Functional Image-Guided Intracranial Radiation Therapy

D. Pafundi, Ph.D., DABR
Assistant Professor, Mayo Clinic

2019 Annual AAPM Joint AAPM-SNMMI Symposium: Nuclear Medicine Theranostics and Functional Image-Guided Radiation Therapy for Precision Oncology

No Disclosures

Acknowledgements

- Radiation Oncology
  - Nadia Laack, M.D.
  - Olivia Scoleri, M.D.
  - Elizabeth Yan, M.D.
  - Padraic Warren, M.D.
  - Mark Zakhary, Ph.D.
  - Yan Zhang, Ph.D.
  - Maasa Seaberg, Ph.D.
  - Jann Sarkaria, M.D.
  - Diane Vogen
  - Tammy Lenz

- Study Coordinators
  - Claire Vagen
  - Nancy Leitz

- Statistics
  - Keith Anderson

- Nuclear Medicine
  - Charleen Hunt, M.D.
  - Val Lowe, M.D.
  - Paul Kemp, Ph.D.
  - Mare Jacobson
  - Terry Simber

- Neuroradiology/Neuro Tech
  - Ian Parney, M.D.
  - Teresa Burris, M.D.
  - Laura Haugen
  - Jennifer Winkler
  - Scott Studebaker

- MR
  - Tim Kaufmann, M.D.
  - Kieran McGee
  - Erin Gray

- Pathology
  - Caterina Giannini, M.D.

Funding

- National Cancer Institute R01 CA178200
- Mayo Clinic NIH Spore grant CA128561
- Brains Together for a Cure
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
- 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
Comparison of AA PET Tracers

**Table 1**

<table>
<thead>
<tr>
<th>PET Tracer</th>
<th>Efficiency</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET</td>
<td>High</td>
<td>Moderate</td>
</tr>
<tr>
<td>FDOPA</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>[18F]FDG</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>[11C]Acetate</td>
<td>Low</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

**[18F]FDOPA PET Imaging of Brain Tumors: Comparison Study with [18F]FDG PET and Evaluation of Diagnostic Accuracy**

Pub Med/ClinicalTrials.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
- **IRB11-003165** – 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

- **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

- **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

- 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 indicated 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
Cyan = GTV(high Residual CE)
Yellow = GTV(low T2 signal)
Green = Gold PET Uptake
Red = HGG Threshold

Applications in Radiotherapy: Target Delineation
MC1078

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

Applications in Radiotherapy: Target Delineation
MC1374

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

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

• 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**

- **18F-DOPA PET** included prospectively into target volumes for an ongoing trial
  - PET_low volume \( (T/N \geq 1.5) \) 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

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

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

Applications in Radiotherapy: Treatment Planning

- **Post-Surgical/Post-Tx Response Assessment/Re-irradiation**
  - MET PET effective for differentiating recurrent metastatic brain tumor from radiation induced changes
  - Priebe et al. 2009: For AA and GBMs, MET PET shows 80% of patients showed significantly different tumor volume than T1-CE MRI alone; also showed significant uptake in 63% of HGG patients where no residual MET PET detected
  - Suchorska et al. 2015: For GBMs, FET PET substantially target their volume than T1-CE
  - Fiseth et al. 2011: Similar findings in LG
  - Galldiks et al. 2015a, Kabir 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. 2013b, Priebe et al. 2011a and 2013: PET PET in GBM with early changes 6-8 weeks after postoperative radiochemo (decrease in tumor/brain ratio >5% sig. long DFS and OS
  - 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
- GLI AA Trial – 200 randomized patients, FET PET

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

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

- Personnel qualifications and responsibilities
- Patient prep
- Radiopharmaceuticals and doses
- Acquisition protocols
- Equipment specifications
- 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 pseudoprogression

- 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