A pilot study of the utility of $^{18}$F-FDOPA-PET for neurosurgical planning and radiotherapy target delineation in glioma patients: biopsy validation of $^{18}$F-FDOPA-PET uptake and biodistribution in brain tumors

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A pilot study of utility of $^{18}$F-FDOPA-PET for neurosurgical planning and radiotherapy target delineation in glioma patients: biopsy validation of $^{18}$F-FDOPA-PET uptake and biodistribution in brain tumors

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Glioma Patients

- Malignant gliomas most common primary brain tumor in adults
- 3 types (WHO) [low grade(I/II) / high grade(III/IV)]
  - Astrocytomas
  - Oligodendrogliomas
  - Mixed oligoastrocytomas
- Glioblastoma multiforme (grade IV astrocytoma) is most common glioma
  - Median 12 to 15 months survival
- Low-grade gliomas
  - > 7 years median survival
- Treatment
  - Surgical resection/biopsy (if eligible)
  - Radiation therapy/Chemotherapy (TMZ)
    - Low grade 45 – 50.4 Gy (IMRT or 3D Conformal)
    - High grade 50.4 – 60 Gy (opt. boost; IMRT or 3D conformal)
- Recurrences (in order of frequency)
  - Central, distant, in field, marginal
Image-Guidance for Surgery and RT

• Gold Standards for Image-Guided Biopsy/Resection and RT
  • MRI (T1 with Gad/T2 weighted and FLAIR)
  • CT (Radiotherapy)

• Surgical Challenges
  • Tumor locations in eloquent brain
  • Tumor heterogeneity (grading) – biopsy only cases
  • Non-enhancing regions (tumor extent)

• Radiotherapy Challenges
  • T2 signal changes – tumor or edema? (Non-uniformity)
  • Inter-observer variability using MRI or CT alone
  • How does biological imaging information change treatment volumes?
    • Inter-observer variability?
    • Tumor extent?
    • Boost volumes/location?
Biological-Based Imaging - PET

**Metabolic-Based Tracer**
- Fluoro-2-deoxy-D-glucose (\(^{18}\)F-FDG)
- Enhanced glucose metabolism in tumors
- Low tumor:background ratio in brain
- Uptake is non-specific (inflammatory lesion uptake)
  - False positives (low specificity)
- Limited role in distinguishing tumor recurrence from radionecrosis

**Amino Acid-Based Tracers**
- \([^{11}\text{C-methyl}]-\text{methionine (}^{11}\text{C-MET)}\) *most studied*
  - \(^{11}\text{C} \) Short physical half-life (~20 minutes)
  - Cannot label with \(^{18}\text{F} \) (~110 minutes)
- 3, 4-dihydroxy-6-[\(^{18}\text{F}\)]-fluoro-L-phenylalanine (\(^{18}\text{F-FDOPA}\))
- Amino acid transport increased in malignant transformations
  - Flux of amino acids into tissue (LAT1-amino acid transporter)
  - Rate of the intracellular amino acid metabolism
- High tumor:background ratio

http://www.med.harvard.edu/JPNM/TF00_01/Sept26/WriteUp.html
Specific Aims

• 1.1. Determine correlation between $^{18}$F-FDOPA PET activity, MRI contrast enhancement, and glioma biopsy histopathology

• 1.2. Compare radiotherapy target volume delineation with and without $^{18}$F-FDOPA PET metabolic imaging information to determine role of metabolic imaging in radiotherapy treatment planning
## Results – Overall Patient Demographics/Pathology

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Gender (M/F)</th>
<th>Location</th>
<th>WHO Grade</th>
<th>Histological Type</th>
<th>Biopsy Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDOPA01</td>
<td>27</td>
<td>M</td>
<td>Right frontal</td>
<td>3</td>
<td>Astrocytoma</td>
<td>(2) M-P+, M-P-</td>
</tr>
<tr>
<td>FDOPA02</td>
<td>58</td>
<td>M</td>
<td>Right temporal</td>
<td>3</td>
<td>Oligoastrocytoma</td>
<td>(3) M-P+1, M-P+2, M-P-</td>
</tr>
<tr>
<td>FDOPA03</td>
<td>21</td>
<td>M</td>
<td>Left frontal</td>
<td>4</td>
<td>Astrocytoma (GBM)</td>
<td>(2) M-P+, M-P+</td>
</tr>
<tr>
<td>FDOPA04</td>
<td>20</td>
<td>M</td>
<td>Right temporal</td>
<td>3</td>
<td>Astrocytoma</td>
<td>(2) M-P+, M-P-</td>
</tr>
<tr>
<td>FDOPA05</td>
<td>32</td>
<td>M</td>
<td>Right temporal</td>
<td>3</td>
<td>Astrocytoma</td>
<td>(3) M-P+1, M-P+2, M-P-</td>
</tr>
<tr>
<td>FDOPA06</td>
<td>69</td>
<td>M</td>
<td>Right frontal</td>
<td>4</td>
<td>Astrocytoma (GBM)</td>
<td>(3) M-P+, M-P+, M-P-</td>
</tr>
</tbody>
</table>

- **M+** = T1-gad enhancing
- **M-** = T1-gad non-enhancing
- **P+** = PET Positive
- **P-** = PET Negative
Results – Histology and Contours
Case 5 – No CE

- **M-P+1 (SUVmax):** Grade 3 Astrocytoma *High cellularity, highly infiltrative, more pleomorphic than +2*
- **M-P+2:** Grade 3 Astrocytoma *High cellularity, solid tumor, highly infiltrative*
- **M-P-:** Grade 3 Astrocytoma *Isolated tumor cells, low cellularity*
Summary – Histology/Contours

**Pathology**
- FDOPA + samples inside T1-gad, + disease (M+P+)
- FDOPA + samples outside T1-gad, + disease (M-P+)
- FDOPA - samples inside FLAIR/outside T1-gad, + disease (M-P-)
- FDOPA - sample outside FLAIR, + disease (1 sample)
- Slight “verbal/visual” correlations between SUVmax and pathology expression
- SUVmax locations indicative of final disease pathology for grading

**Contouring**
- T1-gad not centrally located within the FDOPA
- FDOPA SUVmax not centrally located within T1-gad or within the FDOPA contour
- % FDOPA Volume (Gold Standard) Outside T1-gad
  - 3 cases with CE – Avg. 77.8% (61.3% - 93.1%)
- % FDOPA Volume (Gold Standard) Outside FLAIR
  - Avg. 9.5% (0.3% - 29.1%)
  - Range: 0.5x – 2.9x (3 RadOncs)
Results – Diagnostic Thresholds
Preliminary ROC Data

Comparison of SUVmax uptake ratios for biopsies and PET-based contours.

<table>
<thead>
<tr>
<th></th>
<th>T/N</th>
<th>T/S</th>
<th>T/W</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy-All Grades</td>
<td>&gt; 0.7</td>
<td>&gt; 0.7</td>
<td>&gt; 0.9</td>
</tr>
<tr>
<td>Biopsy-Low Grade</td>
<td>0.7-1.1</td>
<td>0.7-1.1</td>
<td>1.1-1.8</td>
</tr>
<tr>
<td>Biopsy-High Grade</td>
<td>0.9-2.3</td>
<td>0.9-2.4</td>
<td>0.9-2.6</td>
</tr>
<tr>
<td>PET Contour Only</td>
<td>1.0-2.3</td>
<td>1.0-2.4</td>
<td>1.7-2.6</td>
</tr>
<tr>
<td>PET Contour Outside T1</td>
<td>2.0-2.3</td>
<td>2.0-2.3</td>
<td>2.2-2.5</td>
</tr>
<tr>
<td>PET Contour Outside T2</td>
<td>0.9-2.3</td>
<td>0.9-2.3</td>
<td>1.2-2.4</td>
</tr>
</tbody>
</table>

- **T** = tumor
- **N** = normal contralateral brain (centrum semiovale – whole)
- **W** = white matter of cerebral hemispheres (centrum semiovale – only)
- **S** = striatum

- **Pathology+FDOPA Contours (preliminary ROC analysis)**
  - FDOPA uptake found outside T1-gad is disease
  - FDOPA uptake found outside FLAIR is disease
Results – Margin Analysis
Case 3
Summary - Margins

• Current SOC
  • Non-enhancing
    • LGG – 1 cm expansion on FLAIR MRI; No boost
    • HGG (III) – 1 cm expansion on FLAIR MRI; Boost = FLAIR MRI
    • HGG (IV) – 1 cm expansion on FLAIR MRI; Boost = 0.5 expansion on FLAIR MRI
  • Enhancing
    • 1 cm expansion on FLAIR and 1 cm expansion on T1-Gad (Boolean)
    • Boost = 1 cm expansion on T1-gad

• Margins – Our Study
  • 1.5 cm – 5.0 cm expansion of T1-Gad across all RadOncs to include FDOPA (all RadOncs)
Summary - Overall

• 6 patients
  • Final path HGG – All patients
  • No T1-gad enhancement seen in any grade 3 patients
    • Difficult for surgical biopsy (grading)
    • Difficult for surgical resection (tumor extent)
    • Difficult for radiotherapy target delineation
  • Pathology on all M-P+ samples confirmed HGG
  • SUVmax samples predicted final pathology grade in all cases
  • Initial correlation with biopsy samples indicates all regions of FDOPA are positive for disease (outside T1-gad and T2/FLAIR)
    • Foundation for auto-thresholding techniques for FDOPA
  • Further investigation into significant interobserver variability in FDOPA, FLAIR, and T1-Gad contouring

• FDOPA always larger than T1-gad; always present when no enhancement
  • Investigate increase size of boost volume in enhancing cases
  • Investigate create boost volume in non-enhancing LGG
  • Investigate decrease size of boost volume in non-enhancing HGG
Thanks for your attention!