MAYO CLINIC

Functional Image-Guided Intracranial Radiation Therapy

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No Disclosures

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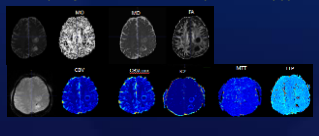
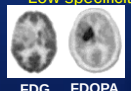
Standard Imaging for Brain Surgery/Radiotherapy: MRI

- Conventional MRI
  - T1-post Gad (enhancing/non-enhancing); disruption of BBB
  - T2 (signal abnormality + edema + treatment effect, necrosis)
- Advanced MRI sequences
  - DWI (Diffusion weighted imaging)
  - Perfusion
  - DTI (Diffusion Tensor Imaging)
  - MRS (magnetic resonance spectroscopy)

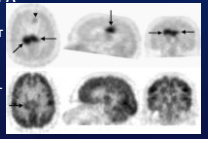


What about PET Imaging?

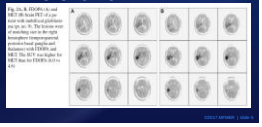
- FDG most common, and FDA approved;
  - high normal background uptake
  - Cannot detect low grade gliomas
  - Low specificity for recurrent tumors



FDG FDOPA

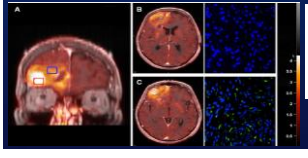


- Amino Acid (AA) PET Tracers, not FDA approved (70s, 80s, and 90s)
  - High tumor uptake to normal background in brain
  - Examples
    - C11-MET (requires on-site cyclotron, 20 min half life)
    - F18-FET
    - F18-DOPA
    - F18-Choline



How do AA PET tracers work?

- Flux of amino acids into tissue (LAT1-amino acid transporter)
- Rate of intracellular amino acid metabolism
- Independent of BBB permeability
- Expression of LAT1 is strongly correlated with FDOPA uptake in patient biopsy samples



J Neurooncol (2013) 111:11–18
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LABORATORY INVESTIGATION

The role of LAT1 in ^{18}F-DOPA uptake in malignant gliomas

Ryan S. Youland · Gaspar J. Kitange · Timothy E. Peterson · Deanna H. Pafundi · Judit A. Ramocsai · Jenny L. Pokorny · Caterina Giannini · Nadia N. Laack · Ian F. Parney · Val J. Lowe · Debra H. Brinkmann · Jann N. Sarkaria

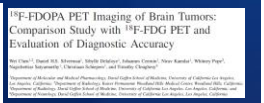
Comparison of AA PET Tracers

Table 1

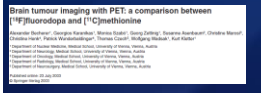
Main Advantages and Limitations of Amino Acid PET Tracers Used for Brain Tumor Imaging

PET Tracer	Advantages	Limitations
MET	Convenient synthesis Most widely tested in multiple centers Better than FDG for low-grade tumors	^{11}C labeled: only 20 min half-life Multiple metabolic pathways (protein/nonprotein) Studies mostly rely on SUVs, no kinetic analysis Glioma recurrence vs radiation injury differentiation suboptimal (~ 80%)
FET	^{18}F labeled: 110 min half-life Low uptake in inflammatory cells Measures system L AA transport: conducive to kinetic analysis, which helps grading Lack of metabolism Glioma recurrence vs radiation injury differentiation excellent (≥ 90%)	Available in limited centers only Limited information on intracranial AA metabolism Limited specificity for gliomas
FDOPA	^{18}F labeled: 110 min half-life Measures system L AA transport Better than FDG for differentiation of glioma recurrence vs radiation injury	Few studies from limited centers Most studies rely on SUVs, limited kinetic analysis
AMT	Not incorporated in proteins but measures metabolism via the immunosuppressive kynurenine pathway Studies tested SUV, kinetic parameters Can differentiate low-grade glioma types	^{11}C labeled: only 20 min half-life All brain tumor studies from a single center

AA = amino acid; AMT = ^{11}C-alpha-methyl-L-tryptophan; FDG = 2-deoxy-2[^{18}F]fluoro-D-glucose; FET = ^{18}F-fluoroethyl-tyrosine; FDOPA = ^{18}F-fluoro-L-dihydroxy-phenylalanine; MET = L-[methyl-^{11}C]methionine; PET = positron-emission tomography; SUV = standardized uptake value



^{18}F-FDOPA PET Imaging of Brain Tumors: Comparison Study with ^{18}F-FDG PET and Evaluation of Diagnostic Accuracy

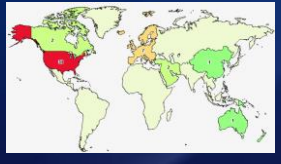


Brain tumour imaging with PET: a comparison between [^{18}F]fluorodopa and [^{11}C]methionine

- Juhasz C, Dwivedi S, Kamson DO, et al. Comparison of Amino Acid Positron Emission Tomoographic Radiotracers for Molecular Imaging of Primary and Metastatic Brain Tumor. Mol Imaging. 2014; 13. doi: 10.2310/7290.2014.00015. [PubMed: 24825818]

Pub Med/ClinialTrials.gov Search

- "PET Brain Radiotherapy"
  - 1 paper 1982, 50 papers in 2015, 35 papers so far in 2019
  - Recruiting, active, but not recruiting, completed, not yet recruiting



Prospective Trials – Mayo Clinic MN, AZ

- ***MC1078*** – Initial pilot; 21 patients (Funded by BTFC, MC Brain SPORE) *Closed
- ***IRB11-002165*** – Non-dose escalation study (Funded by BTFC, MC Brain SPORE) *Open
- ***MC1373*** – Neurosurgical FDOPA Targeting (NCI R01 CA 178200) *Closed
- ***MC1374*** – GMB Dose Escalation Study (NCI R01 CA 178200) *Closed
- ***MC167B*** – FDOPA Treatment of Recurrent High-Grade Glioma (Mayo Clinic Funding) *Open
- ***MC1774*** – Short Course Hypofractionated Proton Beam Therapy using FDOPA for Elderly Patients with Newly Diagnosed GBM (Mayo Clinic Funding) *Open

Applications in Neurosurgical Guidance/Biopsy

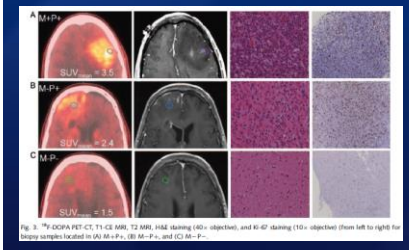


Fig. 3. ^{18}F-DOPA PET-CT, T1-CE MRI, T2 MRI, H&E staining (40× objective), and Ki-67 staining (10× objective) (from left to right) for biopsy samples located in (A) M+P+, (B) M−P+, and (C) M−P−.

Neuro-Oncology Advance Access published March 3, 2013

Biopsy validation of ^{18}F-DOPA PET and biodistribution in gliomas for neurosurgical planning and radiotherapy target delineation: results of a prospective pilot study

Deanna H. Pafundi, Nadia N. Laack, Ryan S. Youland, Ian F. Parney, Val J. Lowe, Caterina Giannini, Brad J. Kemp, Michael P. Grams, Jonathan M. Morris, Jason M. Hoover, Leland S. Hu, Jann N. Sarkaria, and Debra H. Brinkmann

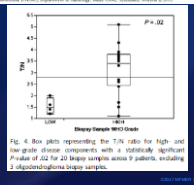
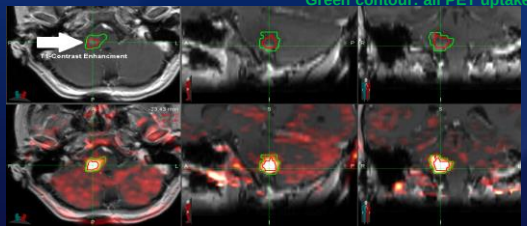


Fig. 4. Box plots representing the T/N ratio for high- and low-grade disease components with a statistically significant P-value of .02 for 20 biopsy samples across 9 patients, excluding 2 oligodendroglioma biopsy samples.

Applications in Neurosurgical Guidance/Biopsy
MC1373

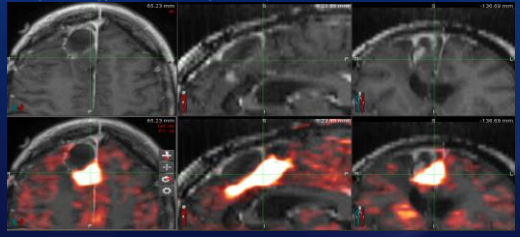
- ***Conventional MRI***: Preliminary report by neurology/neurosurgery benign or low grade (newly diagnosed, biopsy only, right inf pons)
- ***FDOPA PET imaging***: showed high grade disease (based on T/N>2.0)
- ***Final pathology***: Grade IV astrocytoma

Red contour: high grade PET
Green contour: all PET uptake



Applications in Neurosurgical Guidance/Biopsy
MC1373

- ***Conventional MRI***: No contrast enhancement (recurrent, total resection, left parietal)
- ***FDOPA PET imaging***: all PET uptake showed high grade (T/N>2.1)
- ***Final pathology***: Grade IV oligoastrocytoma



Applications in Radiotherapy: Target Delineation

- 80%-90% of tumors recur within or adjacent to primary site
- Balance treating excessive brain (in-field/local failures)
- Balance treating with escalated dose (central failures)
- AA PET Tracers
  - Identify areas of high risk disease for NCE cases
  - Increased volume to both FLAIR and resection cavity volumes
- Miwa et al. 2004: MET uptake located within 3cm of Gd
- Grosu et al. 2005: 74% pts MET outside Gd, MET up to 4.5cm beyond Gd
- Niyazi et al., 2011: FET-defined BTVs significantly > MR-defined GTVs
- Hayes et al. 2018: 83% pts FET outside FLAIR, 71% FET outside resection cavity
- Lohmann et al. 2018: 86% pts FET larger than Gd, 10% FET outside FLAIR

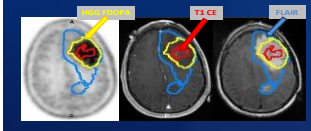
Applications in Radiotherapy: Target Delineation MC1078


Neuro-Oncology Advance Access published March 3, 2013

NEURO-ONCOLOGY

Biopsy validation of ^{18}F-DOPA PET and biodistribution in gliomas for neurosurgical planning and radiotherapy target delineation: results of a prospective pilot study

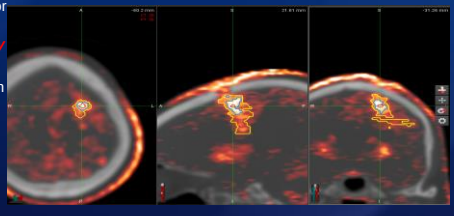
Deanna H. Pafundi, Nadia N. Laack, Ryan S. Youland, Ian F. Parney, Val J. Lowe, Caterina Giannini, Brad J. Kemp, Michael P. Grams, Jonathan M. Morris, Jason M. Hoover, Leland S. Hu, Jann N. Sarkaria, and Debra H. Brinkmann



- **For the patients with visible CE:**
  - **total volume with a PET T/N > 2.0 *outside* the CE volume ranged from 15% - 81%**
  - **high PET activity disease extended 0.5-3.5 cm beyond the CE lesion**

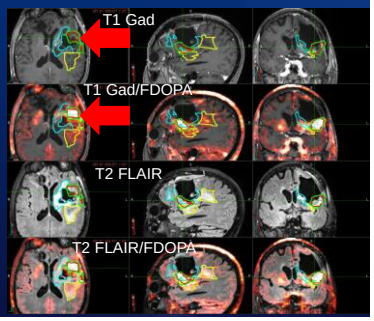
Applications in Radiotherapy: Treatment Planning (IRB 11-002165)

- ***Conventional MRI***: No contrast enhancement for neuro guidance
- ***Final pathology (Biopsy only case)***: Grade II astrocytoma; perhaps biopsy taken in a location that didn't contain HGG components
- ***FDOPA PET Imaging***: Indicates substantial HGG components (***in blue***)
- ***Rad Onc Suspicion:*** Treated patient like grade III AA



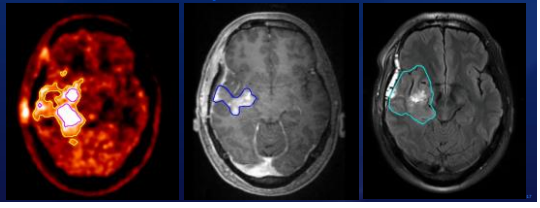
Applications in Radiotherapy: Target Delineation MC1078

Cyan = GTVhigh (Residual CE)
Yellow = GTVlow (T2 signal)
Green = Gold PET Uptake
Red = HGG Threshold



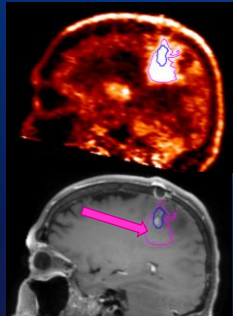
Applications in Radiotherapy: Target Delineation MC1374

- 30 MGMT unmethylated GBM patients, comparing
  - PET volumes: PET_low, PET_high
  - MR volumes: T1CE+cavity, T2 FLAIR



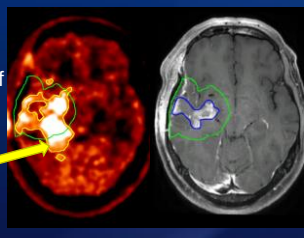
Applications in Radiotherapy: Target Delineation MC1374

- ^{18}F-DOPA-PET identified aggressive disease outside T1CE in over 2/3 of patients
  - T1CE is not sufficient to identify areas of high-grade residual tumor



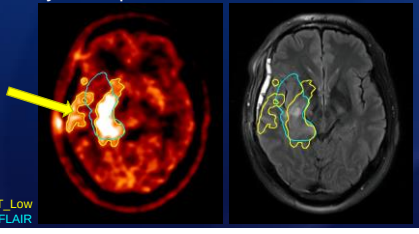
Applications in Radiotherapy: Target Delineation MC1374

- ^{18}F-DOPA-PET identified biologically active disease outside a 1cm expansion of T1CE in nearly 2/3 of patients



Applications in Radiotherapy: Target Delineation MC1374

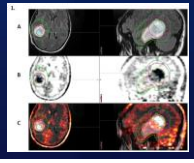
- PET_low volume extended beyond T2-FLAIR signal abnormality for all patients

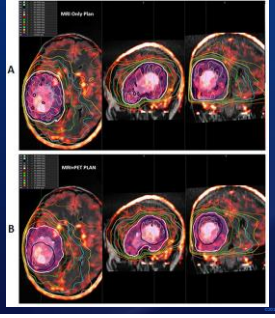


PET_Low
T2 FLAIR

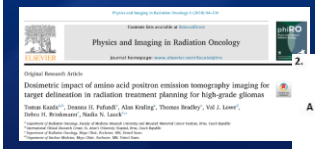
Applications in Radiotherapy: Treatment Planning

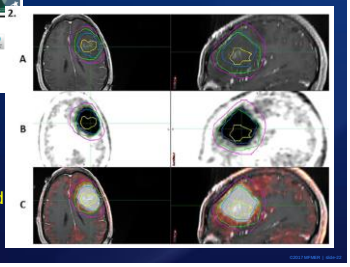
- Non-Contrast Enhancing Patients
  - Reduction in 60 Gy volume





Applications in Radiotherapy: Treatment Planning

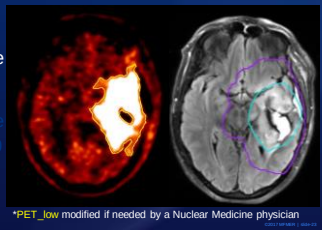




- Contrast Enhancing Patients
  - Increase in 60 Gy volume
  - Priority 1 dose constraints (brain stem, optic nerves, and chiasm) were all met even with increased volume

Applications in Radiotherapy: Treatment Planning MC1374

- 18F-DOPA PET included prospectively into target volumes for an ongoing trial
  - PET_low volume (T/N ≥1.5*) incorporated into PTV5100 cGy volume
  - PET_high volume (T/N > 2.0) incorporated into PTV6000 cGy volume
  - Dose escalation PTV7600 cGy volume targeting most aggressive disease



*PET_low modified if needed by a Nuclear Medicine physician

Applications in Radiotherapy: Treatment Planning MC1374

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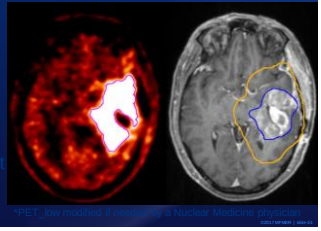

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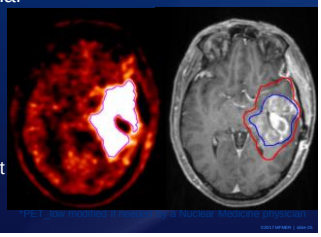


*PET_low modified if needed per a Nuclear Medicine physician

Applications in Radiotherapy: Treatment Planning

- 2016, SIB to 72 Gy; no survival benefit, acute/late toxicities not increased

Integrated boost IMRT with FET-PET-adapted local dose escalation in glioblastomas. Results of a prospective phase II study.

Piroth MD*, Pinkawa M, Holy R, Klotz J, Schaar S, Stoffels G, Galldiks N, Coenen HH, Kaiser HJ, Langen KJ, Eble MJ

- MC1374 Trial opened 12/12/2013, 77 patients accrued/available for toxicity analysis

Non-Hema AE	N (Grade 3+)
Fatigue	7
CNS necrosis	5
Weakness	3
Cognitive	3
Blurred vision	1
Optic Nerve disorder	1
Sepsis	1
Stroke/bleed	1
Vomiting	1
Nausea	1
Headache	1
Psychiatric disorder	1
Edema limb	1
Hypertension	1

Table 2: All Toxicities 2 Grade 3

	N	%
Patients with at least one:	Any	
Grade 3+ Adverse Event	A	4/42
	B	2/24
	C	5/28.1
Grade 4+ Adverse Event	B	2/8.7
Grade 3+ Hem Adverse Event	B	4/8.7
	C	1/3.6
Grade 4+ Hem Adverse Event	B	1/4.3
Grade 5+ Non-Hem Adverse Event	A	2/4.8
	B	6/26.1
	C	5/25.0
Grade 4+ Non-Hem Adverse Event	B	2/8.7

Results

- Trial opened 12/12/2013 77 patients accrued/available for toxicity analysis
  - Grade II patients (Arm A) closed due to poor accrual but included in toxicity analysis
  - Grade IV MGMT methylated (Arm B) patients included as secondary aim and for toxicity analysis
- Toxicities evaluated for safety/stopping rule
  - Grade 5 CNS necrosis 5 (4.4%) patients (Pts) (A,B); 2 patients developed symptoms that resolved in the subsequent cycle so did not count towards stopping rule
  - 1 patient with pre-existing vision dysfunction had Grade 4 optic nerve dysfunction
  - Other neurologic toxicities resolved to < grade 3 and were not counted towards stopping rule
- Other grade 3+ toxicities Table 2
  - 1 Grade 5 event(sepsis) due to temozolomide induced cytopenias
  - MGMT-methylated patients experienced higher rate of RT-related Grade 3+ AE (5 vs 1)

Applications in Radiotherapy: Post-Surgical/Post-Tx Response Assessment/Re-irradiation

- MET PET effective for differentiating recurrent metastatic brain tumor from radiation-induced changes
- Pirotte et al. 2009: For AA and GBMs, MET PET shows 80% of patients show significantly different tumor volume than T1-CE MRI alone; also showed significantly longer OS of HGG patients where no residual MET PET detected
- Suchorska et al. 2015: For GBMs, FET PET substantially larger than volume than T1-CE
- Floeth et al. 2011: Similar findings in LGG
- Galldiks et al. 2015a, Kebir et al. 2016a: FET PET distinguishing GBM pseudo-progression with diagnostic accuracy of at least 85% within 12 weeks and >12 weeks
- Galldiks et al. 2012b, Piroth et al. 2011b and 2013: FET PET in GBM with early changes 6-8 weeks after postoperative radiochemo (decrease in tumor/brain ratio >10% sig. long DFS and OS

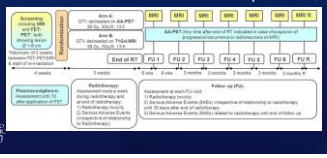
NeuroImage: Clinical

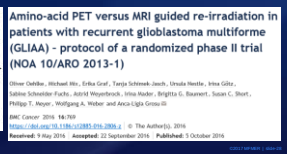
The use of amino acid PET and conventional MRI for monitoring of brain tumor therapy

- Terakawa et al. 2008: MET PET after SRS, 70%-80% spec. and sens. distinguishing recurrent metastatic versus radiation-induced changes
- Lizarraga et al. 2014: FDOPA PET 80%-85% sens. and spec. after SRS
- Cicone et al. 2015: Accuracy of FDOPA 91% versus perfusion MRI 76% identifying mets
- Galldiks et al. 2012c: FET PET similar

Applications in Radiotherapy: Post-Surgical/Post-Tx Response Assessment/Re-irradiation

- Updated RANO criteria is current standard for tumor progression to include "significant" enlarging areas of non-enhancing tumor on T2W and FLAIR imaging, along with T1W-CE
- Re-irradiation requires small margins to spare normal brain
- GLIAA Trial – 200 randomized patients, FET PET





Amino-acid PET versus MRI guided re-irradiation in patients with recurrent glioblastoma multiforme (GLIAA) - protocol of a randomized phase II trial (NOA 10/ARO 2013-1)

Oliver Oehlke , Michael Mix , Erika Graf , Tanja Schimek-Jasch , Ursula Nestle , Irina Gilbz , Sabine Schneider-Fuchs , Astrid Weyerbrock , Irina Hader , Brigitta G. Baumert , Susan C. Short , Philipp T. Meyer , Wolfgang A. Weber and Anca-Ligia Grosu

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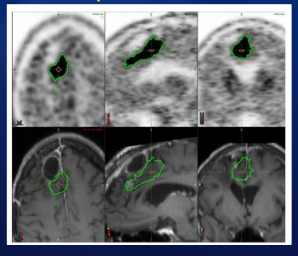
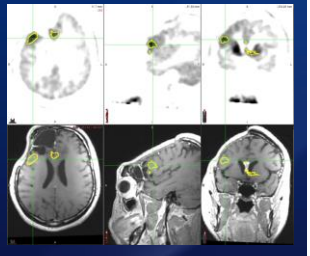
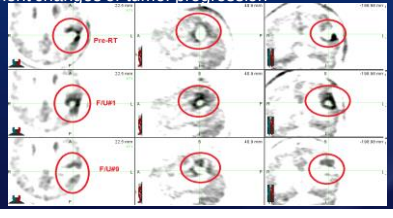
Applications in Radiotherapy: Post-Surgical/Post-Tx Response Assessment/Re-irradiation





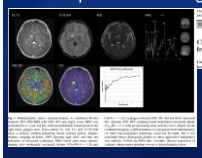
Applications in Radiotherapy: Post-Surgical/Post-Tx Response Assessment/Re-irradiation: MC1374

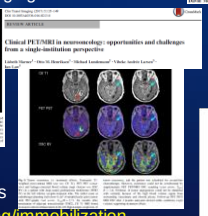
- ***Conventional MRI***: Slowly increasing enhancement over 12 months
- ***FDOPA PET imaging***: Shows *decreasing* FDOPA uptake
- ***Progression?***: Med Onc still on the fence; Neuroradiology still undecided if post-treatment changes or tumor progression



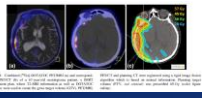
PET/MRI Applications

- Multi-parametric imaging

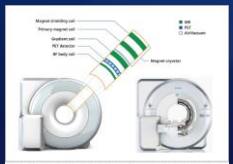




Clinical PET/MRI in neurooncology: opportunities and challenges from a single-institution perspective

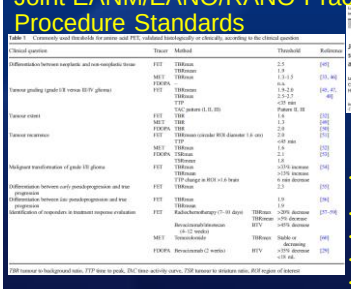


Potential role of PET/MRI in radiotherapy treatment planning



- Technical challenges
  - Patient positioning/immobilization
  - Quantitative metrics standards
  - Attenuation correction factors

Joint EANM/EANO/RANO Practice Guidelines/SNMMI Procedure Standards



Joint EANM/EANO/RANO practice guidelines/SNMMI procedure standards for imaging of gliomas using PET with radiolabelled amino acids and [18F]FDG: version 1.0

Aim

The aim of these standards/guidelines is to assist nuclear medicine practitioners in recommending, performing, interpreting and reporting the results of brain PET imaging in patients with glioma.

- Personnel qualifications and responsibilities
- Patient prep
- Radiopharm. and doses
- Acquisition protocols
- Equip. specs
- QC/QA/Safety
- Interpretation of PET data

Wrap up

- Extensive literature data showing AA PET tracers for intracranial tumors:
  - Identifying disease that extends beyond Gd and FLAIR
  - Identifying the most aggressive regions in these heterogeneous tumors
  - Neurosurgical biopsy and resection guidance/post-surgical
  - Treatment planning without increased toxicities (increased volume, decreased volume, dose-escalation, re-irradiation)
  - Identifying progression from psuedoprogression
- Increase AAPM/SNMMI Collaborations
  - Identifying the unmet needs in Radiation Oncology applications with these AA tracers
  - Which AA tracer? FDA approval?
  - Establish standards
    - QA
    - Imaging acquisition protocols
    - Tumor delineation (e.g. thresholding, manual/automatic contouring)
    - Optimal scanning time (during treatment/after treatment) – interpretation
  - Larger cohort/multi-institutional clinical trials needed

SNMMI SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING

SNMMI SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING CLINICAL TRIALS NETWORK

AMERICAN ASSOCIATION of PHYSICISTS IN MEDICINE Improving Health Through Medical Physics