New Advances in PET and MRI

2014 AAIM Radiology Workshop

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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.

PET IN DEMENTIA

Dementia

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

Causes:

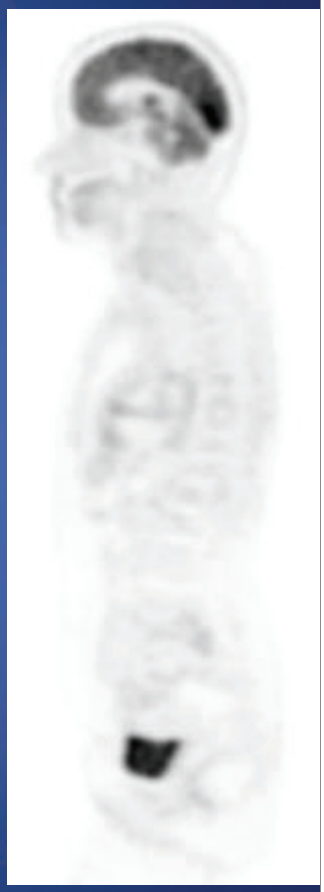
1. Neurodegeneration: Alzheimer, Dementia with Lewy bodies, Frontotemporal dementia
2. Vascular (multi-infarct) dementia
3. 'Reversible': NPH, toxic/metabolic, depression

Imaging evaluation of dementia

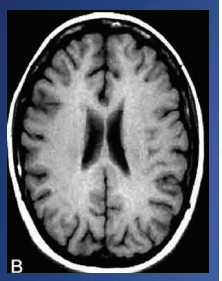
- MRI
  - Evaluate for structural abnormality
  - Exclude 'non-neurodegenerative' etiologies
  - Evaluate regional atrophy patterns – can be subtle
- PET
  - FDG: Evaluate for functional abnormality -- brain metabolic activity is linked to brain activity
  - Amyloid: Evaluate for the presence of abnormal proteins

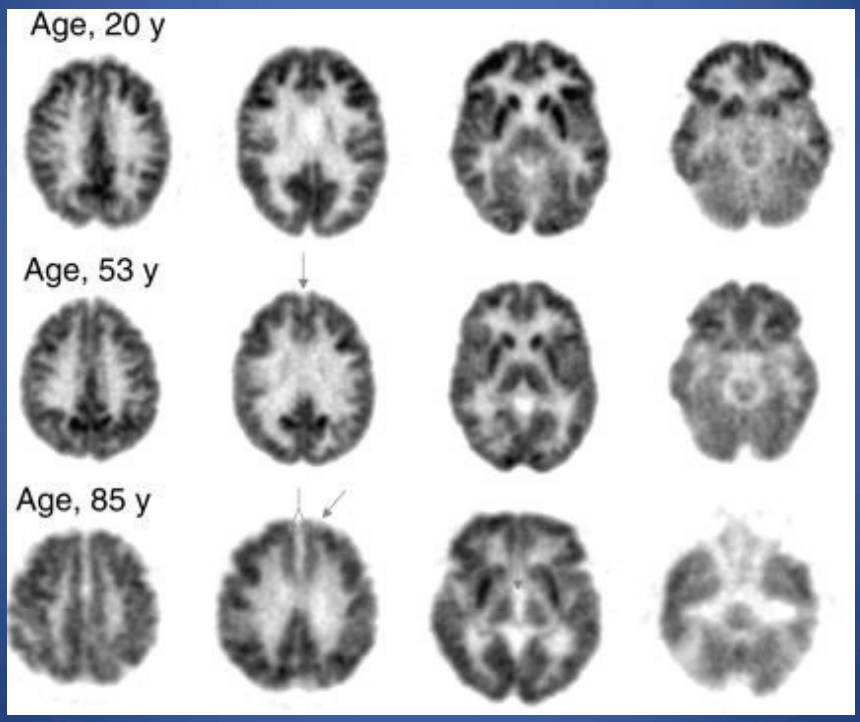
FDG PET

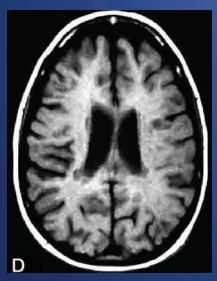
- Most commonly used brain PET tracer
- Brain exclusively uses glucose for energy



Normal FDG PET distribution

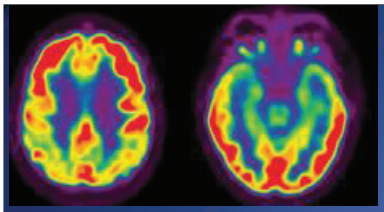






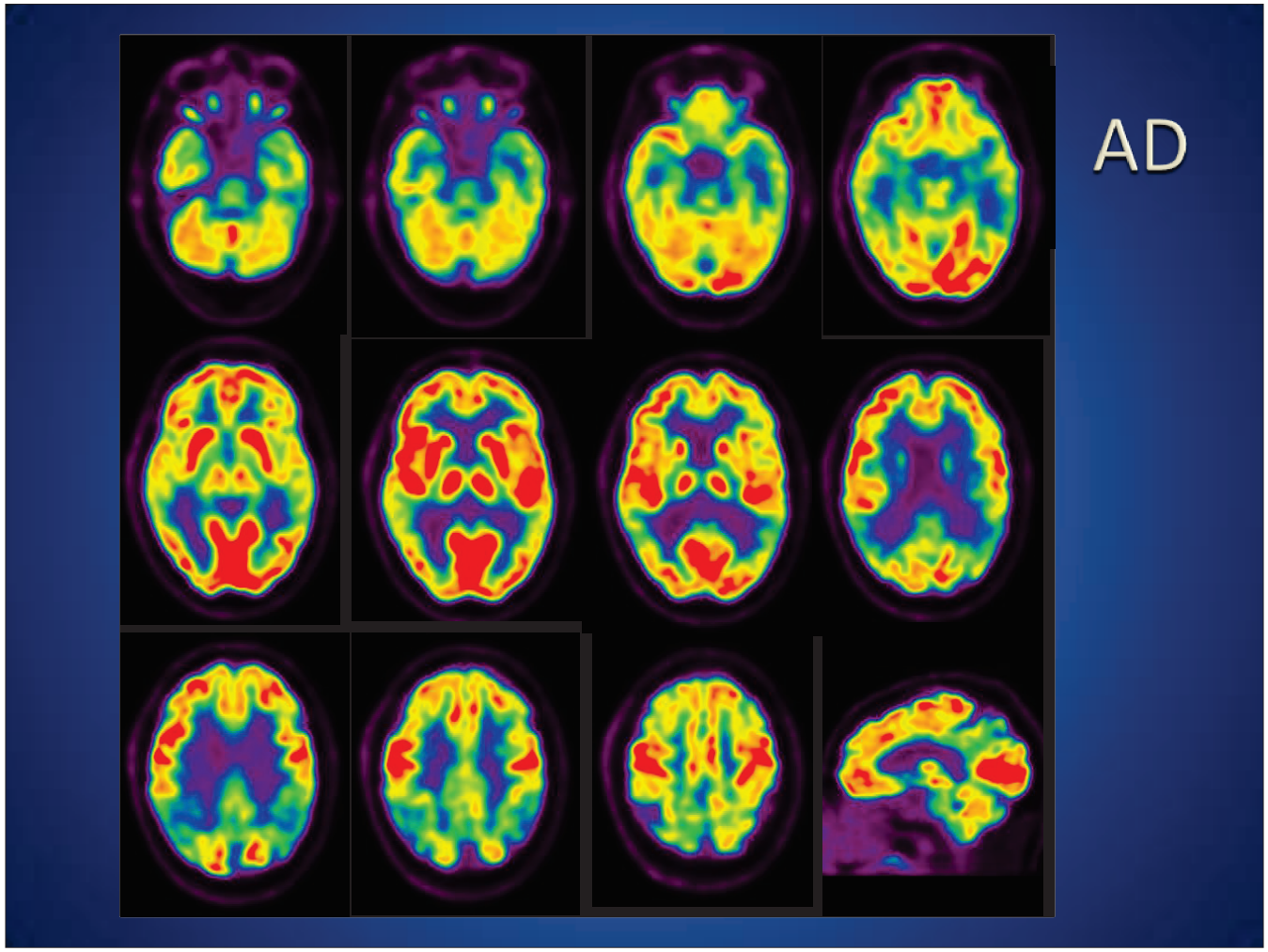
Arrows indicate normal atrophy

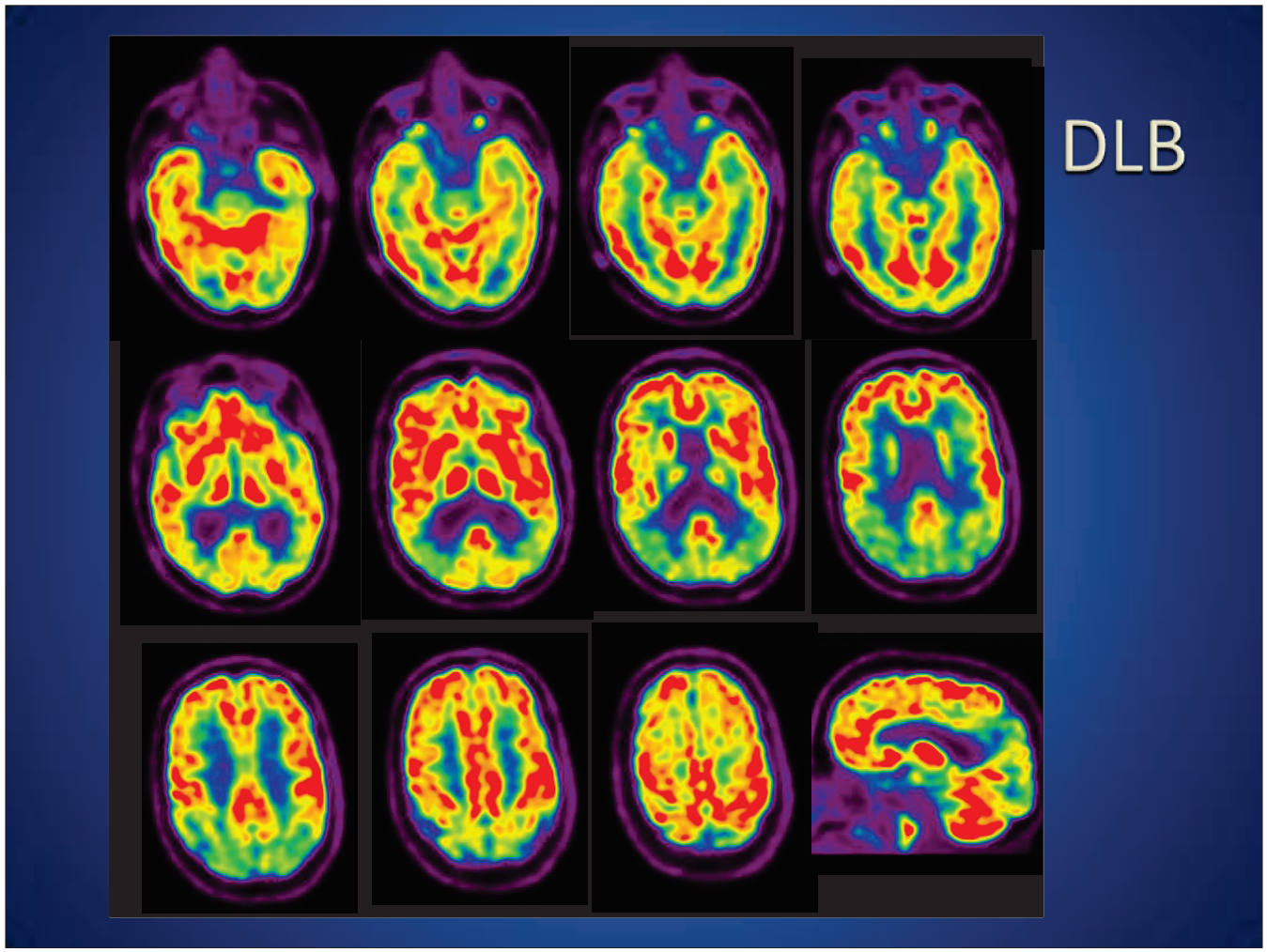
J Nucl Med **April 1, 2004** vol. 45 no. 4 **594-607**



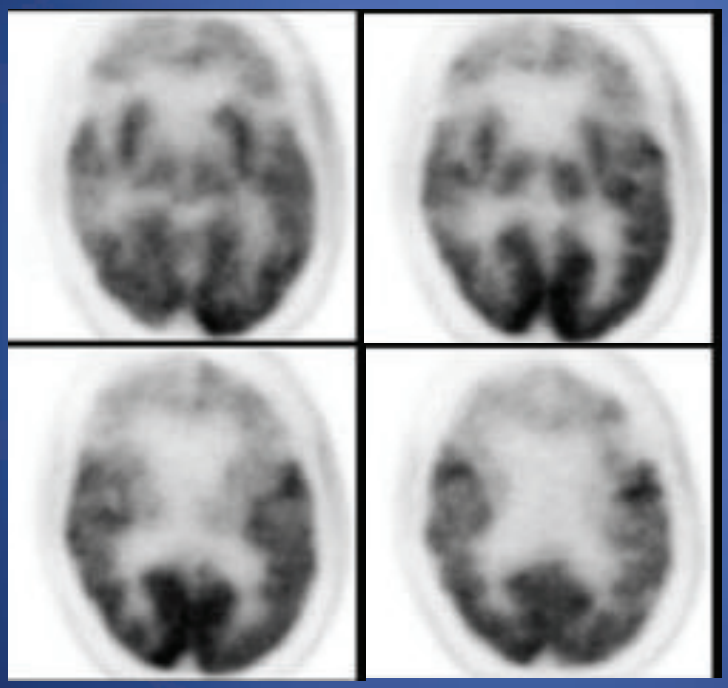
FDG PET in AD

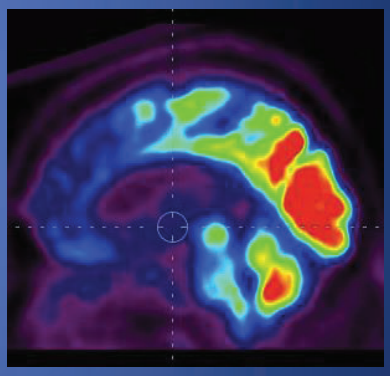
- Hypometabolism correlates with neurodegeneration
  - Temporoparietal hypometabolism
  - Changes are multifactorial: atrophy, metabolic rate, synaptic activity
- Changes predictive of progression of AD and cognitive decline
  - Less severe but **similar** pattern in MCI
- Utility in discriminating between different neurodegenerative conditions


AD

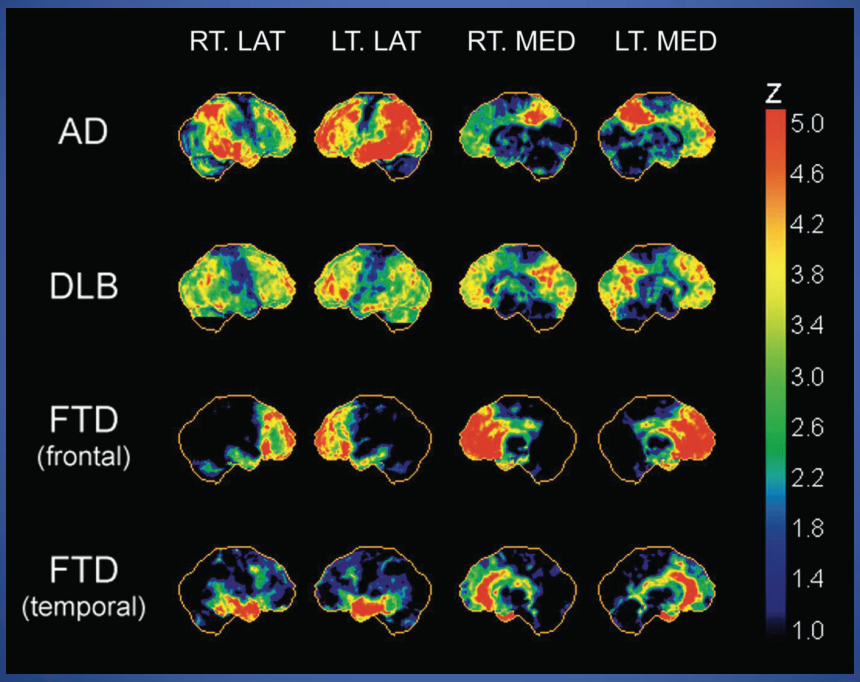

DLB

Frontotemporal dementia





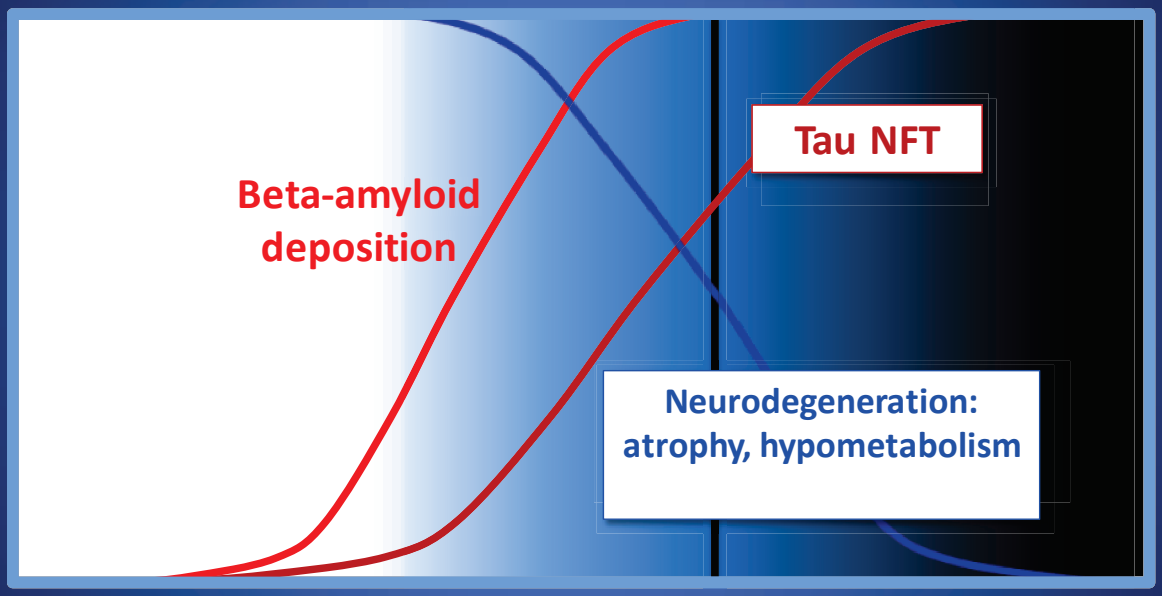
Summary: FDG in dementia



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

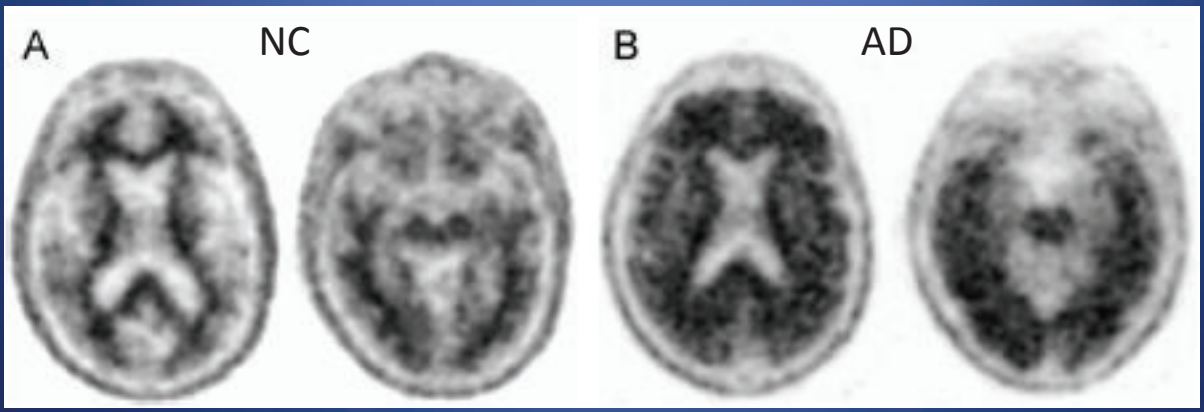


Adapted from Barber 2010

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

F18-florbetapir

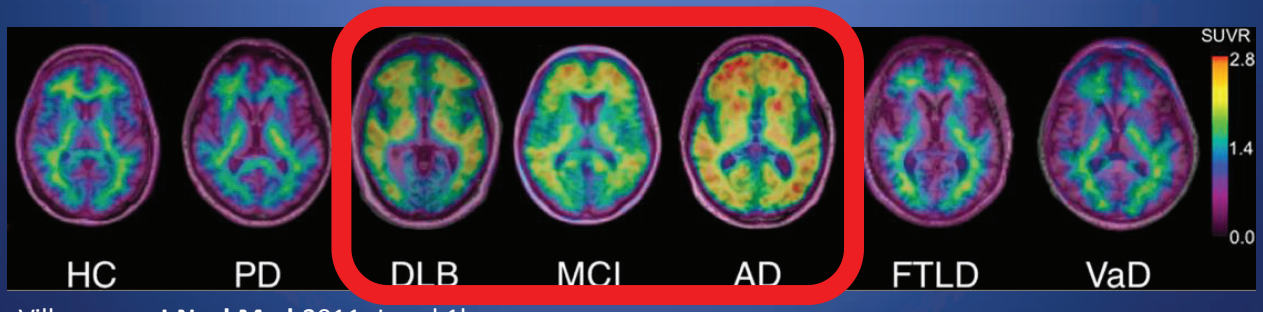


What does 'positive' mean?

- 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



Villemagne **J Nucl Med** 2011: Level 1b

(Potential) Clinical Utility of Amyloid PET

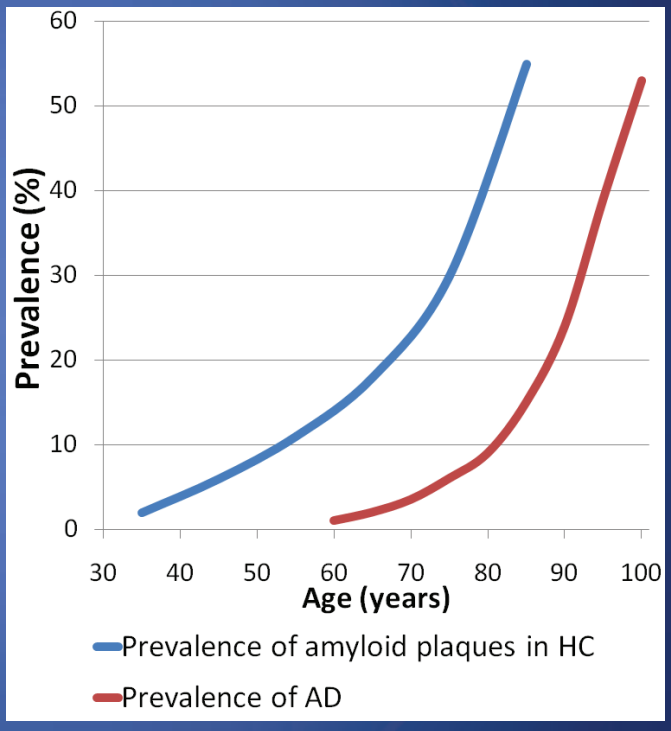
- Prognosis
  - MCI patients with amyloid convert at a high rate to AD (~70%)
  - Amyloid negative MCI patients have low rate of progression to AD (~10%)
  - Correlation with memory decline in MCI and healthy elderly has been shown in several studies
    - NO ASSOCIATION between amyloid levels and decline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

Appropriate*

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

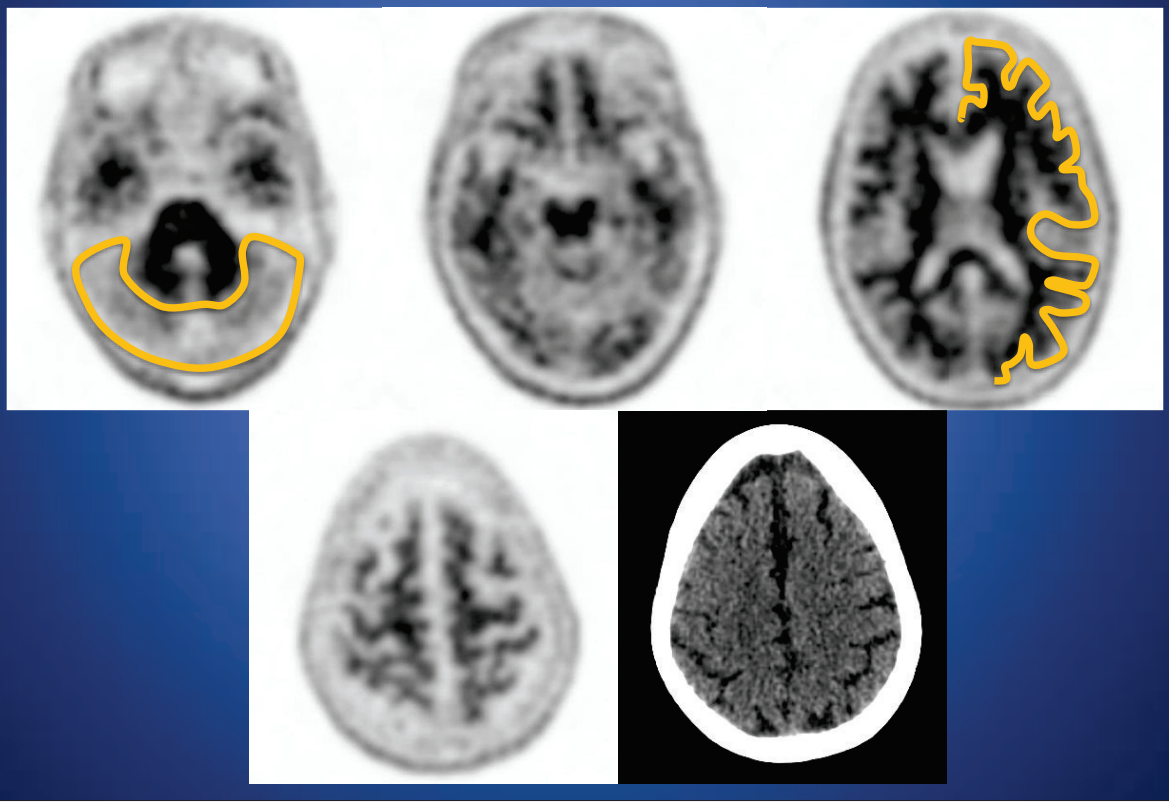
* In cases where clinical management would change

Inappropriate

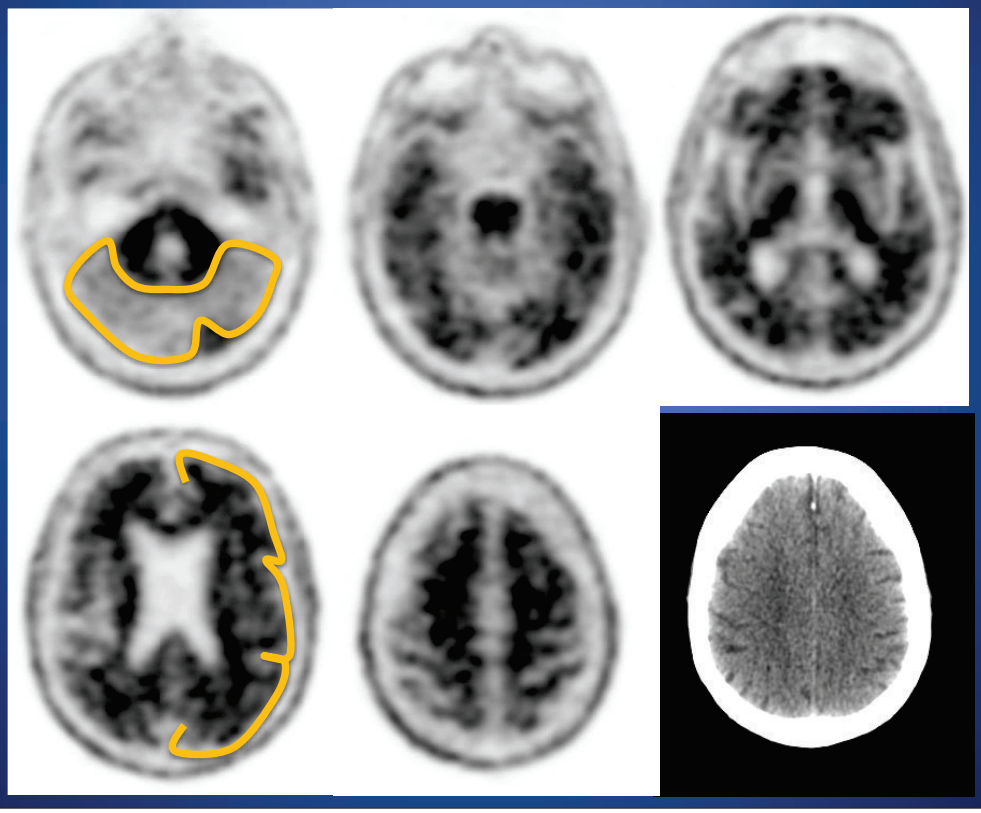
- Probable AD, typical age of onset
- To determine dementia severity
- Cognitive complaints not confirmed by examination
- Asymptomatic
- Family history of dementia/genetic risk only

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)

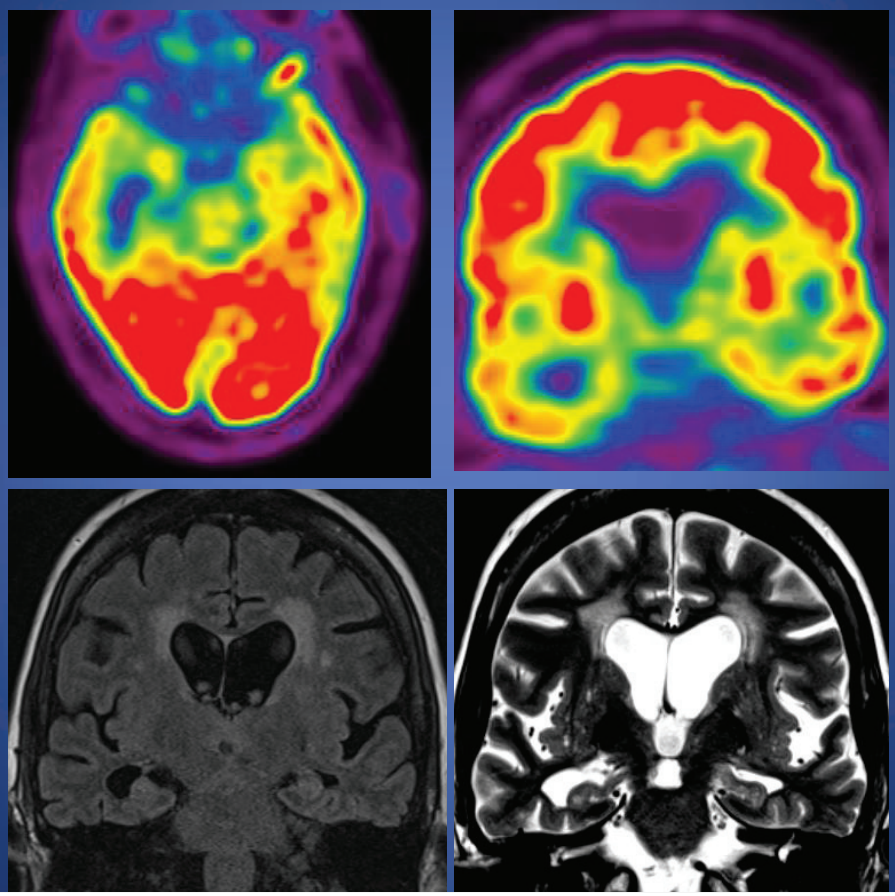
Clinical application of FDG PET in epilepsy

- 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

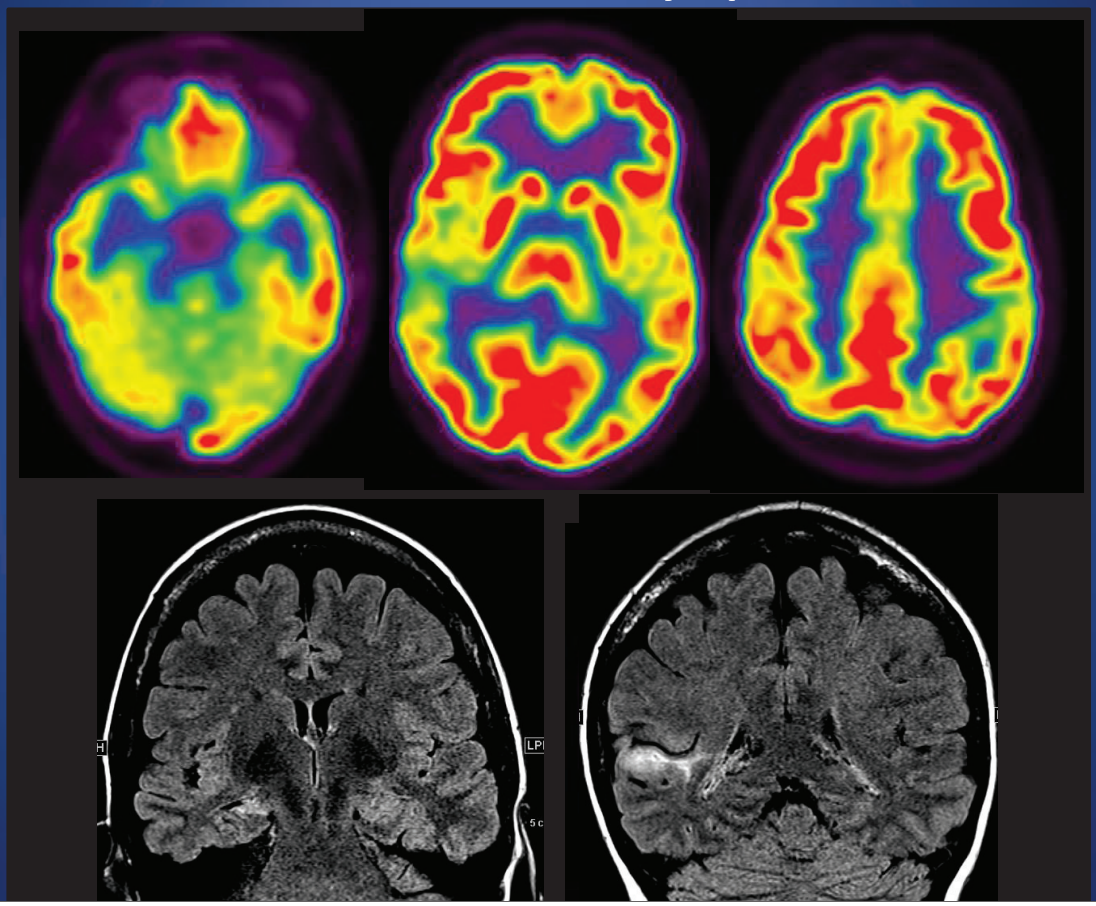
FDG PET in epilepsy

- 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



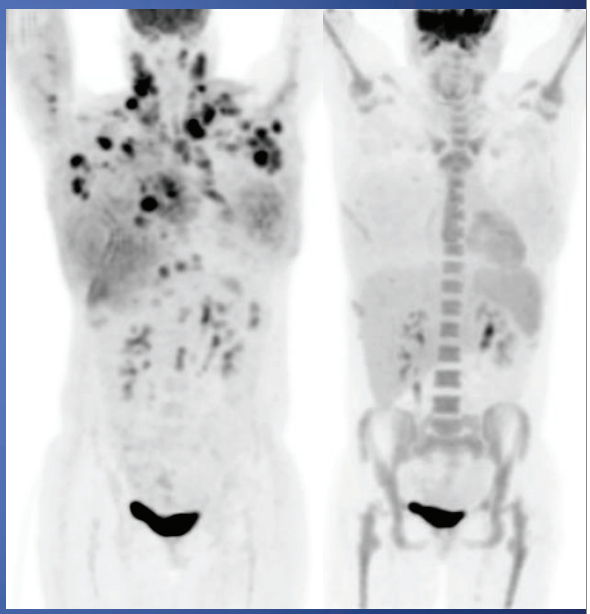
PET FOR ONCOLOGY

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



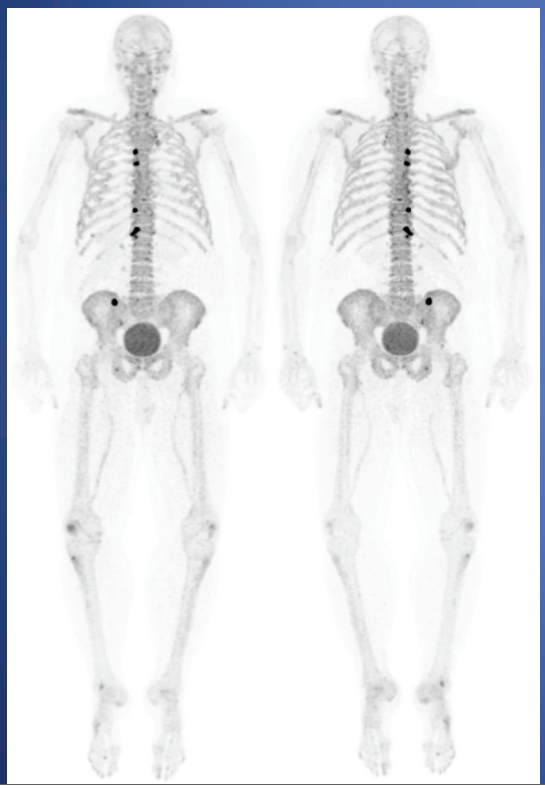
Limitations of FDG PET in oncology

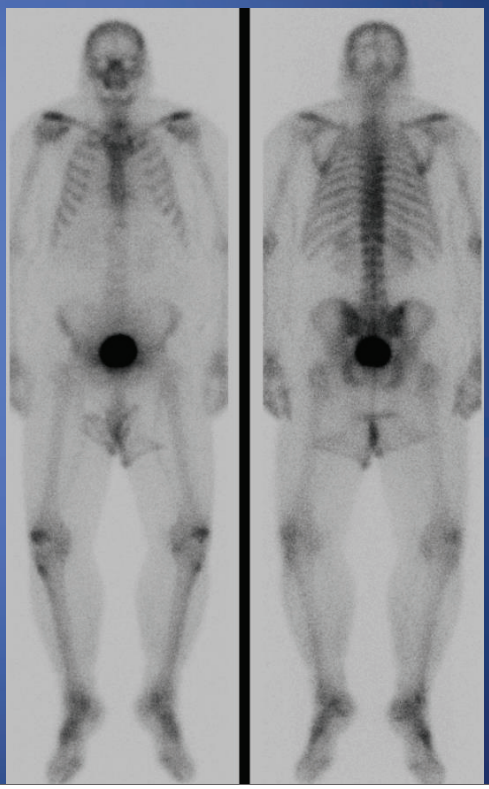
- Metabolic activity varies between cancers
  - Differentiated thyroid cancer, prostate typically have low glucose uptake
- Sensitivity lower for:
  - Small lesions (< 8 mm)
  - Necrotic/cystic lesions with little solid tissue
- Nonspecific
  - Inflammatory, including treatment-related changes, and other 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

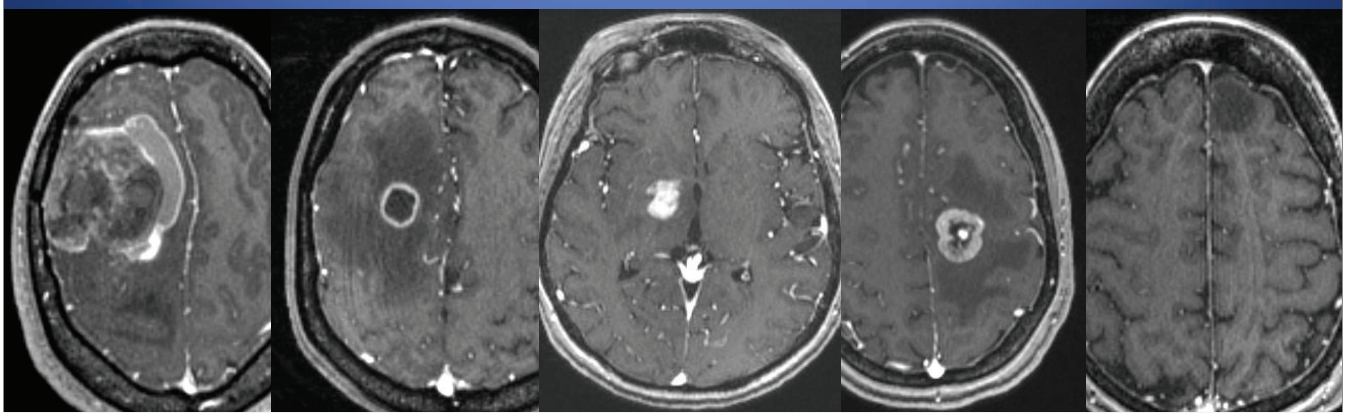
- Low grade glioma (LGG)
- [Some High grade glioma]
- Encephalitis
- Developmental anomalies (focal cortical dysplasia)

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

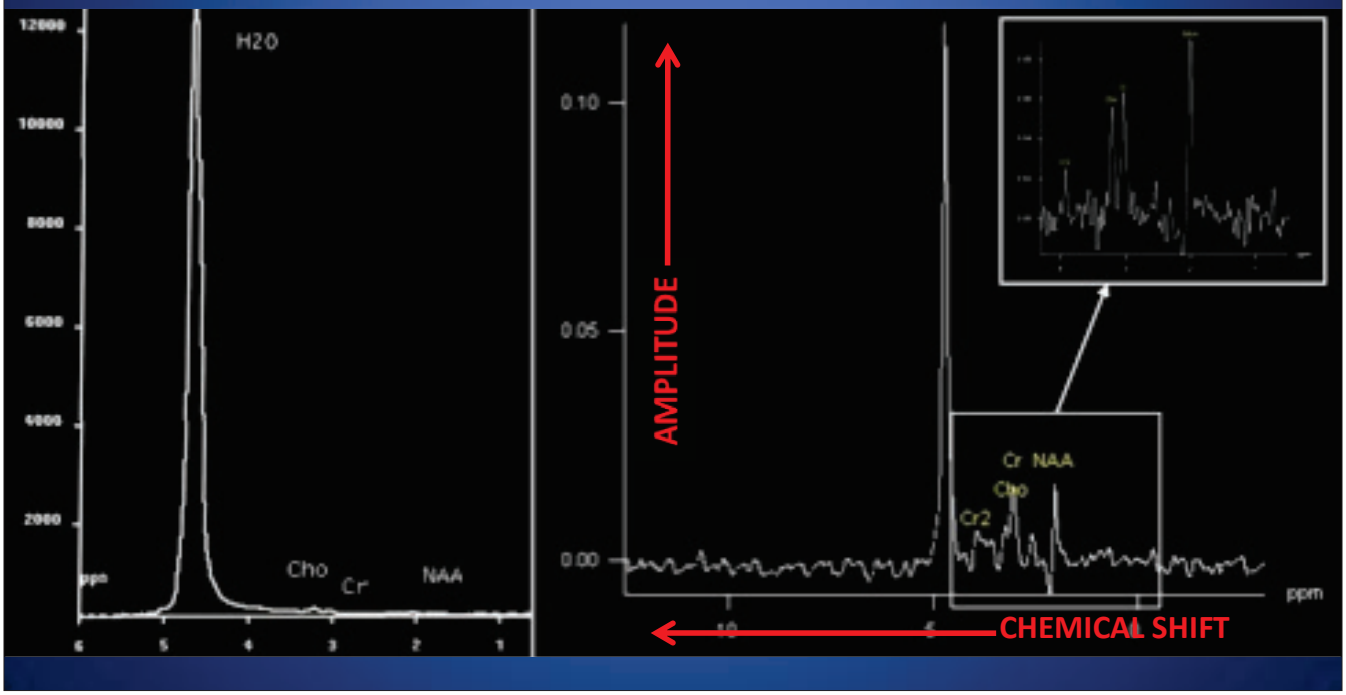


Advanced MR imaging study

- 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

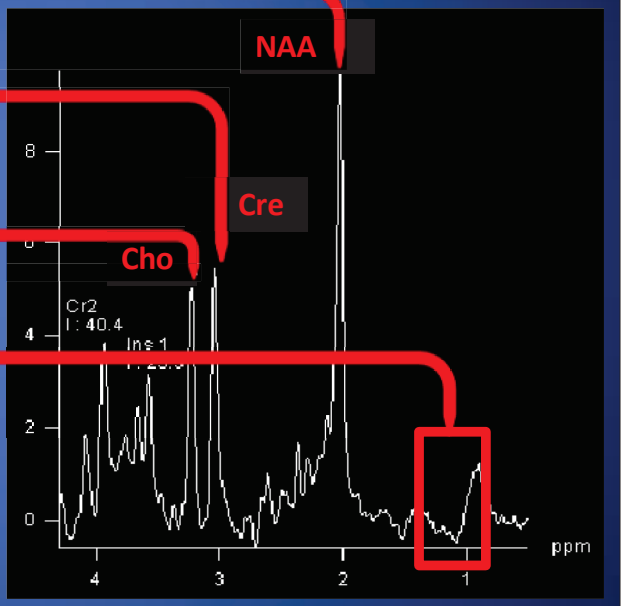
MR spectroscopy (MRS)

- Goal: detect weak signals from small molecules



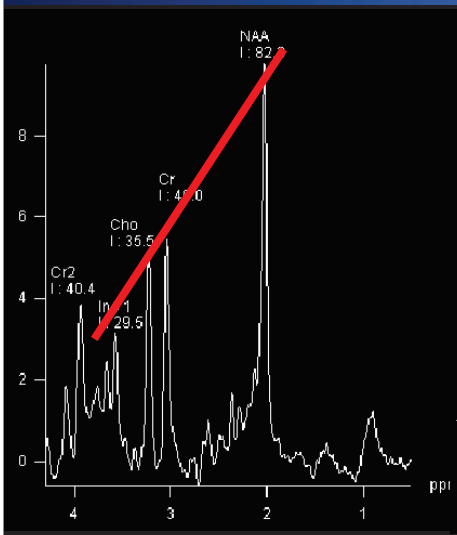
Commonly evaluated CNS metabolites

- 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



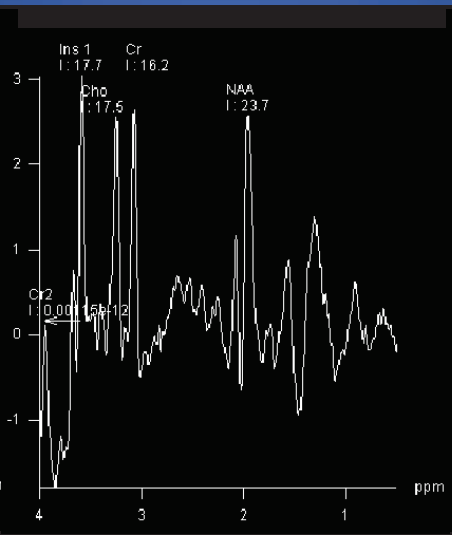
MRS analysis

Normal



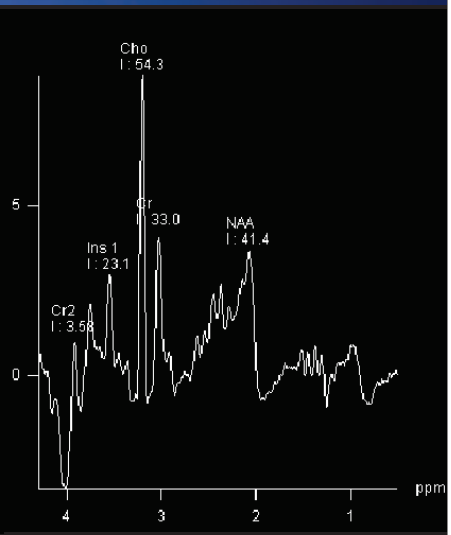
Cho:Cre ≈ 1
Cho:NAA ≈ 0.5

'Indeterminate'



Cho:Cre ≈ 1
Cho:NAA ≈ 1

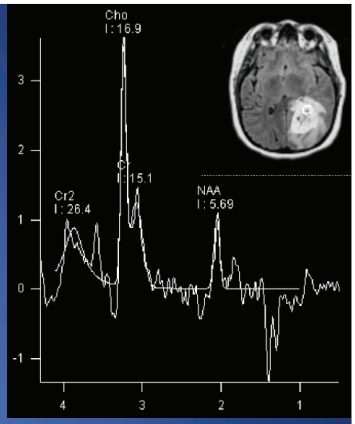
'Neoplastic'



Cho:Cre ≈ 2
Cho:NAA ≈ 2

- 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

	Cho	NAA	Lac	Lip	Myo	Glu	Suc	Acet	Ala	Aa
Low grade tumor	↑	↓			↑					
High grade tumor	↑	↓	↑	↑						
Metastasis	↑	absent[1]	↑	↑						
Oligodendroglioma	↑	↓	↑[2]							
Meningioma	↑	absent							↑	
Gliomatosis cerebri	↑	↓								
Lymphoma	↑	absent[1]		↑						
Radionecrosis	↓	↓	↑	↑						
Abscess	N	↓	↑	↑			↑	↑	↑	↑
Demyelination	↑	↓	↑[3]	↑	↑	↑[3]				

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.

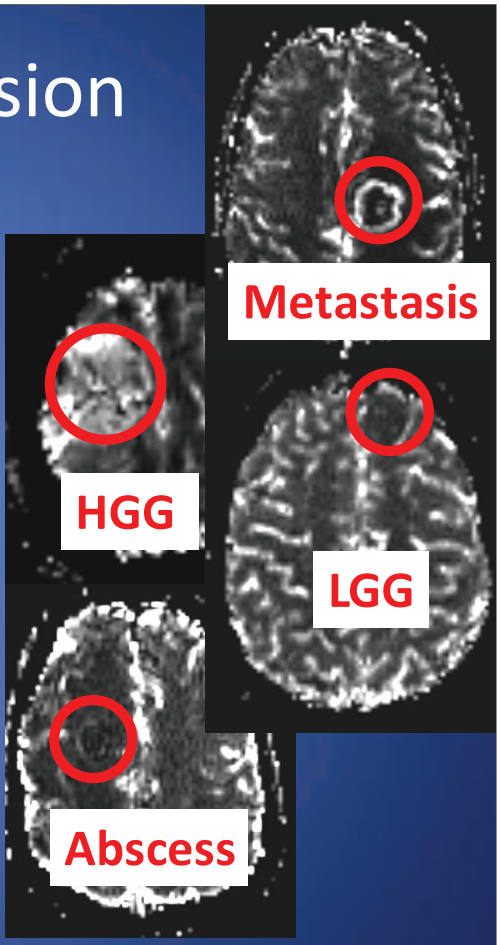
Bertholdo, Brain Proton Magnetic Resonance Spectroscopy, www.ajnr.org

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

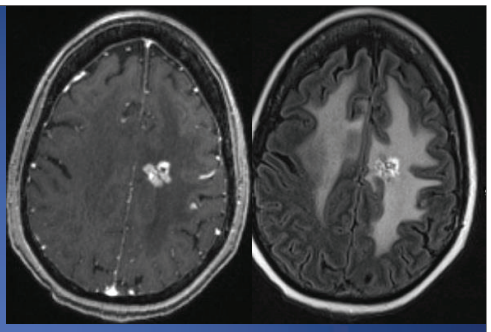
- Cerebral blood volume (CBV) is most useful for neoplasms
- For differential diagnosis:
  - Elevated in HGG, metastases, but also some LGG
- Biopsy planning: target high rCBV
- Prognosis: Higher CBV neoplasms demonstrate progression

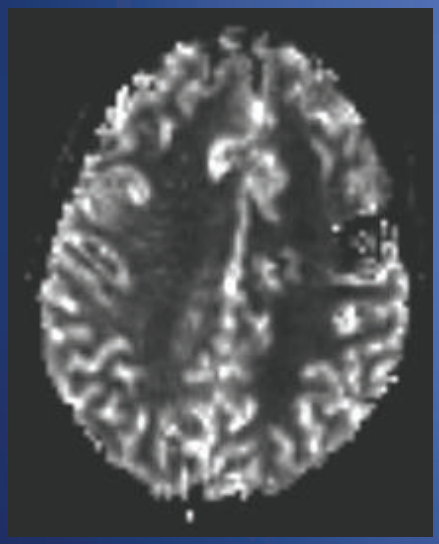


T1 Dynamic contrast enhanced (DCE) MR permeability

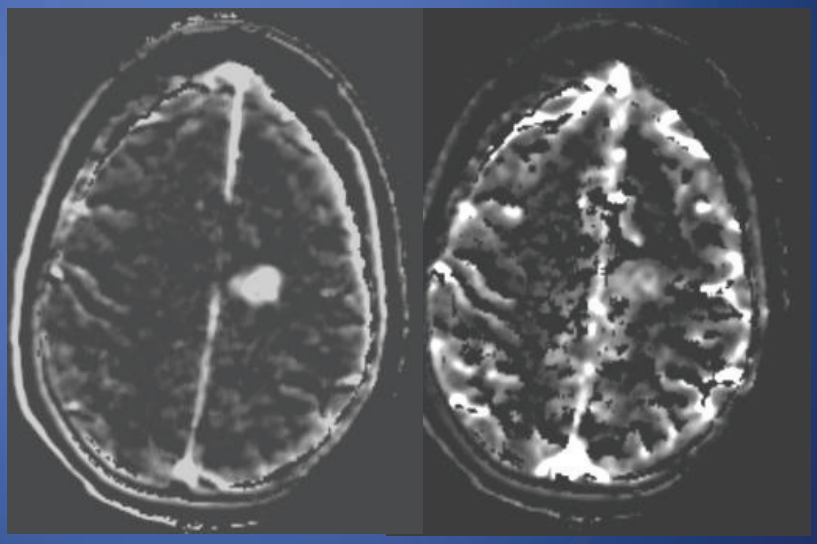
- Newer technology: implementation still evolving, software/methodology not standard
- Various measures of vascularity/vascular integrity
  - K_{trans} : a measure of permeability and blood flow
  - V_p : fractional plasma volume, usually correlates with DSC CBV

Perfusion/permeability



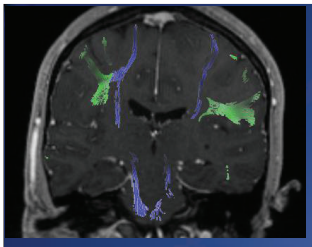


DSC perfusion



K_{trans}

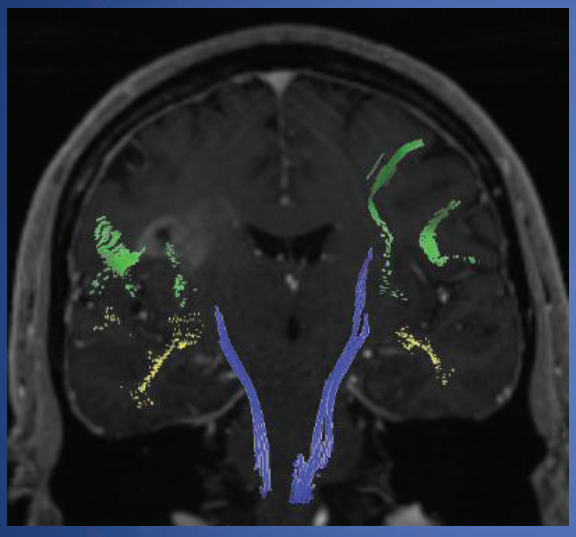
V_p

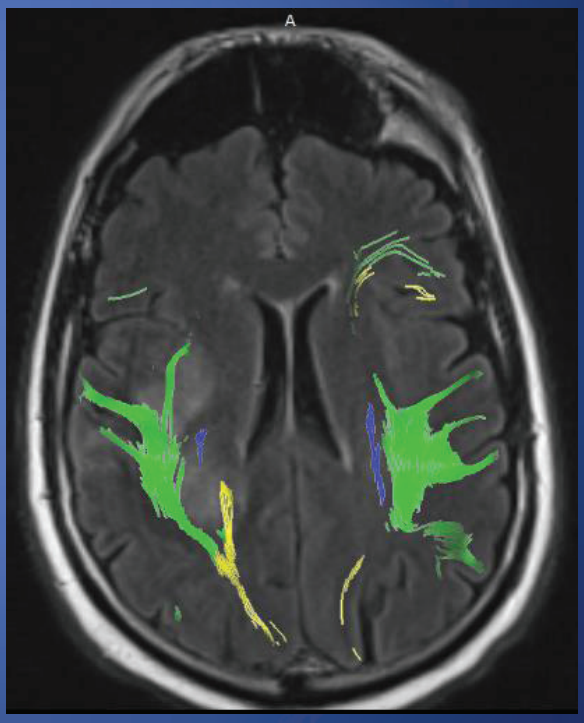


Tractography

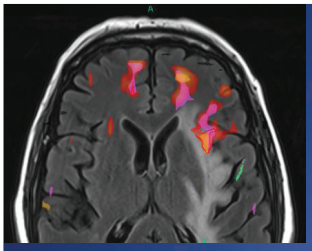
- Diffusion tensor imaging (DTI) – fiber tracking
- Major pathways (CST, SLF, etc)
  - Helpful for surgical/radiation therapy planning (proximity of critical large axon tracts to tumor)
- Pitfalls:
  - Failure of tracking due to disruption – not seeing does not mean not there
  - Only follows dominant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

Tractography: example





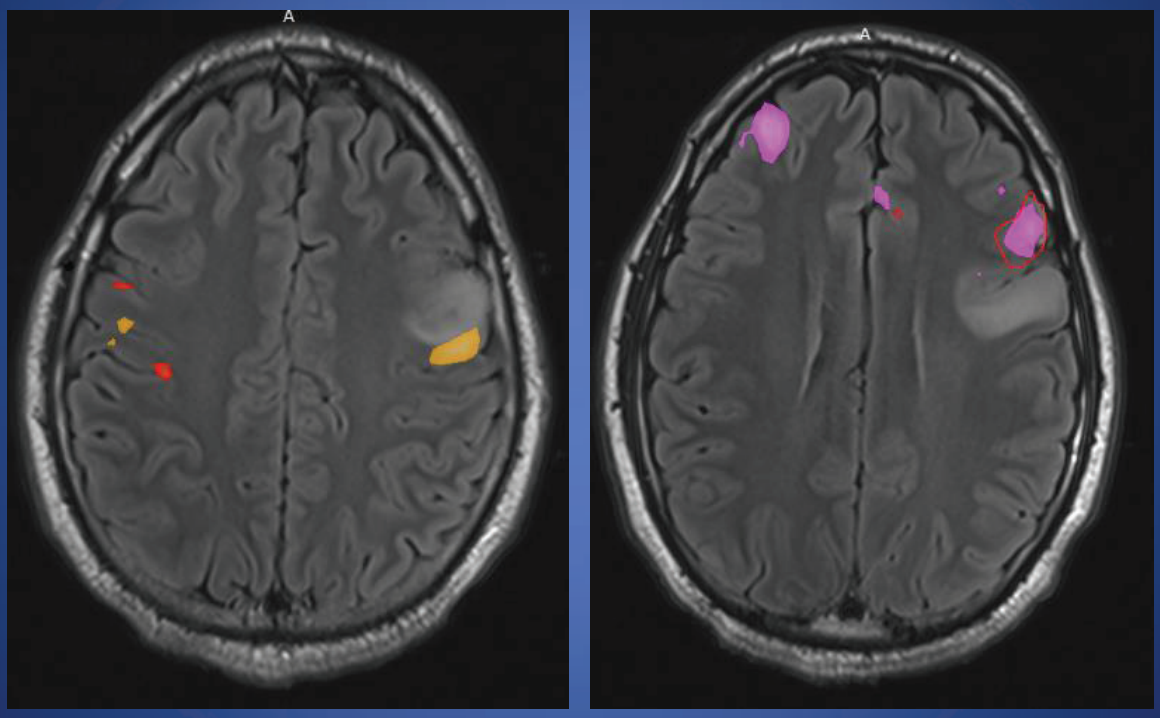
Blue: Corticospinal tract (CST, motor)
Green: Superior longitudinal fasciculus (SLF, language)



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



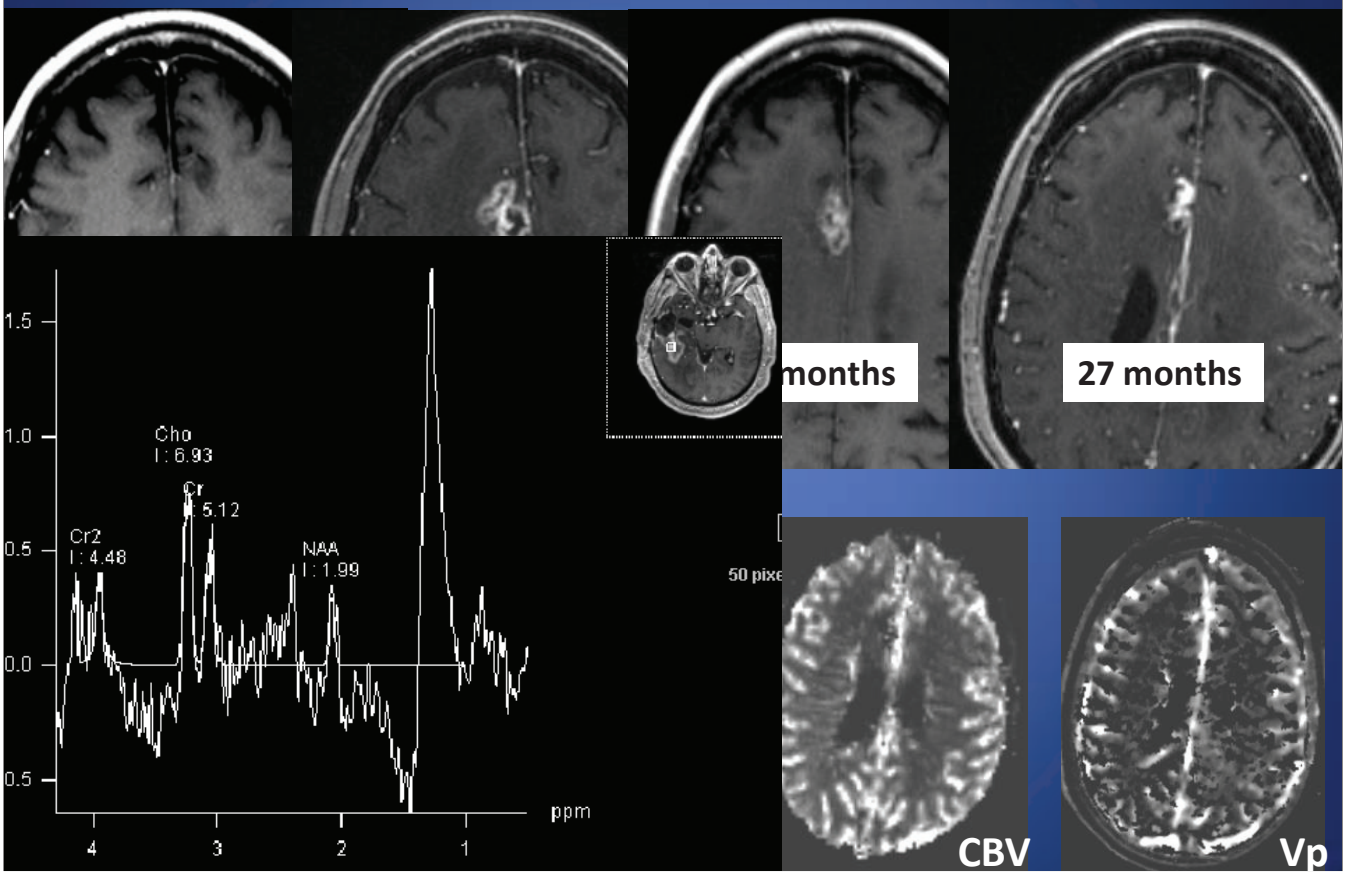
Yellow: facial motor task (motor cortex)
Purple/red: language tasks (Broca's area)

Post treatment course

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

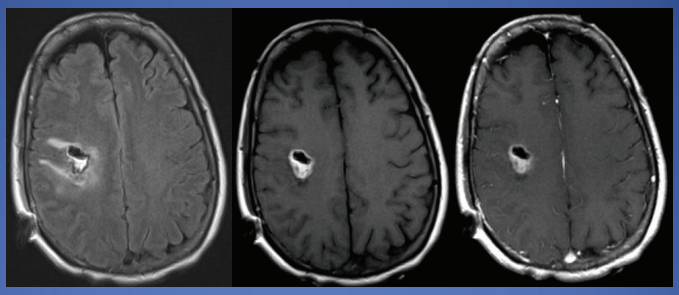
	Response	True Progression	Pseudo-progression	Pseudo-response	Radiation Necrosis
Enhancement	N	Y	Y	N	Y
Mass effect	N	Y	Y	Y	Y/N
Perfusion	N	Y	N	N	Y/N
MRS	Normal	Neoplastic	Normal	Neoplastic	Low metab.
Timing after therapy	?	Any	3-6 months	Any, Avastin	12-18 months

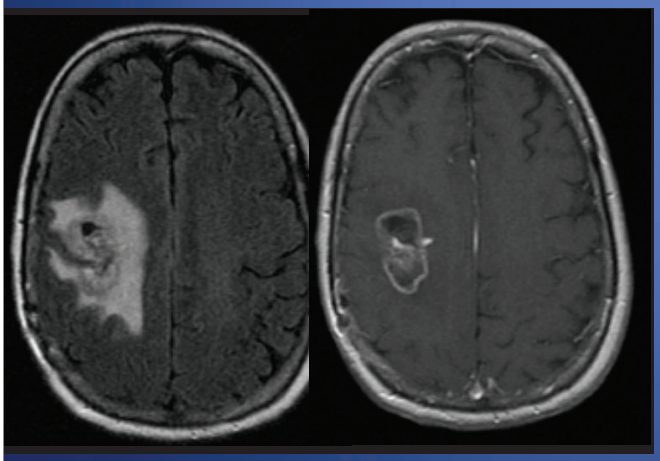
Radiation necrosis after gamma knife



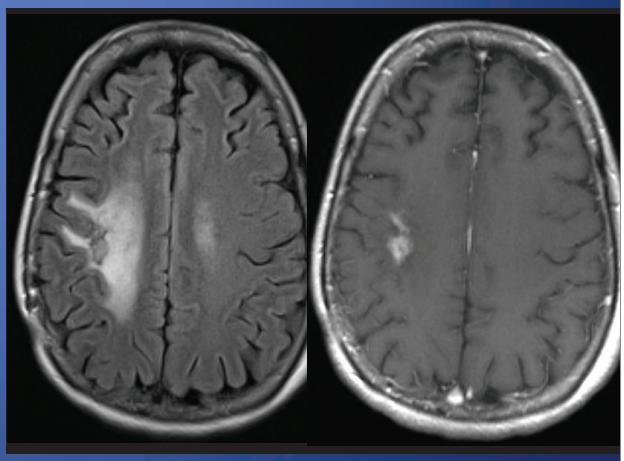
Pseudoprogression

Immediate post-op:
No residual



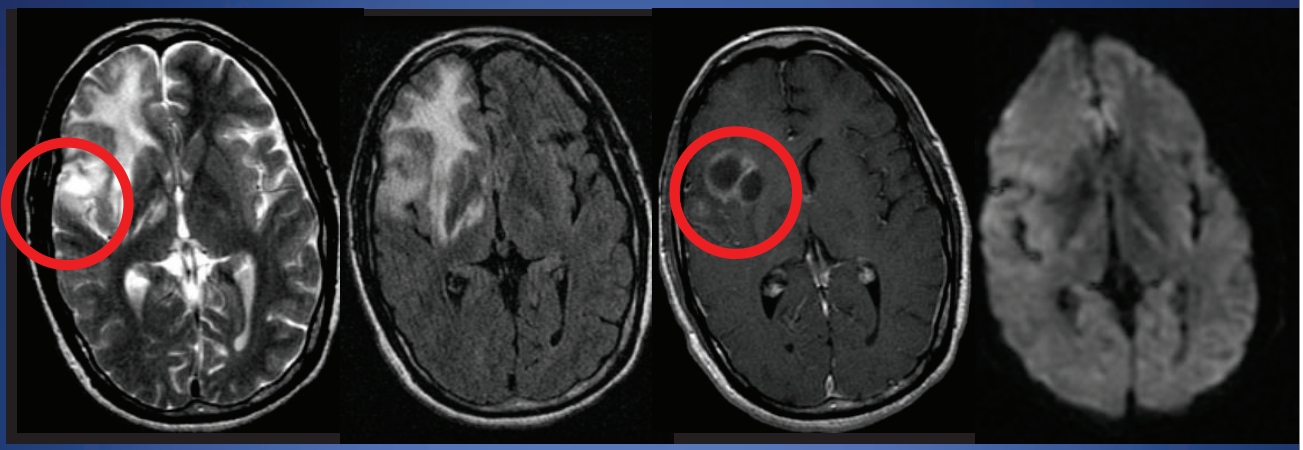


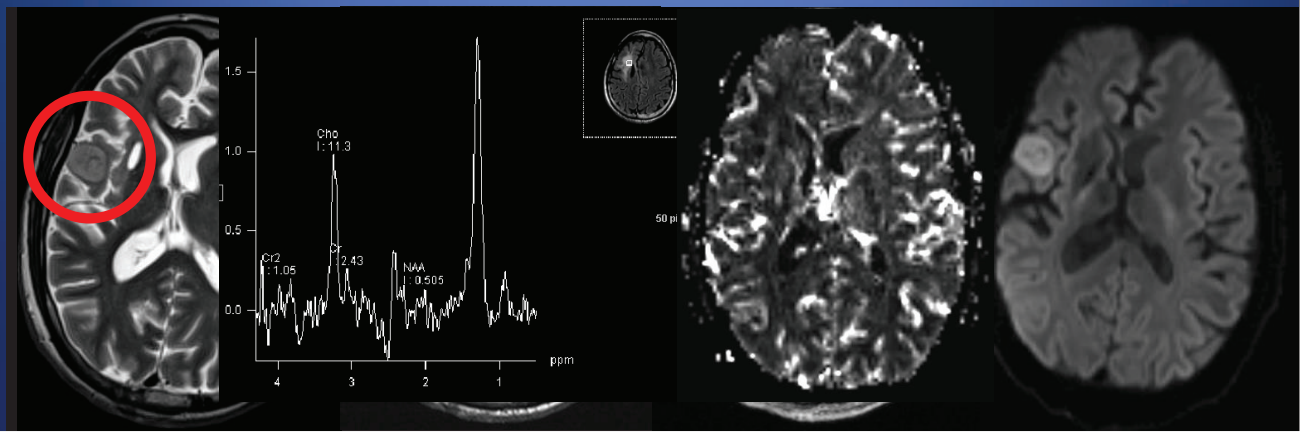
4 months post-op, following chemo/XRT



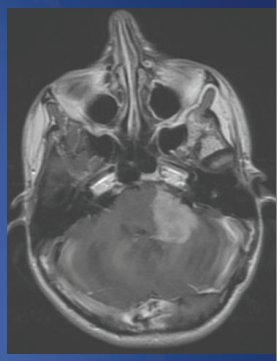
11 months post-op

Pseudoresponse on Avastin

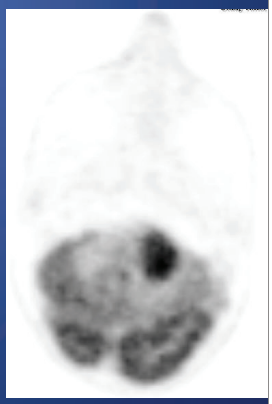




FDG-PET in brain neoplasia

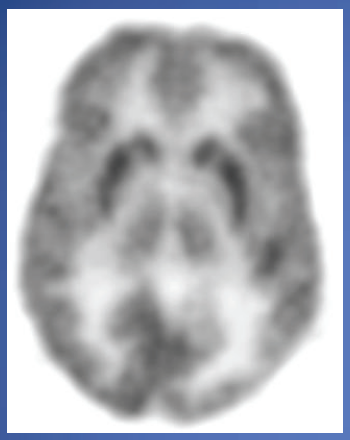


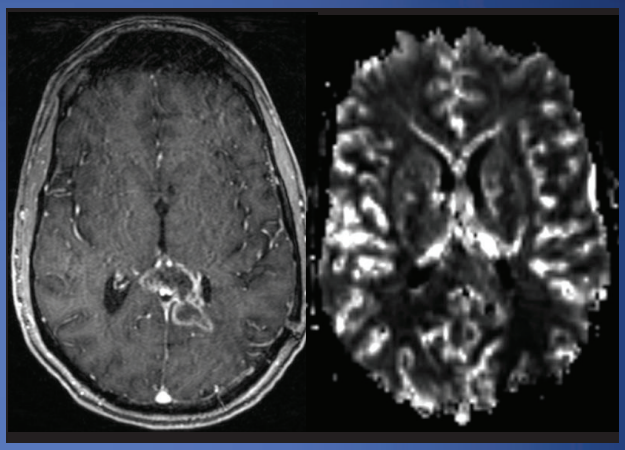
- Only approved tracer useful for evaluating neoplasm
- Limitations:
  - High uptake in normal gray matter; GBM lower
  - Nonspecific
- Uses:
  - Higher uptake seen in higher grade neoplasm
  - Higher uptake is associated with worse prognosis
  - Can be used to evaluate recurrence (high uptake) versus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



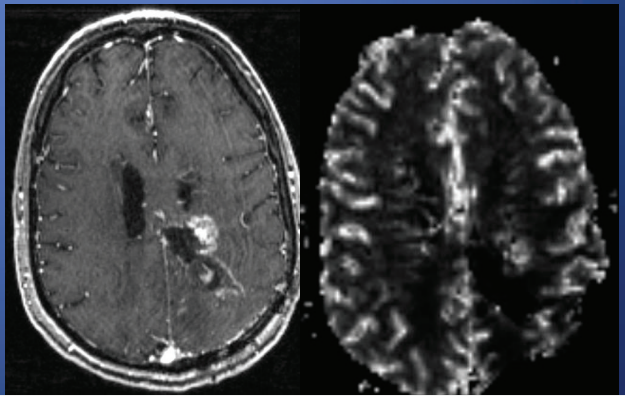
FDG for recurrence

Aug 2011





Aug 2013



PET/MRI

PET/MRI

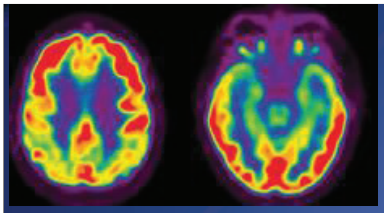
- Technically challenging to build
- Active development (and deployment) by major equipment vendors
- Will allow simultaneous MRI and PET acquisition
  - Need to show benefit above colocalization, which can be performed from separate studies
  - Benefits much clearer for research applications than clinical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

Potential applications of PET/MRI

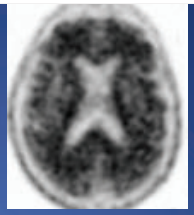
- Neuroimaging
  - Decreased imaging time for brain tumor or demented patients
  - Improved PET resolution with real time motion correction and improved partial volume correction
  - Correlation of PET and MRI functional measures, as 'functional state' can vary if scans separated by time

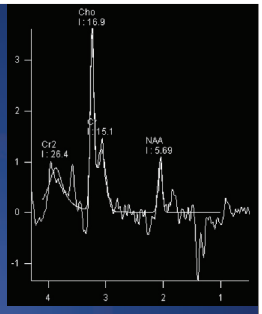
Potential applications of PET/MRI

- 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

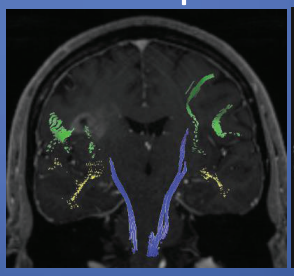


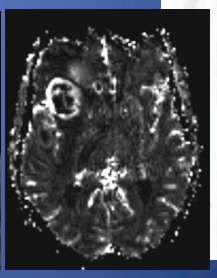
Summary





- 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.