decay)

Only MRI or Nucs gets credit for PET/MRI exam; Only 1 bill allowed; cannot separate charges
MR-Attenuation Correction

Difficult; requires transformation of heterogeneous signal intensity MR images into PET attenuation maps

Currently only 2 methods:
Philips 3 segment: **air, soft tissue, and lungs**
Siemens and GE 4 segment: **air, soft tissue, lungs, and fat**

Bone segmentation not part of current MRAC; may lead to quantitative errors relative to CTAC
PET/CT: Comparison of Quantitative Tracer Uptake Between Germanium and CT Transmission Attenuation-Corrected Images

Yuji Nakamoto, MD, PhD; Medhat Osman, MD, PhD; Christian Cohade, MD; Laura T. Marshall, BS; Jonathan M. Links, PhD; Steve Kohlmyer, MS; and Richard L. Wahl, MD

1Division of Nuclear Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland; 2Department of Environmental Health Sciences, Johns Hopkins School of Public Health, Baltimore, Maryland; and 3General Electric Medical Systems, Milwaukee, Wisconsin

Conclusion: Although quantitative radioactivity values are generally comparable between CT- and germanium-corrected emission PET images, CT-based attenuation correction produced radioactivity concentration values significantly higher than the germanium-based corrected values. These effects, especially in radiodense tissues, should be noted when using and comparing quantitative PET analyses from PET and PET/CT systems.

Key Words: ¹⁸F-FDG PET; CT; attenuation correction; PET/CT

PET/MRI Image Interpretation

May depend of Definition of PET/MR (MR/PET)

Nuclear Medicine and/or Radiology
Consensus or Independent Reads??
Separate PET and MRI reports??

Level of Collaboration dependent on departmental ownership, trust/collegiality, staffing levels, clinical interest/confidence in PET + MR
PET/MRI Billing

PET/MR FDA-approved 2010

No dedicated PET/MR CPT* code

Only PET-only and PET/CT CPT codes

*CPT = Current Procedural Terminology; code to describe a medical procedure/service to a healthcare provider
PET/MRI Billing

For PET/MR w/ PET and clinical MR, charge 2 exams PET-only and clinical MR (anatomic region)

For PET/MR w/ PET and only noncontrast 1-2 MR sequences, charge under PET-only CPT code
TCH Philips Body PET Protocols

PET/CT

FDG Uptake
(60-90 min)

PET (45 min)

1 hr 45 min

MR/PET

FDG Uptake

PET

MRI (45 min)

PET/MR

FDG Uptake

PET

Diffusion MRI

MR/PET

FDG Uptake

PET

Siemens
GE

MR/PET
# PET/CT vs PET/MR Radiation Exposure: TCH Experience

<table>
<thead>
<tr>
<th>Imaging Exam</th>
<th>Total Scan Dose (mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET/CT (Low Dose CT)</td>
<td>11-21</td>
</tr>
<tr>
<td>PET/CT (High Dose, Diagnostic CT)</td>
<td>17.2</td>
</tr>
<tr>
<td>PET/MR</td>
<td>6-11 (45% less than PET/CT)</td>
</tr>
<tr>
<td>PET/CT + Additional Diagnostic CT</td>
<td>16-31</td>
</tr>
<tr>
<td>PET/MR + Additional Diagnostic CT</td>
<td>11-21</td>
</tr>
</tbody>
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Clinician Buy-in
Future Directions

MRI and PET should be used at their full potentials, with improved ability to utilize all MR sequences and coils – Integrated PET/MR

Continued refinement in MR Attenuation Correction Algorithms
Future Directions: Threats

?? Vendor Support for PET/MR; small PET/MR market; no “killer” application for PET/MR identified

PET/CT as competitor: non-dramatic, convenient, cheaper, easier to install/site, culturally non-threatening and reimbursable exam that offers proven high sensitivity & specificity for many applications

Future Hardware/Software advances such as Iterative Reconstruction, CT Dose Modulation Algorithms, new PET detectors will mitigate Radiation Reduction Benefit of PET/MR