Objectives

- To understand the principles and applications of PET (Positron Emission Tomography) scans in the diagnosis and evaluation of dementia, cancer and epilepsy, including amyloid PET and PET bone scan.
- To understand the principles and applications of advanced techniques for the evaluation of brain neoplasia, including Magnetic Resonance Spectroscopy (MRS), Magnetic Resonance Perfusion, and PET.
- Potential applications of combined PET/MRI scans.
Dementia

Disease-related loss of cognitive abilities, such as memory, severe enough to interfere with activities of daily living and functional independence.

Causes:
1. Neurodegeneration: Alzheimer, Dementia with Lewy bodies, Frontotemporal dementia
2. Vascular (multi-infarct) dementia
3. ‘Reversible’: NPH, toxic/metabolic, depression
Imaging evaluation of dementia

• MRI
  – Evaluate for structural abnormality
  – Exclude ‘non-neurodegenerative’ etiologies
  – Evaluate regional atrophy patterns – can be subtle

• PET
  – FDG: Evaluate for functional abnormality -- brain metabolic activity is linked to brain activity
  – Amyloid: Evaluate for the presence of abnormal proteins

FDG PET

• Most commonly used brain PET tracer
• Brain exclusively uses glucose for energy
Normal FDG PET distribution

Arrows indicate normal atrophy

FDG PET in AD

• Hypometabolism correlates with neurodegeneration
  – Temporoparietal hypometabolism
  – Changes are multifactorial: atrophy, metabolic rate, synaptic activity

• Changes predictive of progression of AD and cognitive decline
  – Less severe but similar pattern in MCI

• Utility in discriminating between different neurodegenerative conditions
Patterns of hypometabolism in dementia, presented as Z score; higher value more abnormal
http://interactive.snm.org/docs/JNM_096578_pc_f1.jpg
AMYLOID PET IMAGING

Alzheimer dementia: course

Beta-amyloid deposition

Tau NFT

Neurodegeneration: atrophy, hypometabolism

Age → MCI Probable AD

Adapted from Barber 2010
Amyloid imaging: $^{18}$F compounds

- Florbetapir F18 (Amyvid, Avid/Eli Lilly)
- Flutemetamol F18 (Vizamyl, GE)
- Florbetaben F18 (Neuraceq, Piramal)
- All FDA approved, none reimbursed by CMS

What does ‘positive’ mean?

- Amyloid PET studies detect the presence of cerebral amyloid plaques
  - Detects moderate to severe amyloid plaque with high sensitivity and specificity
  - A positive Amyloid PET does NOT mean a patient has Alzheimer disease
- Amyloid PET provides an early biomarker for the pathology seen in AD
  - Potential to detect pathology before neurodegeneration occurs
(Potential) Clinical Utility of Amyloid PET

• Differential diagnosis
  – High sensitivity, high negative predictive value
  – Potential benefit highest in cases where there is diagnostic uncertainty after initial evaluation
  – Several prospective group studies have shown amyloid PET can distinguish between AD and FTD but not between AD and DLB

• Prognosis
  – MCI patients with amyloid convert at a high rate to AD (~70%)
  – Amyloid negative MCI patients have low rate of progression to AD (~10%)
  – Correlation with memory decline in MCI and healthy elderly has been shown in several studies
    • NO ASSOCIATION between amyloid levels and decline in demented patients
Limitations of amyloid PET

• Detects only one of the two pathologic proteins
  – Patients with little amyloid can be given pathologic diagnosis of AD based on tau NFTs
• Interpretation can be challenging at early stages where diagnosis is more difficult
  – Standardized training for each amyloid tracer

Limitations: Cerebral Amyloid in healthy elderly

• Asymptomatic healthy elderly (HC) can have cortical amyloid
  – Prevalence increases with age
• Specificity of a positive amyloid scan for AD decreases with increasing age

Adapted from Rowe  Neurobiol. Aging 2010
Proposed Appropriate Use Criteria
Society for Nuclear Medicine and Molecular Imaging
and Alzheimer’s Association

**Propriate**

- Persistent or unexplained MCI
- Possible AD (atypical course or mixed etiology)
- Young onset dementia (< 60 years of age)

* In cases where clinical management would change

**Inappropriate**

- Probable AD, typical age of onset
- To determine dementia severity
- Cognitive complaints not confirmed by examination
- Asymptomatic
- Family history of dementia/genetic risk only

Johnson JNM 2013

Florbetapir F18 negative scan
Florbetapir F18 positive scan

PET IN EPILEPSY
Imaging: Seizure focus localization/evaluation

• Standard: surface EEG and MRI
  – Goal: localize seizure focus for possible surgery (focal lesion, temporal lobectomy)

• Adjunct testing, usually for intractable (medically refractory) epilepsy:
  – PET, SPECT
  – Invasive EEG (implanted electrodes)
  – Wada test (via conventional angiogram)

Clinical application of FDG PET in epilepsy

• Adjunct testing when MRI and EEG results are discordant/indeterminate

• High sensitivity (85-90%) for temporal lobe epilepsy

• Lower sensitivity (~55%) for extratemporal epilepsy
  – But can detect cortical dysplasias that are occult on MRI
FDG PET in epilepsy

- Hypometabolism present in seizure focus and adjacent tissue (seizure network)
  - Better prognosis (surgical response) if unilateral and more severe temporal hypometabolism is present
  - Broad seizure network means worse prognosis
  - Can guide invasive EEG lead placement
- FDG PET uptake can be affected by neuroleptics (esp. barbiturates)
- Can affect surgical planning in 50-70%
- Cost effective when MRI/EEG are discordant/indeterminate

Case: mesial temporal sclerosis
Case: cortical dysplasia

PET FOR ONCOLOGY
FDG PET/CT in oncology

- Broadly used modality for cancer staging, restaging, and response assessment
  - Nonspecific radiotracer
- Functional (and structural) data on PET/CT improve characterization
  - Metastases may be small

FDG PET in treatment response

- Treatments may not change size of lesions, especially early
- Allows evaluation of response during therapy
  - Can change from a failing therapy early, sparing side-effects and cost, or stop a successful therapy early
Limitations of FDG PET in oncology

• Metabolic activity varies between cancers
  – Differentiated thyroid cancer, prostate typically have low glucose uptake

• Sensitivity lower for:
  – Small lesions (< 8 mm)
  – Necrotic/cystic lesions with little solid tissue

• Nonspecific
  – Inflammatory, including treatment-related changes, and other processes can be hypermetabolic

Fluoride PET

• PET Bone scan: Sodium Fluoride
• Increased sensitivity, specificity, and accuracy versus traditional nuclear bone scan
  – Improved characterization as benign or malignant (also benefits from CT study)
  – While individual lesion identification is much better, per patient staging is much less improved

• However FDG PET is about as good for bone metastases... and shows soft tissue metastases
  – NaF best where FDG is poor, i.e. prostate
NaF PET vs. Nuclear bone scan

MR spectroscopy
MR perfusion/MR permeability
Tractography
Functional MRI
PET

ADVANCED IMAGING OF BRAIN NEOPLASIA
Brain neoplasm

- Brain metastases (~50% of intracranial neoplasia)
  - Isolated metastasis (~25% of solitary brain tumors)
- Primary neoplasia
  - Meningioma ~40%
  - High grade glioma (HGG), mainly glioblastoma (GBM) ~35%
    - Poor survival: 1 year median, 6 months without treatment and 2 years with best therapy
  - Others: Low grade glioma (LGG), lymphoma, neuronal, etc.

Differential diagnosis of intracranial mass lesions

**Enhancing mass**
- Solitary metastasis
- High grade glioma (HGG)
- CNS lymphoma
- [Some Low grade glioma, esp. oligodendroglioma]
- Meningioma
- Abscess
- Demyelinating lesions

**Non-enhancing mass**
- Low grade glioma (LGG)
- [Some High grade glioma]
- Encephalitis
- Developmental anomalies (focal cortical dysplasia)
Conventional brain MRI

• University of Pennsylvania conventional MRI exam:
  – T1 axial and sagittal
  – T2 axial
  – FLAIR axial
  – Diffusion-weighted imaging (DWI)
  – T1 post contrast axial and coronal

• Conventional images alone yields important information, but performance is moderate
  – Law et al AJNR 2003: Amongst exclusively glioma cases, in classifying high grade gliomas: sensitivity 73%, specificity 65%, PPV 86%, and NPV 44%

Conventional MRI: enhancement

• Amongst glioma, enhancement, necrosis, and mass effect are correlated with with higher grade
• Development of enhancement in a LGG indicates conversion to HGG
• Homogeneous favors lymphoma, meningioma
• Necrosis favors HGG, metastasis, abscess
Advanced MR imaging study

- Conventional sequences, with/without contrast
- MR spectroscopy (MRS)
- MR perfusion: dynamic susceptibility (DSC)
- MR permeability: dynamic contrast-enhanced (DCE)
- Tractography and functional MRI (fMRI) as needed
- Goal: improve diagnosis with multiparametric evaluation

MR spectroscopy (MRS)

- Goal: detect weak signals from small molecules
Commonly evaluated CNS metabolites

- N-acetylaspartate (NAA, 2.0 ppm): neuronal marker
- Creatine (Cre, 3.0 ppm): ‘reference peak’, energy metabolism
- Choline (Cho, 3.2 ppm): cell membrane synthesis
- Lipids (0.9-1.3 ppm): normally absent; associated with necrosis/hypoxia
- Lactate (1.3 ppm, doublet): normally absent; anaerobic metabolism

MRS analysis

- Area under peak corresponds to concentration
- Evaluation: Usually semi-quantitative ratios are used (Cho:NAA, NAA:Cre, Cho:Cre)
Applications of MRS

- Low specificity
- Can evaluate for tissue infiltration
- Can be helpful for grading neoplasia
  - Lower NAA:Cho indicates higher grade
- Can be useful in non-neoplastic disorders
  - Abscess
  - Metabolic diseases with characteristic metabolites
- Mainly used for problem solving

Summary: MRS

<table>
<thead>
<tr>
<th></th>
<th>Cho</th>
<th>NAA</th>
<th>Lac</th>
<th>Lip</th>
<th>Myo</th>
<th>Glu</th>
<th>Suc</th>
<th>Acet</th>
<th>Ala</th>
<th>Aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade tumor</td>
<td>↑</td>
<td></td>
<td>↓</td>
<td></td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High grade tumor</td>
<td>↑</td>
<td></td>
<td></td>
<td>↑</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastasis</td>
<td>↑</td>
<td>absent</td>
<td>↑</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>↑</td>
<td></td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningioma</td>
<td>↑</td>
<td>absent</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gliomatosis cerebri</td>
<td>↑</td>
<td></td>
<td></td>
<td>↑</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>↑</td>
<td>absent</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radionecrosis</td>
<td>↓</td>
<td></td>
<td></td>
<td>↑</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abscess</td>
<td></td>
<td>↓</td>
<td></td>
<td>↑</td>
<td></td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demyelination</td>
<td>↑</td>
<td></td>
<td></td>
<td>↑</td>
<td></td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. H-MRS changes in tumors and differential diagnosis. ↑ increased peak; ↓ reduced peak; N normal peak; Cho - choline; NAA - N-acetylaspartate; Lac - lactate; Lip - lipids; Myo - myoinositol; Glu - glutamine; Suc - succinate; Acet - acetate; Ala - alanine; Aa - amino acids.
1 NAA is absent in the core of the tumor, but may be present where it infiltrates brain parenchyma or with voxel bleeding.
2 The presence of lactate depends on the grade of the tumor.
3 Lac and Glu are increased only in the early stage of the disease.
MR perfusion/permeability

- Evaluate neoangiogenesis, blood brain barrier
  - Neoplasms will at some point require neovascularization to support further growth (‘angiogenic switch’)
  - Neoangiogenesis associated with abnormal, leaky endothelium
- Blood flow and vascular integrity can be evaluated by several MRI techniques
  - DSC (Dynamic susceptibility contrast) perfusion
  - DCE (Dynamic contrast enhanced) permeability
  - ASL (Arterial spin label): no contrast injection

DSC MR perfusion

- Cerebral blood volume (CBV) is most useful for neoplasms
- For differential diagnosis:
  - Elevated in HGG, metastases, but also some LGG
- Biopsy planning: target high rCBV
- Prognosis: Higher CBV neoplasms demonstrate progression
T1 Dynamic contrast enhanced (DCE) MR permeability

- Newer technology: implementation still evolving, software/methodology not standard
- Various measures of vascularity/vascular integrity
  - $K_{\text{trans}}$ : a measure of permeability and blood flow
  - $V_p$ : fractional plasma volume, usually correlates with DSC CBV
Tractography

• Diffusion tensor imaging (DTI) – fiber tracking
• Major pathways (CST, SLF, etc)
  – Helpful for surgical/radiation therapy planning (proximity of critical large axon tracts to tumor)
• Pitfalls:
  – Failure of tracking due to disruption – not seeing does not mean not there
  – Only follows dominant pathways (crossing, sharp turning pathways lost)

Tractography: example

Blue: Corticospinal tract (CST, motor)
Green: Superior longitudinal fasciculus (SLF, language)
Functional MRI

- Functional eloquence shows inter-individual variability
  - Precise knowledge can help surgical planning to minimize deficits
- BOLD (Blood oxygen level dependent): changes in activity result in slight changes in blood oxygenation, detectable by MRI
- Pitfalls:
  - Lack of activation does not mean lack of function: Pathology can interfere with MRI success
  - Not all activating foci are eloquent: ‘Pseudoreorganization’ seen when physiologic changes in brain interfere with activity-BOLD relationship

fMRI: example

Yellow: facial motor task (motor cortex)
Purple/red: language tasks (Broca’s area)
Post treatment course

- Response
- True progression: any time
- Pseudoprogression (Temodar + XRT)
  Pseudoresponse (Avastin)
- Radiation necrosis

<table>
<thead>
<tr>
<th>Enhancement</th>
<th>Response</th>
<th>True Progression</th>
<th>Pseudoprogression</th>
<th>Pseudoresponse</th>
<th>Radiation Necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>Mass effect</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y/N</td>
<td></td>
</tr>
<tr>
<td>Perfusion</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y/N</td>
<td></td>
</tr>
<tr>
<td>MRS</td>
<td>Normal</td>
<td>Neoplastic</td>
<td>Normal</td>
<td>Neoplastic</td>
<td>Low metab.</td>
</tr>
<tr>
<td>Timing after therapy</td>
<td>?</td>
<td>Any</td>
<td>3-6 months</td>
<td>Any, Avastin</td>
<td>12-18 months</td>
</tr>
</tbody>
</table>

Radiation necrosis after gamma knife

- 3 months after GK
- 27 months after GK
Pseudoprogression

Immediate post-op:
No residual

4 months post-op, following chemo/XRT
11 months post-op

Pseudoresponse on Avastin

[Images of brain scans]
FDG-PET in brain neoplasia

• Only approved tracer useful for evaluating neoplasm
• Limitations:
  – High uptake in normal gray matter; GBM lower
  – Nonspecific
• Uses:
  – Higher uptake seen in higher grade neoplasm
  – Higher uptake is associated with worse prognosis
  – Can be used to evaluate recurrence (high uptake) versus radiation necrosis (low uptake)
  – Metastases and lymphoma tend to have much higher uptake than gliomas (both LGG and HGG)

FDG for recurrence

Aug 2011

Aug 2013
PET/MRI

- Technically challenging to build
- Active development (and deployment) by major equipment vendors
- Will allow simultaneous MRI and PET acquisition
  - Need to show benefit above colocalization, which can be performed from separate studies
  - Benefits much clearer for research applications than clinical radiology
Potential applications of PET/MRI

• Neuroimaging
  – Decreased imaging time for brain tumor or demented patients
  – Improved PET resolution with real time motion correction and improved partial volume correction
  – Correlation of PET and MRI functional measures, as ‘functional state’ can vary if scans separated by time

• Cardiac imaging
  – Improved PET localization during cardiac cycle

• Pediatrics
  – Decreased radiation dose versus PET/CT

• Oncology
  – Can not simply combine traditional whole body PET with traditional regional MRI studies
Summary

- **Advances in PET imaging**
  - Dementia/neurodegeneration: FDG and amyloid PET
  - Epilepsy
  - Oncology: FDG and NaF bone PET scan

- **Advanced imaging for brain neoplasia**
  - MR spectroscopy
  - Perfusion/Permeability
  - Tractography and fMRI
  - PET

- **Potential applications of combined PET/MRI scans.**