UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE

Department of Radiology

Division of Nuclear Medicine

Didactic

Brain Tumor Imaging: primary tumors and differentiation of radiation necrosis vs tumor recurrence

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Aims of this lecture

- Provide an overview of brain tumors
- Review blood-brain barrier
- Review conventional MRI of brain tumors
- Discuss metabolic imaging in brain tumors
- Differentiation of radiation necrosis versus tumor recurrence

Type of cell	Neoplasm
Glial cells:	
Astrocyte	Astrocytoma
Oligodendrocyte	Oligodendroglioma
Ependyma	Ependymoma
Choroid plexus	Choroid plexus tumors (papilloma, carcinoma)
Nerve sheath cells	
Schwann cells	Schwannoma
Fibroblasts/Schwann cells	Neurofibroma
Mesenchymal cells	
Meninges	Meningioma
Blood vessels	Hemangioblastoma
Bone	Sarcoma
Lymphocytes, leukocytes	Lymphoma, leukemia, myeloma, Langerhans cell histiocytosis
Germ cells	Germinoma, Teratomatous types (embryonal carcinoma, yolk sac tumor, teratoma, choriocarcinoma)
Other neuroepithelial cells	Craniopharyngioma, Rathke's cleft cyst
Endoderm, mesoderm, ectoderm	Epidermoid/dermoid, lipoma, harmatoma

WHO Classification of Glial Tumors

Grade I		• low proliferative potential	possibility of cure (surgical resection alone)	
Grade II	▪ + cytological atypia	• low-level proliferative activity • generally infiltrative in nature • often recur • tend to progress to higher grades of malignancy		Survive >5 yrs
Grade III	• + nuclear atypia/ anaplasia • + brisk mitotic activity		adjuvant radiation +/- chemotherapy	Survive 2-3 yrs
Grade IV	• + microvascular proliferation • + /- necrosis • cytologically malignant, • mitotically active, • necrosis-prone neoplasms	• rapid pre- and postoperative disease evolution • fatal outcome. • In some- • Widespread infiltration of surrounding tissue • craniospinal dissemination	adjuvant radiation +/- chemotherapy	Depends upon therapy, Survive <1 yr

Introduction

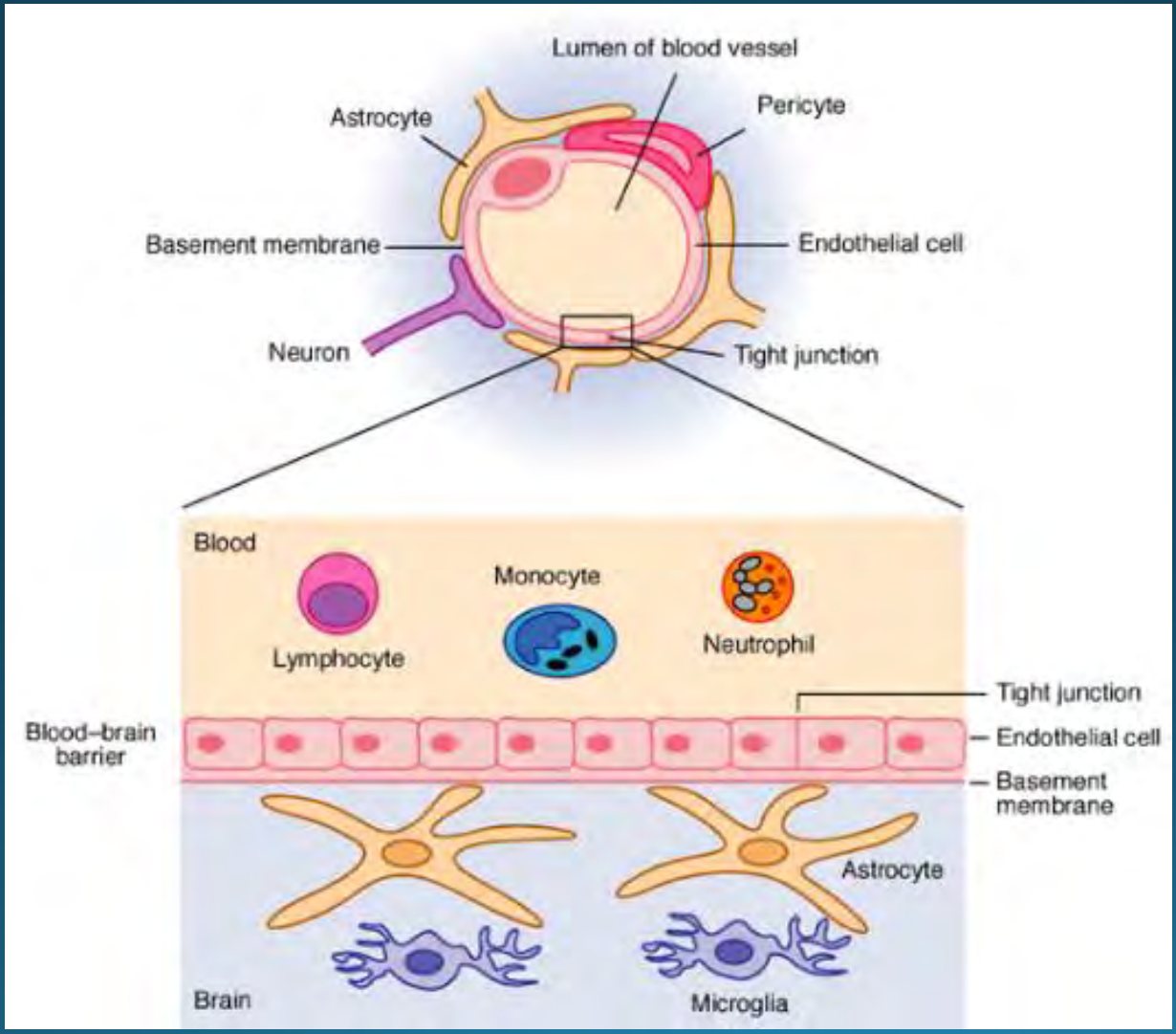
- Brain tissue and brain tumors are separated from the blood by the blood–brain barrier (BBB)
- Tracers reach brain tumors only if
  - Tumor causes disruption of BBB (e.g., glioblastoma)
  - Tumor develops from tissues that do not have a BBB (e.g., meningioma), or
  - Tumor is a metastasis (from within blood vessels)

Introduction

- BBB components:
  - Tight junctions
  - Astrocytes
  - Endothelial cell walls
  - Enzymes in vessel walls
  - ‘Efflux pumps’ in vessel wall

Introduction

- Blood Brain Barrier



Introduction

- Challenges in imaging brain tumors:
  - BBB may be intact in low grade gliomas (no enhancement)
  - Commonly mixed aplasia within tumor (important in biopsy)
  - Infiltration of normal brain tissue by gliomas (important in surgery and local therapies)
  - Radiation necrosis may mimic recurrence (treatment response assessment)

Introduction

- Tumors that disrupt BBB –high grade gliomas - assessable and quantifiable by MRI
- Tumors with intact BBB –low-grade gliomas – still can be detected by MRI
- What's the role of nuclear imaging?
  - Limited role in detection of brain tumors
  - Role based on tracers that use specific transporters to cross intact BBB, rather than damaged BBB

Conventional Imaging - MRI

- MRI:
  - Current gold standard in imaging
  - Depends on:
    - Breakdown of BBB
    - Angiogenesis with leaky capillaries
  - High sensitivity to size, localization, morphology

Conventional Imaging - MRI

- MRI current gold standard but has limitations:
  - Unreliable in low-grade gliomas (no enhancement)
  - Unreliable in early treatment response assessment (anatomical changes occur late; Dexamethasone may reduce apparent tumor size on MRI)
  - Unable to distinguish tumor from radiation changes

Metabolic Imaging – PET and SPECT

- Metabolic imaging with PET is complementary to MR imaging
- Roles of PET imaging include:
  - Differential diagnosis
  - Treatment planning
  - Treatment response prediction
  - Treatment response assessment
  - Distinguish local recurrence from radiation necrosis

Metabolic Imaging – PET and SPECT

- PET radiotracers:
  - Glucose tracers
  - Amino acid tracers
  - Nucleotide analog tracers
  - Hypoxia agents
- SPECT radiotracers: Radioiodinated amino acids:
  - L-3 (123I)iodo-methyl tyrosine (IMT)
  - P-(123I)iodo-L phenylalanine

Metabolic Imaging – PET and SPECT

- Examples of tracers:
  - Glucose tracer
    - 18F-FDG
  - Amino acid tracer
    - 11C-methionine (MET)
  - 18F-labeled amino acid/nucleotide analogue tracers
    - O-(2-[18F]fluoroethyl-L-tyrosine (FET)
    - 3,4-dihydroxy-6-[18F]-fluoro-L-phenylalanine (F-DOPA)
    - 3-O-methyl-6-[18F]fluoro-L-DOPA (metabolite of F-DOPA)
    - 18F-choline (FCH)
  - Hypoxia agents
    - 18F-fluoromisonidazole (FMISO)

Metabolic Imaging – 18F-FDG PET

- High grade tumors – High FDG uptake
- FDG uptake has prognostic value
  - High FDG uptake in previously low-grade tumor establishes diagnosis of anaplastic transformation

Metabolic Imaging – 18F-FDG PET

- Limitations of FDG-PET:
  - Hypermetabolic brain vs mildly hypermetabolic tumors (low-grade and recurrent high-grade tumors)
    - Low-grade tumors uptake = that of normal white matter
    - High-grade tumors uptake <= that of normal gray matter
  - Variable FDG uptake: High-grade tumors uptake may be equal to or > than white matter uptake, especially after treatment

Metabolic Imaging – 18F-FDG PET

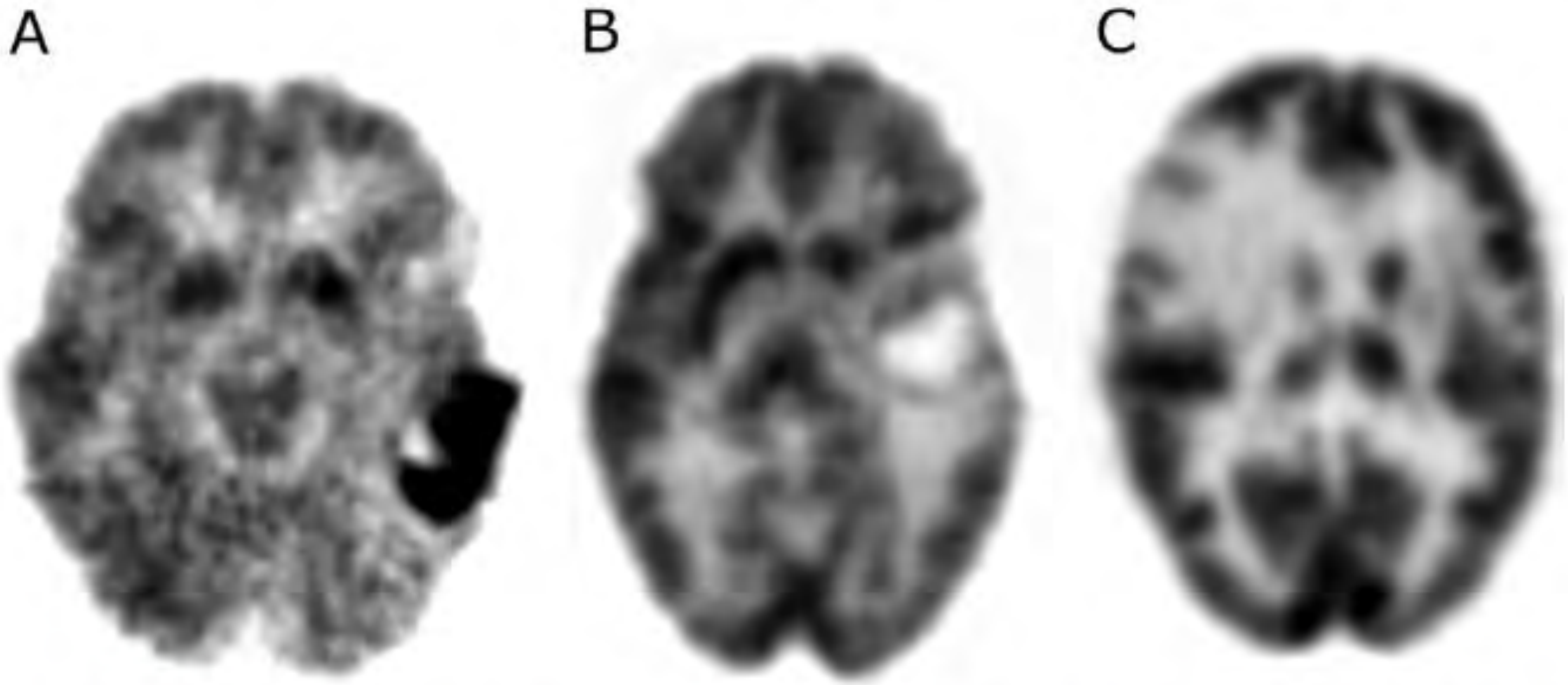


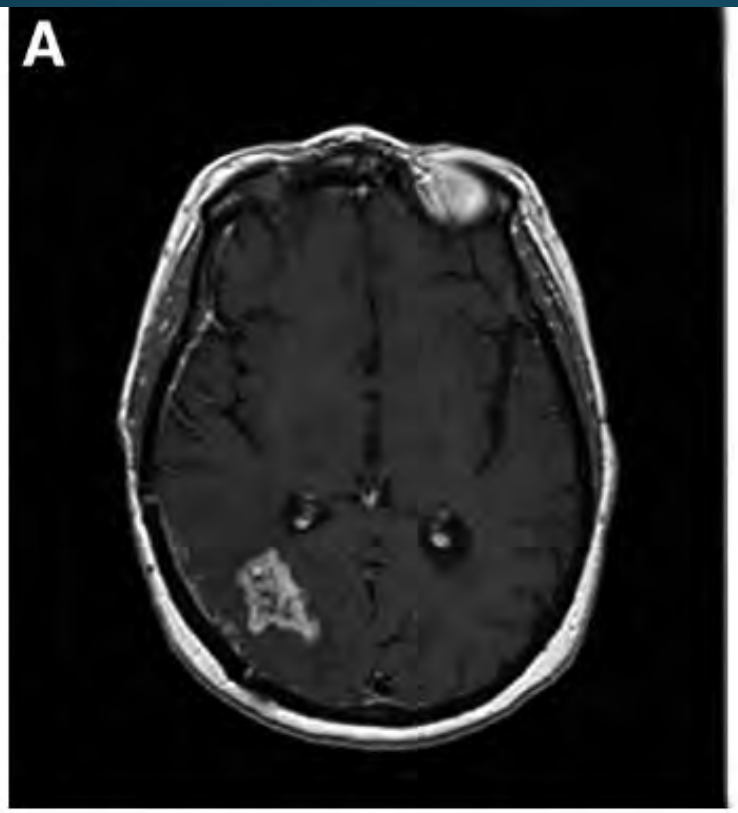
Figure 1 Variable FDG-PET uptake in newly diagnosed tumors. (A and B) Left temporal glioblastoma; (C) right frontal grade II mixed glioma.

Metabolic Imaging – 18F-FDG PET

- Image interpretation
  - Co-register with MRI to delineate area of interest
    - Improves FDG-PET performance
    - Recurring tumor may have FDG uptake equal to or lower than normal cortex
  - Compare FDG uptake to background in adjacent brain
    - Increased uptake that corresponds to abnormalities on MRI indicates recurrence even when equal to or less than cortical uptake

Metabolic Imaging – 18F-FDG PET

- Image interpretation



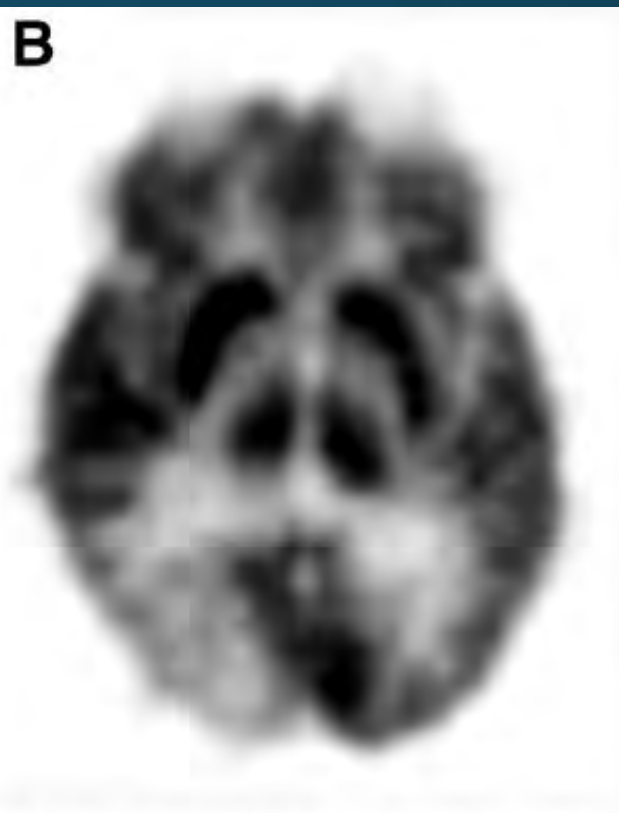


Figure 2 Image coregistration of FDG-PET and MRI. Shown are (A) MRI and (B) FDG-PET images from a 59-year-old woman with recurrent right parieto-occipital glioblastoma. MRI shows a contrast enhancing lesion that is slightly increased compared with the previous study. FDG-PET showed moderate uptake lower than the normal gray matter, but greater than the expected background of the adjacent brain tissue and corresponded to the abnormal contrast enhancing region on MRI. Surgery demonstrated recurrent glioblastoma.

Metabolic Imaging – 18F-FDG PET

- Delayed imaging 3 – 8 hrs after injection:
  - Early studies - glucose loading enhances brain tumor detection - 27% increase in tumor: gray matter ratio
  - Not clinically feasible - involves IV glucose infusion and blood glucose monitoring
  - Delayed imaging at 3 to 8 hours improves distinction between tumor and normal gray matter
    - At longer time interval, FDG degradation and glucose excretion from normal brain is higher than from tumor

Metabolic Imaging – 18F-FDG PET

- Delayed imaging

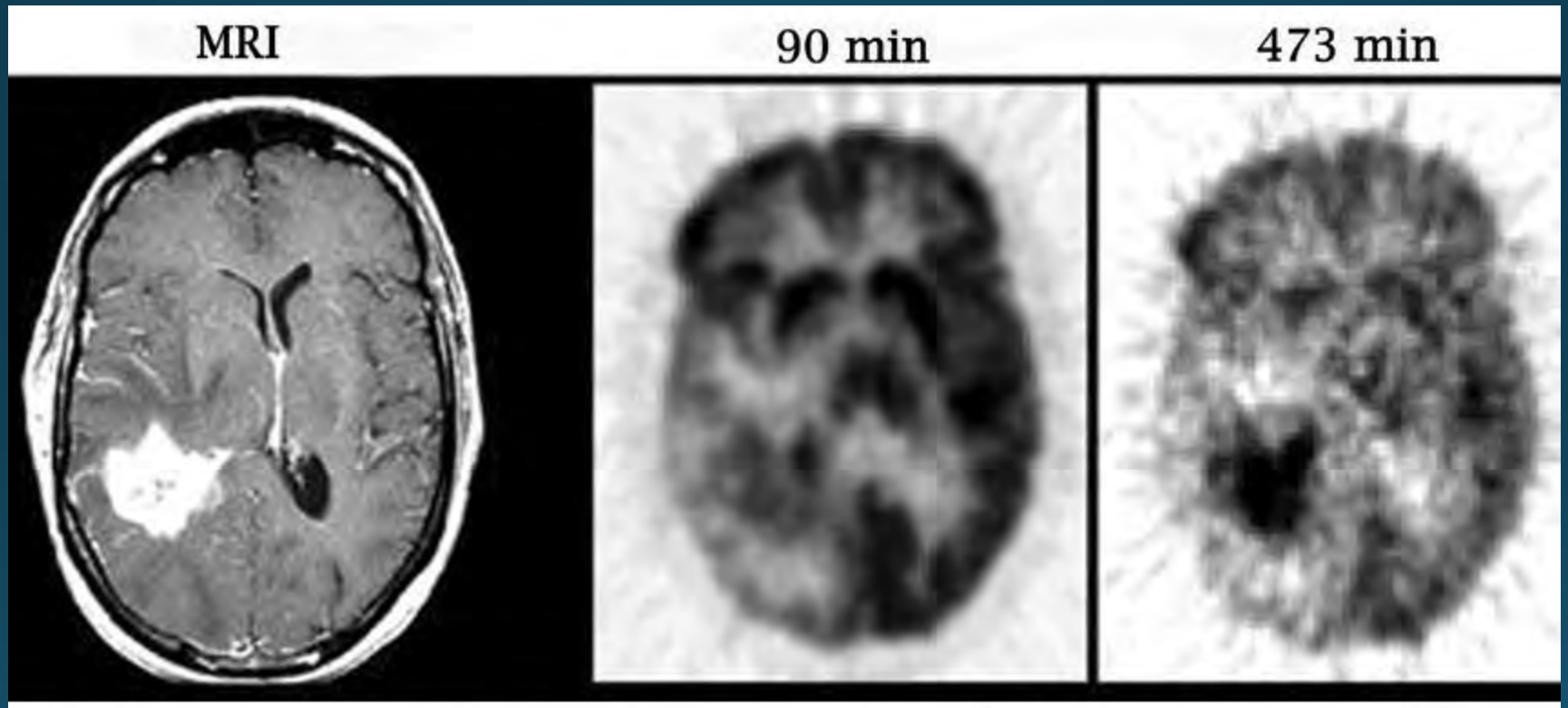


Figure 3 A 45-year-old woman with a recurrent right temporal glioblastoma. MRI shows contrast enhancement. Note the much more prominent tumor to gray matter delineation at the later time point, 473 minutes, compared with 90 minutes. (Reprinted by permission of the Society of Nuclear Medicine from Spence et al.[14])

Metabolic Imaging – Amino Acids PET

- High uptake in tumor tissue + low uptake in normal brain tissue = high tumor: brain contrast
- Greater sensitivity than FDG for tumors that are hypo- or iso-metabolic to normal cortex
- Superior accuracy to FDG in evaluating recurrent low- and high-grade gliomas
- Amino acids or amino acid analogue tracers used

Metabolic Imaging – Amino Acids PET

- Mechanism of action
  - Amino acids transported into cells by carriers
  - Amino acid transporters up-regulated in malignancies

Differential Diagnosis with PET

- Solitary ring-enhancing lesion
  - Negative FDG-PET excludes glioblastoma
  - Positive FDG-PET – malignancy, inflammation, infection
  - FDG, FET and FCH are positive in malignant and non-malignant lesions
- Brain abscess – FET uptake less than MET & FDG
- Cortical infarction - FET and MET uptake at periphery

Treatment Planning with PET

- Hypoxic tumors
- Disrupted angiogenesis decreases ability of O2 to diffuse through tissues
- Hypoxia is associated with progression
- Hypoxia is associated with resistance to radiotherapy

Treatment Planning with PET

- FMISO - Hypoxia agent
- FMISO metabolites get trapped in hypoxic cells
  - Uptake is independent of perfusion
  - Uptake is independent of BBB disruption
  - Uptake correlates with VEGFR-R1 expression
  - Uptake by high-grade but not low-grade gliomas

Treatment Response with PET

- FLT evaluates tumor cell proliferation
  - Uptake correlates with thymidine kinase-1 activity and with proliferation index Ki-67
  - TK-1 enzyme is expressed in DNA synthesis phase of cell cycle
  - FLT is Phosphorylated by TK-1 into FLT monophosphate that gets trapped in cells
  - FLT is a prognostic marker
  - Potential for monitoring treatment response

Tumor recurrence versus radiation necrosis

- MR findings of tumor recurrence versus radiation necrosis
- Role of PET
- Role of MR spectroscopy

Why do tumors enhance?

- Usually are either WHO grade III or IV (glioblastoma multiforme - GBM)
- Due to breakdown of the blood brain barrier

MR with contrast

- Usually obtain T1 weighted MR with contrast and fat saturation
- Features of tumor recurrence
  - Nodular and mass like enhancement
  - Associated vasogenic edema on T2 weighted imaging or FLAIR
  - Increasing enhancement or increasing edema

Features of radiation necrosis

- More linear enhancement than nodular
- Usually the temporal increase in vasogenic edema is not as prominent (although not entirely reliable)

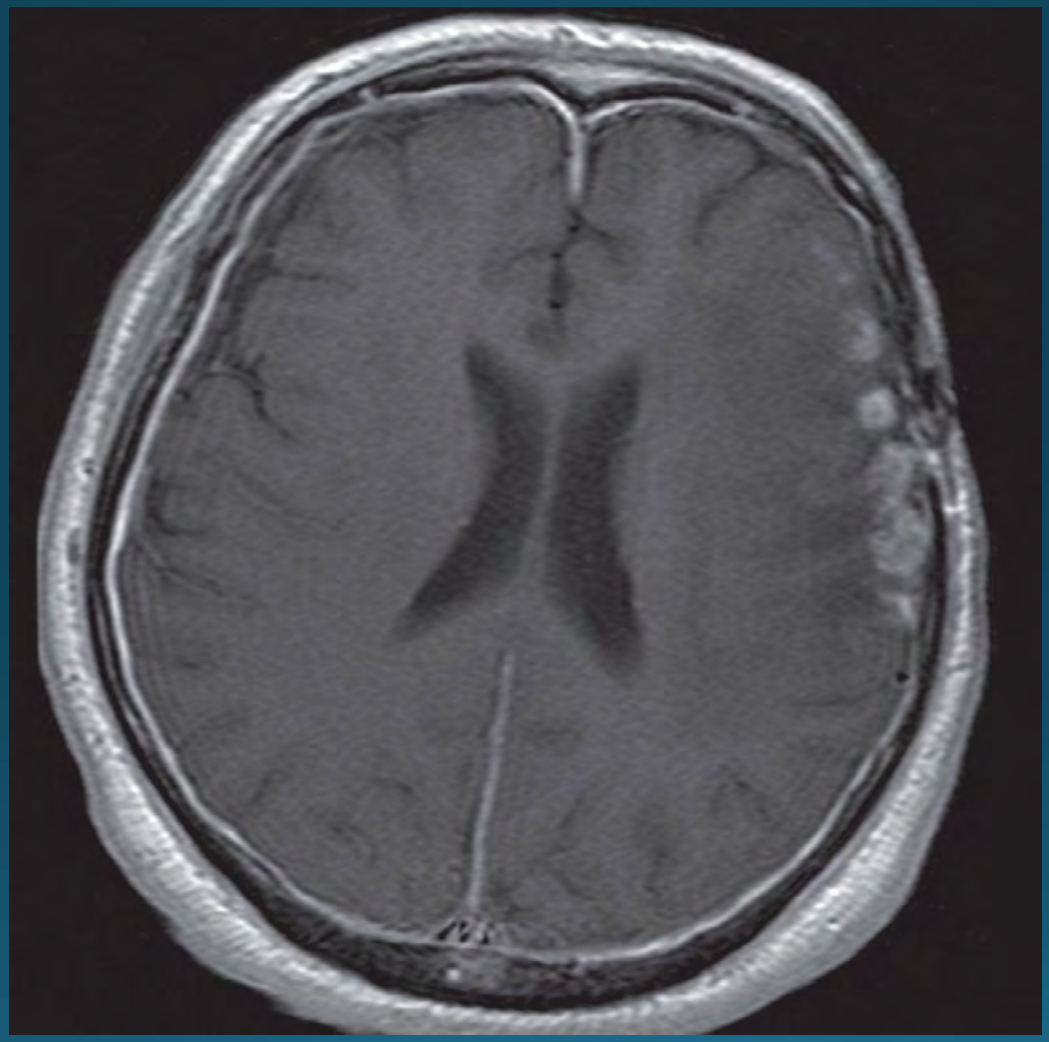
Other complicating factors

- Use of Avastin
  - VEGF inhibitor sometimes used to treat GBM due to the theory that high grade tumors proliferate via angiogenesis
  - Avastin can cause enhancement similar to tumor recurrence in some cases

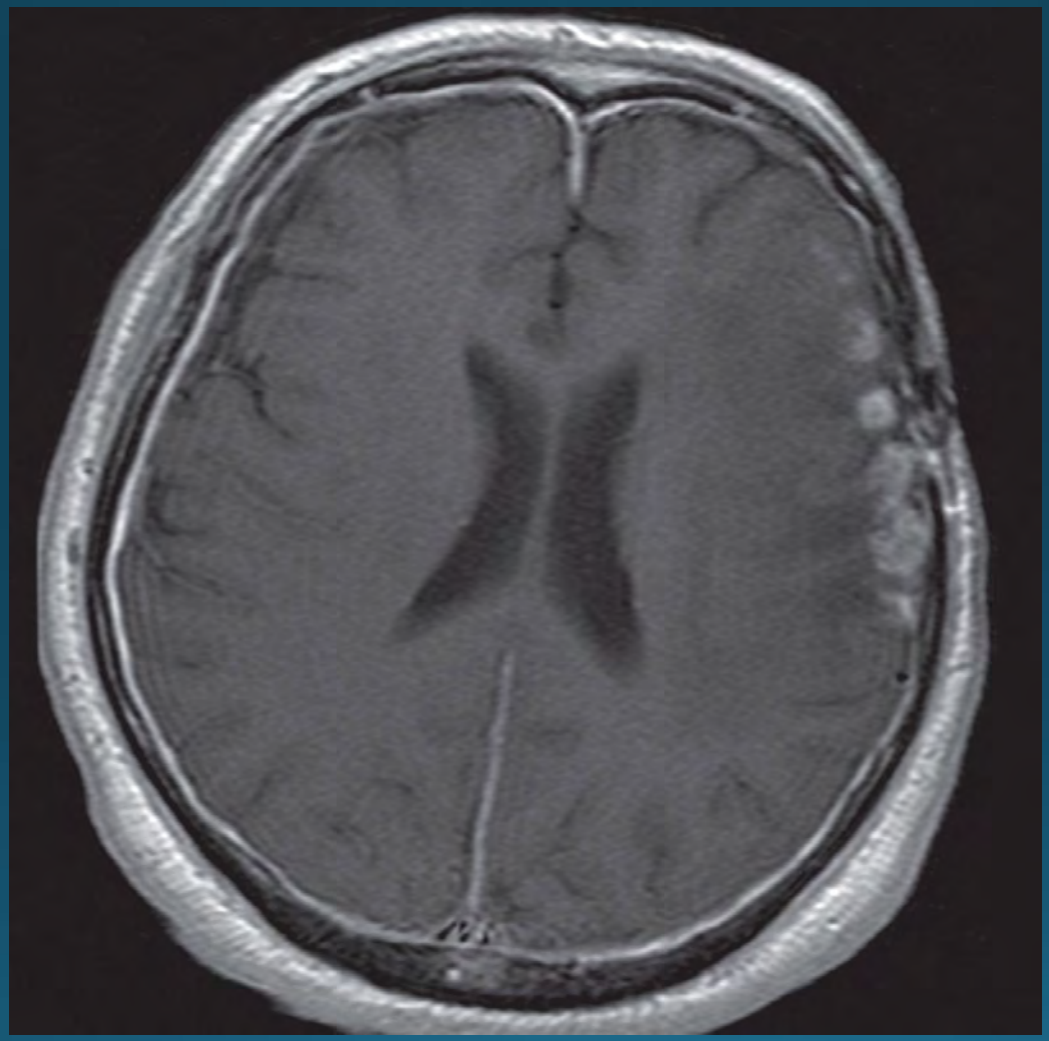
MR

- Therefore, it is difficult to distinguish tumor recurrence and radiation necrosis based on MR enhancement characteristics alone
- The next image demonstrates this
- Usually we rely on temporal characteristics to help us as well but due to the < 1 year survival of patients with GBM, it is not as helpful to obtain serial imaging

Is this tumor recurrence or radiation necrosis?



Radiation necrosis in a 67-year-old man with a history of squamous cell carcinoma of the scalp and nodal neck metastases.



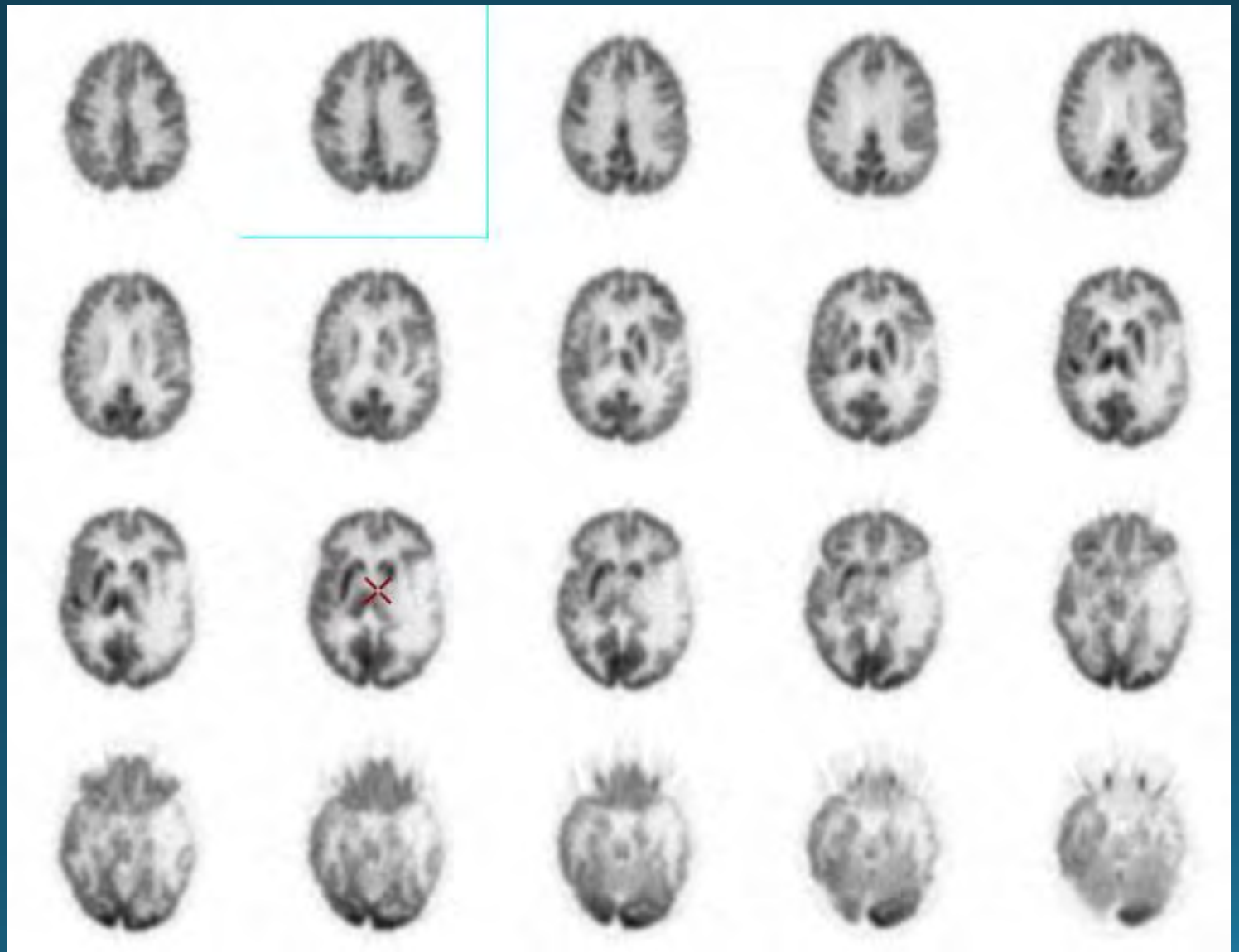
Shah R et al. Radiographics 2012;32:1343-1359

RadioGraphics

Role of PET

- PET allows greater ability to distinguish tumor recurrence versus radiation necrosis
- Simply, tumor is FDG avid whilst necrotic tissue is not

Recurrence vs Radiation Necrosis



Legend to previous PET figure

Hypometabolism within the entire left temporal lobe, as well as in adjacent portions of left fronal and parietal lobes, seen on 1- and 4-hour PET images. In the setting of prior radiation therapy, this finding is consistent with radiation necrosis.

Dual time point imaging

- Most institutions perform 1- hour and 4-hour delayed PET brain images
- This is called dual time point imaging
- Tumor usually shows persistent or increased enhancement at 1 and 4 hour imaging

FDG-PET in primary brain glioma

- The basis for FDG-PET imaging in primary brain gliomas is based on ability of rapidly growing tumor cells to sustain high rates of glycolysis under anaerobic conditions.
- FDG uptake in tumors is due to increased (1) metabolism, (2) number of glycolytic enzymes, and (3) increased cellular transport (hexokinase II overexpressed)

FDG-PET in primary brain glioma

- One drawback of CNS tumor imaging is that FDG PET has limited ability to distinguish uptake in primary CNS neoplasms from the normally high background gray matter brain activity- especially for small lesions and low grade lesions
- Uptake generally correlates with grade (exceptions: pilocytic astrocytoma and pituitary adenoma may have high FDG uptake).

Tumor Recurrence vs. Radiation Necrosis

- With a sensitivity of 75% and a specificity of 81%, ^{18}F-FDG combined with MRI can distinguish recurrent tumor from radiation necrosis (19 metastases, 10 gliomas). Chao IJC 2001.
- Specificity limited by ^{18}F-FDG in macrophages that infiltrate tissue after radiotherapy.

Other radiotracers

- 11C-L-methylmethionine (11C-MET) measures amino acid uptake (protein synthesis → tumor proliferation), highly sensitive for tumors, good correlation with tumor grade, and low background in normal brain.
- Limitations
  - short physical half-life, requiring on-site cyclotron, and by lack of specificity (uptake in inflammation).

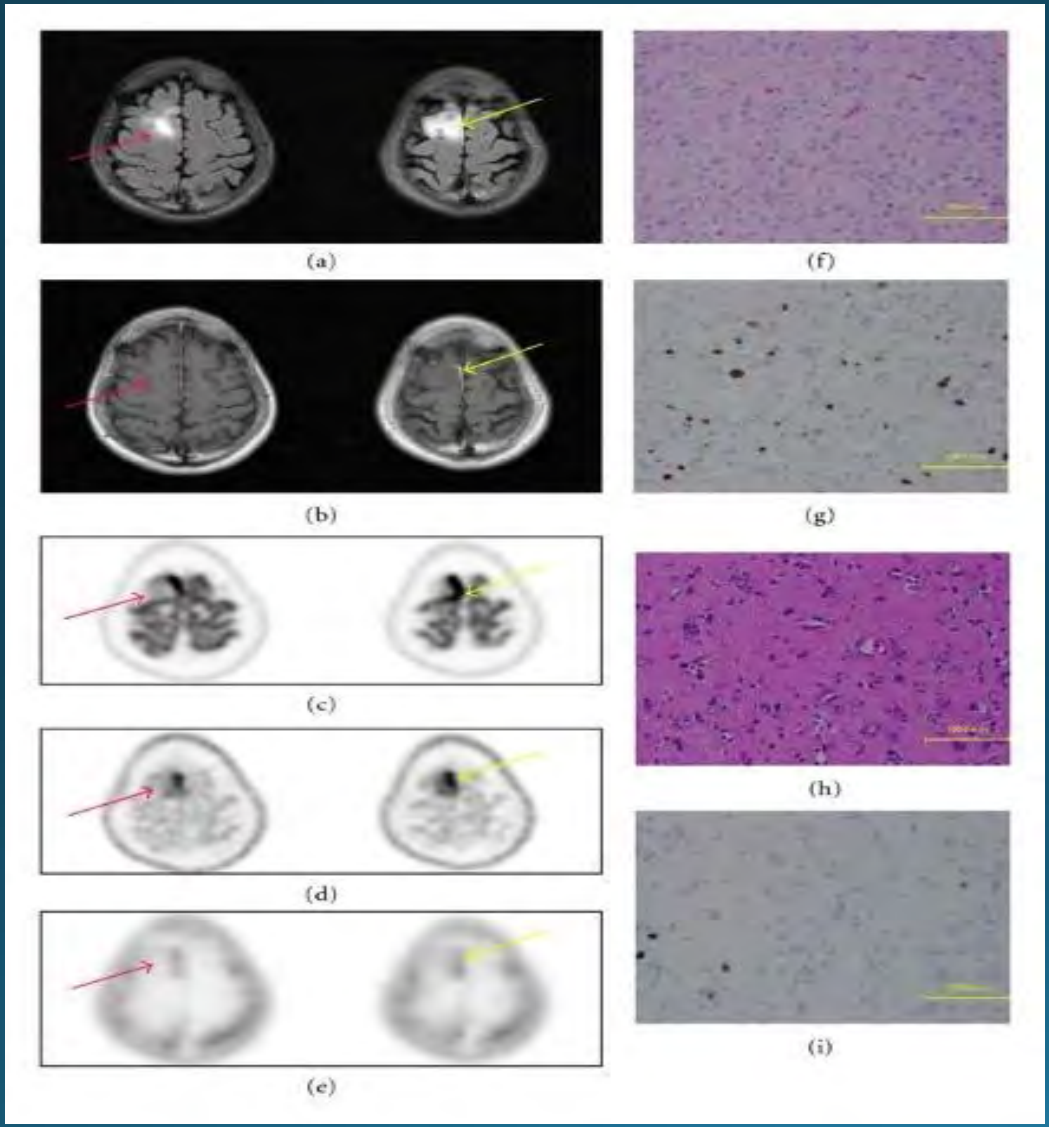
Other radiotracers

- 11C-MET and 18F-FLT have shown higher tumor to background uptake, correlating with higher Ki-67 indices (seen in higher WHO grade gliomas such as III and IV) then FDG PET alone.

Other radiotracers

- 18F-FLT (fluorothymidine) measures thymidine kinase-1 activity (tumor proliferation), good sensitivity for gliomas, good correlation with grade, and no background in normal brain. Also limited by lack of specificity.

18F-FLT/11C-MET images



Legend for previous figure

- 31-year-old woman with high intensity in the right frontal lobe in FLAIR MRI (a) and slightly enhanced lesion in Gd-enhanced MRI (b). FDG-PET demonstrated increased FDG uptake within the tumor (c). MET-PET demonstrated increased MET uptake within the tumor (d). FLT-PET demonstrated increased FLT uptake within the tumor

Legend continued

- (e). Areas of different enhancement and uptake between FDG, MET, and FLT are projected on the tumor, in order to perform histological sampling for further correlation during the resection (yellow arrow, red arrow). Yellow arrow demonstrates anaplastic astrocytoma

Legend continued

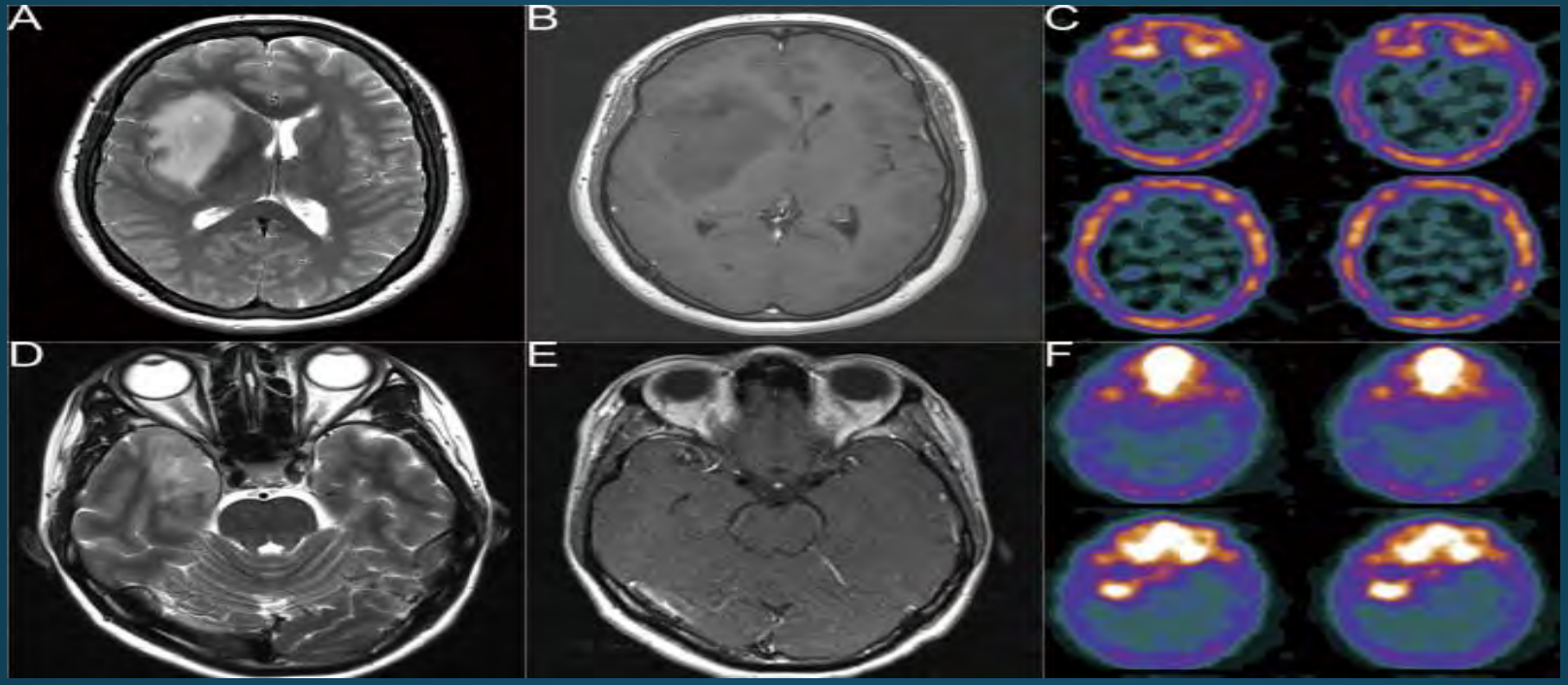
- (f) within T/N ratio of FDG-PET (2.85), MET-PET (4.57), and FLT-PET (9.65). Ki-67 index from the specimen indicated by yellow arrow was 20% (g). Red arrow demonstrates diffuse astrocytoma area (h) within T/N ratio of FDG-PET (0.76), MET-PET (2.08), and FLT-PET (4.65). Ki-67 index from the specimen indicated by red arrow was 8% (i).

Other radiotracers

- 18F-fluoromisonidazole (18F-FMISO) evaluates tissue hypoxia (metabolites of the agent are trapped exclusively in hypoxic cells).
- Uptake indicates resistance to radiation and chemotherapy, worse prognosis (observed in high grade gliomas).

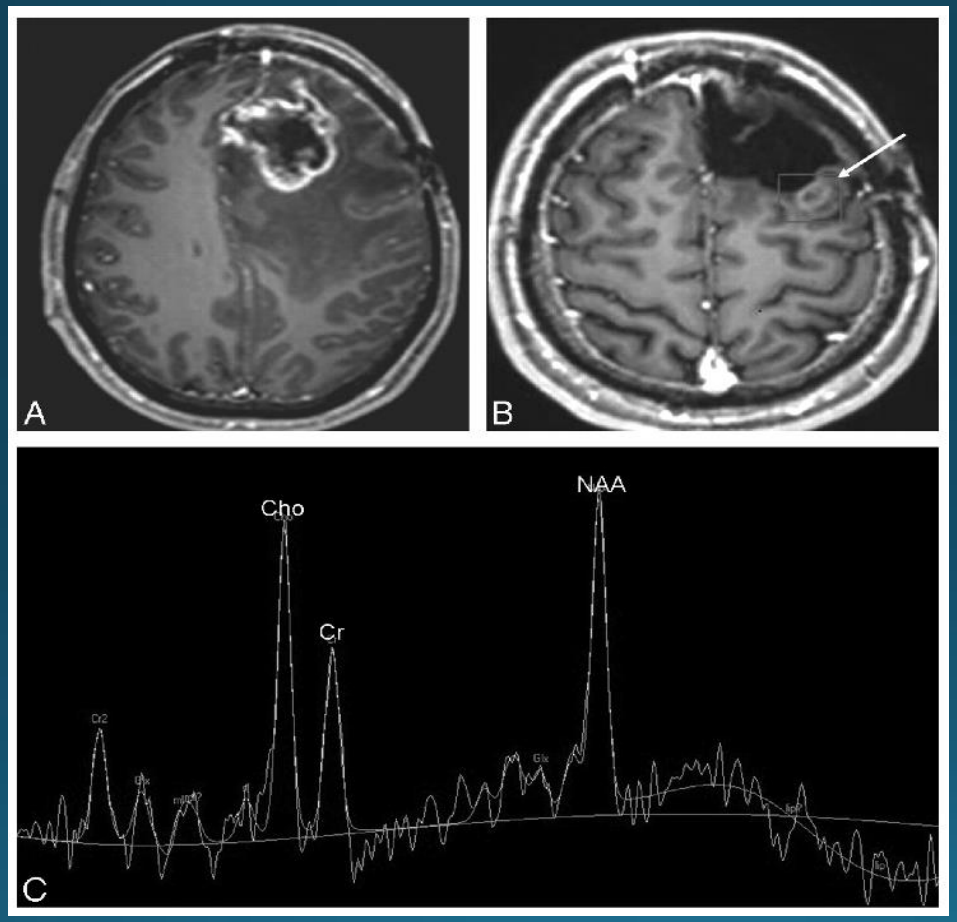
Other radiotracers

- Thallium-201
  - Increased uptake on Thallium-201 has been associated with a decreased progression free survival (PFS) period when studying low grade gliomas
  - Therefore, can be used to predict progresion in either biopsy proven and/or resected gliomas



A – T2WI MRI demonstrates focal area of increased signal intensity in the deep white matter of the right frontal lobe
B- Corresponding T1WI demonstrates low signal intensity in the same region
F- Thallium-201 SPECT demonstrates increased radiotracer uptake in the Corresponding region

MR spectroscopy – tumor recurrence



MRS – a brief overview

- Multivoxel spectroscopy
- Suppress water peak and allow measurements of metabolites
- Creatine – metabolism of brain energy
- Choline – in membrane. Related to cellular proliferation
- NAA – marker of neuronal integrity
- Can calculate ratios

MRS

- Tumor – usually elevated choline to creatinine ratio (demonstrated in figure). NAA peak also usually suppressed due to decreased neuronal integrity
- Radiation necrosis – suppression of the choline, creatinine and NAA peaks.

Summary

- Metabolic imaging with PET is complementary to MR imaging. MR has difficulty distinguishing recurrent tumor from radiation necrosis, particularly in those patients on Avastin
- Roles of PET imaging include:
  - Differential diagnosis
  - Treatment planning and response prediction
  - Treatment response assessment
  - PET has greater sensitivity for tumor recurrence than MR alone, especially for high grade gliomas e.g. GBM

Suggested Articles

1. Nakajima T, Kumabe T, Kanamori M, Saito R, et. al. Differential diagnosis between **radiation necrosis** and glioma progression using sequential proton magnetic resonance spectroscopy and methionine positron emission tomography.,Neurol Med Chir (Tokyo). 2009 Sep;49(9):394-401.
2. Mullins ME, Barest GD, Schaefer PW, et. al. **Radiation necrosis versus glioma recurrence: conventional MR imaging** clues to diagnosis., AJNR Am J Neuroradiol. 2005 Sep;26(8):1967-72.
3. Mullins ME, Barest GD, Schaefer PW, et. al. Radiation **necrosis versus glioma recurrence: conventional MR** imaging clues to diagnosis, AJNR Am J Neuroradiol. 2005 Sep;26(8):1967-72.
4. Terakawa Y, Tsuyuguchi N, Iwai Y, Yamanaka K, et. al. **Diagnostic accuracy** of **11C-methionine PET** for **differentiation** of recurrent brain tumors from radiation necrosis after radiotherapy., J Nucl Med. 2008 May;49(5):694-9. doi: 10.2967/jnumed.107.048082. Epub 2008 Apr 15.
5. Park KJ, Kang SH, Park DH, et. al. **Usefulness** of **thallium-201 SPECT** for **prediction** of **early** progression in low-grade astrocytomas diagnosed by stereotactic biopsy., Clin Neurol Neurosurg. 2012 Apr;114(3):223-9. doi: 10.1016/j.clineuro.2011.10.023. Epub 2011 Nov 21.
6. **Jacobs** AH, Thomas A, Kracht LW, et. al. 18F-fluoro-L-thymidine and 11C-methylmethionine as markers of increased transport and proliferation in brain tumors., **J Nucl Med**. 2005 Dec;46(12):1948-58.