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


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Background. Delineation of glioma extent for surgical or radiotherapy planning is routinely based on MRI. There is increasing awareness that contrast enhancement on T1-weighted images (T1-CE) may not reflect the entire extent of disease. The amino acid tracer $^{18}$F-DOPA (3,4-dihydroxy-6-$^{18}$F fluoro-L-phenylalanine) has a high tumor-to-background signal and high sensitivity for glioma imaging. This study compares $^{18}$F-DOPA PET against conventional MRI for neurosurgical biopsy targeting, resection planning, and radiotherapy target volume delineation.

Methods. Conventional MR and $^{18}$F-DOPA PET/CT images were acquired in 10 patients with suspected malignant brain tumors. One to 3 biopsy locations per patient were chosen in regions of concordant and discordant $^{18}$F-DOPA uptake and MR contrast enhancement. Histopathology was reviewed on 23 biopsies. $^{18}$F-DOPA PET was quantified using standardized uptake values (SUV) and tumor-to-normal hemispheric tissue (T/N) ratios.

Results. Pathologic review confirmed glioma in 22 of 23 biopsy specimens. Thirteen of 16 high-grade biopsy specimens were obtained from regions of elevated $^{18}$F-DOPA uptake, while T1-CE was present in only 6 of those 16 samples. Optimal $^{18}$F-DOPA PET thresholds corresponding to high-grade disease based on histopathology were calculated as T/N > 2.0. In every patient, $^{18}$F-DOPA uptake regions with T/N > 2.0 extended beyond T1-CE up to a maximum of 3.5 cm. SUV was found to correlate with grade and cellularity.

Conclusions. $^{18}$F-DOPA PET SUV$_{max}$ may more accurately identify regions of higher-grade/higher-density disease in patients with astrocytomas and will have utility in guiding stereotactic biopsy selection. Using SUV-based thresholds to define high-grade portions of disease may be valuable in delineating radiotherapy boost volumes.

Keywords: $^{18}$F-DOPA PET, glioma target delineation, image-guided biopsy planning, image-guided radiation therapy, PET-MRI image registration.

MRI is currently the gold standard for image-guided neurosurgical resection or biopsy and target volume delineation in radiation therapy (RT) planning of brain tumors. MRI findings typically include a heterogeneous area of contrast enhancement (CE) of solid tumor surrounded by a large area of vasogenic edema. However, anaplastic tumors can present with non–contrast enhancement (NCE) of lesions on MRI, which makes surgical planning for biopsy or resection and RT delineation of high-grade tumor volumes challenging. Dependence on CE from MRI alone can lead to inaccurate grading of the tumor, insufficient resection of highly aggressive disease, and undertreatment in areas of aggressive disease. Reliance on the T2 signal abnormality, which
includes a heterogeneous mixture of tumor and normal brain, can lead to unnecessary RT of normal brain. PET provides visual information about biological processes and shows promise for improving tumor delineation accuracy for RT and surgical planning of gliomas, which would positively impact accurate assessment of prognosis and improved treatment efficacy.

In contrast to the high glucose metabolism in normal brain from 18-fluoro-deoxyglucose (18F-FDG) PET, amino acid PET tracers, such as 3,4-dihydroxy-6-[18F] fluoro-L-phenylalanine (18F-DOPA), demonstrate high uptake in tumor tissue and low uptake in normal brain tissue.\(^1\)\(^-\)\(^3\) Amino acid transport is generally increased in malignant transformation due to the flux of the amino acid to the tissue, the intrinsic activity of the amino acid transporter, and the rate of the intracellular amino acid metabolism.\(^4\)\(^-\)\(^5\) Limited studies evaluating the sensitivity of 18F-DOPA indicated that although 18F-FDG PET demonstrated a higher absolute standard uptake value (SUV) than 18F-DOPA, the sensitivity for detection of low- or high-grade tumors was 96% for 18F-DOPA vs 61% for 18F-FDG.\(^2\)\(^,\)\(^6\)

The objectives of this study were to compare pathology findings from biopsies taken in concordant and discordant regions of T1-weighted CE and 18F-DOPA uptake, to determine correlations of high-grade and low-grade pathology components with 18F-DOPA PET SUV, and from these analyses to develop 18F-DOPA PET thresholds to guide clinical decision making and RT target delineation.

**Materials and Methods**

**Patients**

Ten patients (mean age ± SD, 40.8 ± 18.9 y) with newly diagnosed or recurrent brain tumors received stereotactic tumor resection or biopsy under MRI guidance with registered 18F-DOPA PET at the Mayo Clinic, Rochester, between October 2010 and September 2011. Approval for this prospective study was obtained from the Mayo Clinic Institutional Review Board. Written informed consent was obtained for each patient prior to enrollment through Mayo Clinic study coordinator personnel.

**18F-DOPA PET/CT**

PET was performed on a GE Discovery 690 PET/CT system. 18F-DOPA was injected intravenously at a dose of 5 mCi ± 10%. A CT scan was acquired, and the PET scan was started 10 min after tracer injection. PET sinograms were reconstructed with a fully 3D ordered-subset expectation maximization algorithm consisting of 3 iterations with 36 subsets into a 300-mm field of view with a pixel size of 1.17 mm and slice thickness of 3.27 mm.

**Stereotactic Craniotomy for Resection or Biopsy**

Patients underwent either a craniotomy with full or partial resection or a stereotactic biopsy due to the location of the tumor in eloquent brain or presence of functioning motor cortex neurons in the tumor itself. Prior to neurosurgery, MRI scans (GE Signa HDxt 1.5T) were acquired including a 3D T1-weighted spoiled gradient series (repetition time/echo time/number of excitations = 20 ms/6 ms/1) after administration of gadolinium–diethylenetriamine pentaacetic acid contrast and either a 2D T2-weighted fast spin echo series (4000/106/2) or a T2-weighted fluid-attenuated inversion recovery (FLAIR) series (11 002/154/1) with contiguous 3-mm-thick slices (field of view 24 × 24 cm, matrix size 256 × 256).

The 18F-DOPA PET scan was rigidly registered to the T1 MRI scan using MIM Maestro software. The registered PET images were transferred to the Stealth Station Neuronavigation System (Medtronic Sofamor Danek). During planning prior to resection or biopsy, each of the following was sought, per protocol, for potential biopsy locations: a T1-CE and PET avid region (M+P+), a T1-NCE and PET avid region (M−P+), a region with T1-CE but without visible PET uptake (M+P−), and a T1-NCE region without visible PET uptake (M−P−). In our cohort, we did not find any visually apparent or biopsy-amenable regions with T1-CE but without visible PET uptake (M+P−). In cases without T1-CE, stereotactic biopsy samples were based on locations with various 18F-DOPA uptake levels. Furthermore, the biopsy locations and number of biopsy samples planned per patient were selected only if perceived safe by the operating neurosurgeon (ie, not in eloquent parts of brain or in proximity to blood vessels, functioning motor cortex neurons within the tumor based on motor mapping, etc). For patients undergoing resection, 1–3 simulated stereotactic biopsy sample locations, ~1 cm\(^2\) in size, were planned and acquired during the resection. For patients receiving only a stereotactic biopsy, 3 locations with various PET SUVs were targeted along a single trajectory. Table 1 provides demographic information and the acquired sample identification for each patient. Figure 1 illustrates Stealth screen captures with blue needle intersections indicating planned biopsy locations on trajectory views of 18F-DOPA PET overlaid on T1-CE MRI, as well as axial PET-CT and T1-CE MRI with a 5-mm radius contour around the corresponding Stealth biopsy coordinate location. The PET color maps show varying degrees of intensity, which are representative of the SUV (ie, a brighter region corresponds to a higher SUV). Figure 1A was planned for a biopsy location with T1-CE and PET avidity (M+P+), while Fig. 1B was planned for a biopsy location with neither T1-CE nor PET avidity (M−P−).

**Histopathology and Immunohistochemistry**

Each tissue sample from concordant and discordant MRI and PET locations was processed for
histopathology and graded independently, using the WHO grading system for central nervous system tumors by an expert neuropathologist blinded to radiologic imaging using hematoxylin and eosin (H&E) stain. For patients with high- and low-grade disease components, final diagnosis was based on the highest-grade component. Ki-67 antigen staining (Dako) was done with a Dako autostainer by the Mayo Clinic Tissue Acquisition and Cell Molecular Analysis facility and quantitated by digital image analysis. The average cellularity and average Ki-67 index were calculated based on a minimum of 3 digital images per sample and over 1000 total nuclei. Slides were viewed on an Axioplan2 upright microscope at 100× and 400× magnification using a 10× or 40× objective lens. For histopathological analysis, images were captured with an

<table>
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<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, y</th>
<th>Surgical Location</th>
<th>WHO Grade</th>
<th>Histologic Type</th>
<th>Newly Diagnosed or Recurrent</th>
<th>Surgical Type</th>
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<td>Resection</td>
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<td>Biopsy</td>
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<td>Astrocytoma</td>
<td>Newly diagnosed</td>
<td>Resection</td>
</tr>
</tbody>
</table>

Abbreviation: GBM, glioblastoma multiforme.

Fig. 1. Screen capture of biopsy planning using the registered 18F-DOPA PET and T1-CE MRI in the Stealth Neuronavigation System for blue needle locations (left), MiMi PET-CT Fusion (middle), and T1-MRI (right) at (A) M+P+ (red circle) and (B) M−P− (green circle).
AxioCam color camera (Carl Zeiss) attached to the microscope with a 0.63× C mount. To assess cellularity, H&E-stained slides were digitally imaged using a low-power (10×) objective, and the ratio of total nuclear area to total cellular area was calculated using KS 300 software (Carl Zeiss). The proportion of Ki-67–stained nuclei to total number of nuclei was calculated (Ki-67 index) using the same objective and imaging software.

Image Analysis
A 5-mm radius contour was created around each coordinate point within MIM Maestro to account for the biopsy sample size as well as uncertainties in the physical biopsy volume and stereotactic biopsy coordinates. The normal reference brain volume was defined by contouring the contralateral normal brain tissue at the level of the centrum semiovale, the normal striatum, and the normal white matter. Image analysis for each biopsy region of interest was then performed using tumor uptake ratios. Ratios of maximum tumor SUV (SUV$_{\text{max}}$) to mean SUV (SUV$_{\text{mean}}$) of the contralateral normal brain tissue (T/N) were then correlated with the pathology to develop PET thresholds for high-grade disease. An experienced nuclear medicine physician and experienced neuroradiologist contoured the abnormal $^{18}$F-DOPA PET and the T1- and T2-weighted MRI volumes, respectively, and these were defined as the gold standard volumes. The derived PET thresholds were then applied to the $^{18}$F-DOPA PET images to determine the volume of high-grade disease relative to total contoured PET volume and relative to the discordant PET, T1-CE, and T2-weighted MRI volumes.

Statistics
Analysis was performed using JMP 9 software (SAS Institute). Comparisons were made between detection of high-grade gliomas (HGGs) and low-grade gliomas (LGGs) based on visual assessment of T1-CE with MRI and $^{18}$F-DOPA positivity at each biopsy location. Differences in detection of tumor grade with $^{18}$F-DOPA SUV$_{\text{max}}$ and T/N ratio were assessed based on 1-way ANOVA and nonparametric comparisons using the Wilcoxon method. Correlations of cellularity and Ki-67 as continuous variables with quantitative $^{18}$F-DOPA PET SUV$_{\text{mean}}$ were tested by linear regression analysis. $P < .05$ was considered statistically significant.

Results
Pathology and Visual-based Imaging Correlations
Pathology confirmed glioma in all 10 patients. $^{18}$F-DOPA uptake was seen in 9 patients (90%), while T1-CE was present in only 6 patients (60%). $^{18}$F-DOPA uptake was detected in all 8 pathologically confirmed HGGs and in 1 of 2 pathologically confirmed LGGs, while T1-CE was detected in 6 (75%) HGGs and in 0 LGGs. A total of 23 stereotactic biopsy samples were removed and classified as astrocytoma ($n = 16$, 69.6%), oligoastrocytoma ($n = 4$, 17.4%), oligodendroglioma ($n = 2$, 8.7%), or no disease ($n = 1$, 4.3%). Each biopsy sample was graded independently and classified as WHO grade II ($n = 6$, 26.1%), WHO grade III ($n = 8$, 34.8%), WHO grade IV ($n = 8$, 34.8%), or no disease ($n = 1$, 4.3%, sample from oligodendroglioma patient). Table 2 provides a summary of the biopsy results for each sample obtained in concordant and discordant PET and MR regions. As expected, CE was not seen on MRI for any LGG biopsy sample. However, $^{18}$F-DOPA uptake was associated with 3 of 6 LGG biopsy samples: 2 oligodendroglioma and 1 astrocytoma. Thirteen of 16 (81%) high-grade biopsy specimens were obtained from regions of elevated $^{18}$F-DOPA uptake, while T1-CE was present for only 6 of those 16 samples (38%). Based on the 23 biopsy samples, $^{18}$F-DOPA PET had a higher sensitivity (72.7% vs 27.3%) and negative predictive value (14.3% vs 5.9%) compared with T1-CE MRI. The specificity and positive predictive value for both imaging modalities were 100%. The overall accuracy for the detection of malignant glioma was higher for $^{18}$F-DOPA (73.9%) than for T1-CE MRI alone (30.4%).

Histopathology and Immunohistochemistry With $^{18}$F-DOPA PET SUV Parameters
The $^{18}$F-DOPA PET contours drawn for the 9 of 10 patients with uptake had an SUV$_{\text{max}}$ of 4.4 ± 1.4 (range: 2.0–6.1) and an SUV$_{\text{mean}}$ of 2.7 ± 0.7 (range: 1.6–3.6). Twenty-two of 23 biopsies were positively confirmed for glioma based on pathology. Table 3 shows the average, standard deviation (SD), and minimum and maximum SUV$_{\text{max}}$ and SUV$_{\text{mean}}$ for biopsy samples with confirmed glioma. The grade II oligodendroglioma sample taken from the region of highest uptake had the highest SUV$_{\text{max}}$ and SUV$_{\text{mean}}$: 6.2 and 5.1, respectively, compared with any grade IV (SUV$_{\text{max}}$ = 5.0, SUV$_{\text{mean}}$ = 4.0), grade III (SUV$_{\text{max}}$ = 3.3, SUV$_{\text{mean}}$ = 2.6), or grade II (SUV$_{\text{max}}$ = 1.9, SUV$_{\text{mean}}$ = 1.6) astrocytoma sample taken from the region of highest uptake. Without the oligodendroglioma biopsy samples, the SUV$_{\text{max}}$ in grade II samples was reduced to an average of 1.6 ± 0.3 (range: 1.2–1.9, $n = 4$). A correlation was found between SUV$_{\text{max}}$ and tumor grade across biopsy samples excluding oligodendrogliomas ($P = .0005$) (Fig. 2), with a statistically significant difference found between grade II and grade IV disease ($P = .008$) and between grade III and grade IV ($P = .024$), but no difference between grade II and grade III ($P = .174$). $^{18}$F-DOPA PET SUV$_{\text{max}}$ is a parameter that can predict tumor grade. However, additional low-grade samples are needed to determine any significance between grade II and grade III disease.

Correlations of cellularity and Ki-67 as continuous variables with quantitative $^{18}$F-DOPA PET SUV$_{\text{mean}}$ were tested using linear regression analysis. Excluding the 3 oligodendroglioma biopsy samples, a significant correlation was found between $^{18}$F-DOPA SUV$_{\text{mean}}$.
and cellularity ($P = .01$), and approaching significance between SUV$_{\text{mean}}$ and Ki-67 ($P = .053$). Figure 3 illustrates corresponding imaging and pathological results for stereotactic biopsy samples for an M$+P+$ region (blush of CE), M$+P-$ region, and an M$-P-$ region. Registered $^{18}$F-DOPA PET-CT, T1-CE MR, and T2 MR images are shown (Fig. 3, left to right), overlaid with a 5-mm radius region of interest about the stereotactic biopsy coordinate location; for each sample location, digital images for staining by H&E (40× objective) and Ki-67 (10× objective) are shown, where visual decrease in cellularity (40.9%, 16.9%, and 5.1%) and decrease in positive Ki-67 staining (29.5%, 28.9%, and 0.4%) with decreasing SUV$_{\text{mean}}$ (3.5, 2.4, and 1.5) are evident. The significant correlation of $^{18}$F-DOPA PET mean uptake with cellularity provides a noninvasive quantification of these parameters.

Table 2. A summary of biopsy results for each sample

<table>
<thead>
<tr>
<th>Patient</th>
<th>Location</th>
<th>Sample</th>
<th>WHO Grade</th>
<th>Histologic Type</th>
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<tbody>
<tr>
<td>FDOPA01</td>
<td>Right frontal</td>
<td>M$+P+$</td>
<td>II</td>
<td>Astrocytoma</td>
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<tr>
<td>FDOPA02</td>
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<td>Oligoastrocytoma</td>
</tr>
<tr>
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<td>Oligoastrocytoma</td>
</tr>
<tr>
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<td>III</td>
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<tr>
<td>FDOPA06</td>
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<td>M$+P+$</td>
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<td>Astrocytoma (GBM)</td>
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<td>M$-P-$</td>
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<td>Astrocytoma</td>
</tr>
</tbody>
</table>

Abbreviation: GBM, glioblastoma multiforme.

Table 3. SUV$_{\text{max}}$ and SUV$_{\text{mean}}$ statistics for the biopsy samples

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<th></th>
<th>Average</th>
<th>SD</th>
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<th>Max</th>
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<td>SUV$_{\text{mean}}$</td>
<td>SUV$_{\text{max}}$</td>
<td>SUV$_{\text{mean}}$</td>
</tr>
<tr>
<td>All positive tumor samples ($n = 22$ of 23)</td>
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<td>2.6</td>
<td>1.5</td>
<td>1.2</td>
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<tr>
<td>No oligodendrogliomas ($n = 20$ of 23)</td>
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<td>2.4</td>
<td>1.4</td>
<td>1.0</td>
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<tr>
<td>All WHO grade II ($n = 6$)</td>
<td>2.9</td>
<td>2.4</td>
<td>2.1</td>
<td>1.8</td>
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<td>No oligodendrogliomas WHO grade II ($n = 4$)</td>
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<td>1.3</td>
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<tr>
<td>All WHO grade III ($n = 8$)</td>
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<tr>
<td>All WHO grade IV ($n = 8$)</td>
<td>4.4</td>
<td>3.0</td>
<td>0.8</td>
<td>0.7</td>
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</table>

Fig. 2. Box plots representing the $^{18}$F-DOPA SUV$_{\text{max}}$ for WHO grades II, III, and IV disease for 20 biopsy samples across 9 patients, excluding 3 oligodendroglioma biopsy samples.
Biopsy-based $^{18}$F-DOPA Threshold Analysis and Volume Comparisons

Ratios of the SUV$_{\text{max}}$ for each biopsy sample to normal contralateral brain SUV$_{\text{mean}}$ (T/N) were computed and compared with the grade of that biopsy sample. Normal contralateral brain had low $^{18}$F-DOPA uptake, with an average SUV$_{\text{mean}}$ of 1.1 ± 0.2 (10 patients, range: 0.9–1.6). For all 23 biopsy samples, T/Ns of 1.2–5.9 and 1.1–5.1 were calculated for LGG and HGG samples, respectively. Without the 3 low-grade oligodendroglioma samples, T/Ns of 1.2–2.0 and 1.1–5.1 were calculated for LGGs and HGGs, respectively. Excluding the oligodendroglioma biopsy samples, a strong correlation ($P < .05$) was found between T/N and grade stratification, with a statistically significant difference ($P = .02$) comparing the T/Ns for HGGs vs LGGs (Fig. 4).

Given the overlap in the T/N range for high-grade and low-grade disease, a T/N > 2.0 was used to define “high-grade” disease components of the PET contours drawn by the nuclear medicine physician for each HGG patient (Fig. 5). Table 4 shows the percentages of PET volume with T/N > 2.0 threshold (defined as HGG) outside and within T1-CE MRI gold standard volumes, and the percentage of gold standard T2/FLAIR volume outside the T/N > 2.0 threshold for high-grade disease per PET uptake. Mathematically, these percentages were determined based on taking the HGG PET (T/N > 2.0) volume outside the T1-CE volume divided by the total HGG PET volume, taking the HGG PET volume inside the T1-CE volume divided by the total HGG PET volume, and taking the T2/FLAIR volume outside the HGG PET volume divided by the total T2/FLAIR volume, respectively. For the 6 patients with T1-CE, the percentage of $^{18}$F-DOPA PET volume with a T/N > 2.0 that was outside the T1-CE contoured volume was on average 47.3% ± 25.5% (range: 15.1%–81.0%). With respect to the T2/FLAIR signal abnormality, $^{18}$F-DOPA PET uptake was always contained within the MRI signal abnormality, excluding non-disease-related uptake seen outside the T2/FLAIR in blood vessels. Table 4 shows...
that the T2/FLAIR volume outside the high-grade threshold 18F-DOPA PET uptake volume was on average 87.3% ± 37.6% (range: 70.6%–99.9%). In the 3 WHO grade III astrocytoma NCEs on MRI, the percentages of T2/FLAIR outside the HGG 18F-DOPA PET threshold T/N > 2.0 volume were 99.9%, 96.1%, and 91.7%. Figure 6 illustrates coronal and sagittal views of gold standard T/N > 2.0 HGG PET and FLAIR contours for the WHO grade III NCE patient with 91.7% FLAIR outside the HGG PET volume. These results show the utility of 18F-DOPA PET for neurosurgical resection and RT boost planning guidance in both CE and NCE tumors.

### Discussion

Conventional T1-CE MRI represents the standard of care for image-guided biopsy, surgical resection, and planning of RT for brain tumors. For both surgical and radiation planning, T1-CE MRI is used to identify regions of highest grade or malignant potential. However, approximately one-third of HGGs demonstrate no enhancement, while benign tumors—such as pilocytic astrocytoma, infection, demyelination, and treatment effect—commonly do enhance. Although used to define the extent of tumor infiltration relative to normal neuro-anatomic structures, abnormal T2/FLAIR signal is known to contain both regions of nonmalignant vasogenic edema and nonuniform tumor infiltration and therefore is not targeted for neurosurgical biopsy planning in patients with T1-CE. In tumors without T1-CE, guidance for biopsy location is limited to the relatively nonspecific T2/FLAIR signal. In HGGs without T1-CE, the entire T2 signal abnormality is targeted for high-dose RT, due to the lack of differentiation on T2 among tissue with highly aggressive disease, minimal disease, or vasogenic edema.

Table 4. Concordant and discordant volume percentages of threshold HGG 18F-DOPA PET (T/N > 2.0) relative to the T1-CE gold standard and T2/FLAIR gold standard volumes

<table>
<thead>
<tr>
<th>Patient</th>
<th>% Threshold T/N &gt; 2.0 HGG PET Volume Outside T1-CE Volume</th>
<th>% Threshold T/N &gt; 2.0 HGG PET Volume Inside T1-CE Volume</th>
<th>% T2/FLAIR Volume Outside Threshold T/N &gt; 2.0 HGG PET Volume</th>
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</thead>
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<td>99.9</td>
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<td>84.3</td>
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<td>84.5</td>
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<tr>
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<td>N/A</td>
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*aNo T1-CE.
bNo high-grade disease per PET threshold.
cNo PET uptake.

Fig. 5. Registered 18F-DOPA PET-CT (A), T1-CE MRI (B), and T2-FLAIR MRI (C) contours drawn by the neuroradiologist and the 18F-DOPA representing the region of high-grade disease components defined by T/N > 2.0.
Alternate imaging modalities beyond conventional MRI are needed for selective targeting capabilities of highest density/aggressive tumor in neurosurgical and RT planning.

Molecular-based imaging with PET in combination with anatomic-based MRI and CT imaging can improve the accuracy of tumor delineation. As previously discussed, amino acid PET tracers have high uptake in tumor tissue and low uptake in normal brain tissue compared with metabolic tracers. There is visible PET uptake for tumors that do not enhance with MRI because many amino acid tracers are actively transported across an intact blood–brain barrier, while contrast can accumulate only where there is blood–brain barrier disruption. The majority of relevant clinical and research experience with amino acid tracers for gliomas have been focused on \([1\text{C}]\text{-methionine (11C-MET) and 18F-fluoro-ethyltyrosine (FET) PET.} When imaging cerebral lesions, 18F-DOPA provides equivalent visual and quantitative SUV information to 11C-MET but offers a significantly longer physical half-life of 18F (109 min) compared with 11C (20 min). This is significant, as 11C tracers can be used only at institutions with an on-site cyclotron, limiting their use to essentially large academic centers and not generally applicable in practice. Normal uptake of 18F-DOPA in the basal ganglia can present challenges when trying to distinguish between normal brain and adjacent tumor, which is absent with PET PET uptake. This is the first study to evaluate the utility of integrating 18F-DOPA PET metabolic imaging into neurosurgical resection or biopsy planning and RT target delineation of gliomas.

In this report we demonstrate that 18F-DOPA PET uptake intensity correlates with histopathological findings in astrocytomas. Specifically, 18F-DOPA PET SUV\(_{\text{max}}\) strongly correlates with tumor grade, with significant differences found between WHO grades II and IV and WHO grades III and IV. Our results are in agreement with previous studies using 11C-MET PET, which also lacked a correlation between WHO grades II and III, and with a previous study of 18F-DOPA PET, which found correlations between all 3 grades in newly diagnosed patients. In our study, a larger sample of WHO grade II biopsies is likely needed to show a difference between WHO grades II and III. The results in Table 2 from our study also agree with a study by Arbizu et al., which reported a significant association between tumor grade and stereotactic biopsy sample location (eg, M+P+, M−P−) with MET PET. The ability of SUV\(_{\text{max}}\) to predict grade could be valuable in stereotactic biopsy planning, especially in NCE tumors.

Our results also show that cellularly significantly correlates with 18F-DOPA PET SUV\(_{\text{mean}}\), while the correlation between proliferative activity and SUV\(_{\text{mean}}\) approaches significance. SUV\(_{\text{mean}}\) was chosen as the correlation parameter because it may be more representative of the entire cellular area used in calculations of both cellularity and Ki-67 than SUV\(_{\text{max}}\). Our results are in disagreement with previous studies showing a strong correlation between 18F-DOPA PET SUV\(_{\text{max}}\) and Ki-67 in newly diagnosed astrocytomas. Our statistical analysis includes both newly diagnosed (\(n = 16\)) and recurrent (\(n = 4\)) astrocytoma samples. The Ki-67 statistical analysis will be recomputed once more patients have been accrued to make a more formal comparison with stratified newly diagnosed and recurrent astrocytoma samples. The ability of 18F-DOPA PET to predict degree of cellularity provides an alternative image-guidance mechanism in the absence of T1-CE, when selectively targeting the most highly aggressive disease components for RT boost dose and stereotactic biopsy planning. In cases with visible T1-CE, this tracer provides further insight regarding the degree of extension of the highly cellular disease components located beyond the T1-CE lesion for more accurate RT target delineation and resection extent. Our data suggest that regions of 18F-DOPA avidity may better delineate regions for resection/biopsy and for high-dose RT delivery.

Exclusion of the oligodendroglioma patient from the histopathological analysis was based on the unique PET uptake properties of this tumor type. We found that 18F-DOPA SUV\(_{\text{max}}\) was substantially greater for WHO grade II oligodendroglioma patient samples (range: 5.0–6.1) compared with the WHO grade II astrocytomas (range: 1.2–1.9). In fact, this WHO grade II oligodendroglioma patient exhibited the highest uptake of all 10 patients. Figure 7 illustrates the substantially higher uptake property in the WHO grade II oligodendroglioma patient compared with a WHO grade II astrocytoma patient. Previous studies by Hatakeyama et al. reported similar findings with the amino acid tracer 11C-MET PET, possibly reflecting cellular density differences and cell turnover rates in oligodendrogliomas. Alternatively, this may reflect a unique aspect of amino acid metabolism for this particular histologic type. Similar studies with perfusion MR in...
low-grade glial neoplasms found that oligodendroglia-
mos frequently present with high relative cerebral
blood volume foci.14 Given the lack of CE in low-grade
tumors, the uniquely high 18F-DOPA PET uptake prop-
erties of WHO grade II oligodendrogliomas could prove
to be valuable for image guidance in neurosurgical resec-
tion extent. Additional data are necessary to understand
the full implications and appropriate use of high
18F-DOPA PET uptake for WHO grade II oligodendro-
gliomas in RT delineation and dose guidance.

T1-CE MRI is targeted during neurosurgical planning
and RT delineation of the higher radiation dose boost
volume based on the presumption that this region con-
tains the highest density of tumor and/or highest-grade
disease. Since edema is often very large and tumor infil-
tration is irregular, T2 signal changes are not generally
considered targets for resection and often are treated
with a lower radiation dose prescription in HGG. The
results from this study suggest that a T/N threshold >
2.0 may define the high-grade/highly cellular portion
of 18F-DOPA uptake volume. This threshold is consist-
ent with a previous study by Chen et al12 in which an
average T/N of 2.5 ± 0.73 was found as the diagnostic
threshold for high-grade brain tumors imaged with
18F-DOPA PET. Our study shows that in the 6 patients
with visible CE, PET-defined “high-grade” disease ex-
tended 0.5–3.5 cm beyond the CE lesion based on the
18F-DOPA PET threshold. As extent of surgical resec-
tion is associated with improved survival,15 incorporat-
ing 18F-DOPA PET could provide neurosurgeons with
a more accurate delineation of high-grade/high-density
disease components for neurosurgical resection planning
as compared with T1-CE MR planning alone. For RT of
HGG, typically a 1- to 2-cm uniform expansion is placed
around the grossly defined tumor (visible on imaging) or
visible resection cavity plus any residual T1-CE to create
a planning target volume, which is then targeted for RT
boost dose. While 3 of 5 HGG patients with T1-CE con-
tained 100% of the 18F-DOPA PET volume (T/N > 2.0)
within the standard 1-cm expansion of T1-CE, 2 WHO
grade IV patients had T/N > 2.0 volume extending well
beyond the 1-cm expansion around the T1-CE (2.5 cm,
3.5 cm). Similar results have been found utilizing
11C-MET PET,16,17 with Miwa et al16 reporting that an
average distance of 3.0 cm and Grosu et al17 report-
ing that an average distance of 4.5 cm outside T1-CE
was necessary to cover 100% of the amino acid tracer
in GBM patients. In a retrospective study using the
amino acid tracer FET PET, Niyazi et al18 reported a
statistically larger gross tumor volume using FET-
based volumes compared with MRI-based volumes and
a statistically significant difference in the geometric loca-
tion between PET and MRI-based volumes on a
conformity index calculation. These data suggest that
amino acid–based PET imaging provides additional vi-

cualization of high-grade/high-density disease that
extends beyond T1-CE MRI for more accurate target
delineation.

In the remaining 4 patients without CE (n = 3 WHO
grade III, n = 1 WHO grade II), 18F-DOPA uptake was
visible in all WHO grade III patients. Ledezma et al13
also demonstrated that 18F-DOPA uptake was increased
in tumors that were non-enhancing on MRI. HGGs are
known to infiltrate into the surrounding reactive
edema as visualized on T2-weighted MRI. In HGG
cases with no CE on MRI, the high-dose RT target is
the entire T2 signal abnormality with or without a
1-cm uniform expansion. After applying a 1-cm expan-
sion to the high-grade disease as defined by the
18F-DOPA PET threshold volume and a 1-cm expansion
to the T2/FLAIR MRI volume and subtracting out struc-
tures outside of brain tissue, significant portions of T2/
FLAIR-defined targets (95.2%, 70.2%, and 71.0%) ap-
ppeared to be without “high-grade” tumor. Grosu et al17
also reported T2 signal abnormality extension outside
the MET PET uptake for all 18 patients in their study.
Our results show that all 18F-DOPA PET uptake is con-
tained within the T2/FLAIR volume, which is in dis-
agreement with studies showing the amino acid tracer
MET PET uptake extending beyond the T2 signal abnor-
mality on half the patients, and up to 4.0 cm.17 Another
study, by Arbizu et al14 reported that the T2/FLAIR
MRI pathologic area was larger than the MET PET in
87.5% of their patients, and selective biopsies in a T2/
FLAIR-positive and MET PET–negative region showed
no tumor or less aggressive lesions. In agree-
ment, our data suggest that integrating 18F-DOPA with
MRI can differentiate regions of more aggressive and/
or higher-density disease within the heterogeneous T2
signal abnormality for more selective targeting of the
surgical resection area and RT boost dose in NCE
WHO grade III astrocytomas.
In summary, 18F-DOPA PET metabolic imaging demonstrates significant correlation with histopathological markers of grade and cellularity. An optimal 18F-DOPA PET threshold (T/N > 2.0) can be used to reliably differentiate areas of high-grade astrocytoma not otherwise recognized with standard MRI. Our results suggest that 18F-DOPA PET SUV\textsubscript{max} may more accurately identify regions of higher-grade/higher-density disease in patients with astrocytomas and will have utility in guiding stereotactic biopsy and RT targeting. Future studies will investigate the role of 18F-DOPA PET with relative cerebral volume in perfusion MRI for targeting the most aggressive disease components. Our preliminary data in oligodendrogliomas are provocative and suggest that 18F-DOPA has a different mechanism of uptake, and the significant intensity allows visualization of disease that could guide surgical resection and RT target delineation regardless of grade.

**Conclusion**

Our results suggest that 18F-DOPA PET SUV\textsubscript{max} may more accurately identify regions of higher-grade/higher-density disease in patients with astrocytomas and will have utility in guiding stereotactic biopsy selection. Using SUV-based thresholds to define high-grade portions of disease will be valuable in RT planning of boost doses. Future incorporation of 18F-DOPA PET into clinical practice for neurosurgical resection or biopsy and RT planning will evaluate the influence of 18F-DOPA PET on local control and survival outcomes.

**Funding**

This work was supported by a generous grant from Brains Together for a Cure and by a Mayo Brain Tumor NIH SPORE grant (CA108961).

**Acknowledgments**

The authors thank S. Keith Anderson for expert statistical analyses and Steven J. Goerss and Laura M. Haugen for expert assistance with neurosurgical navigation software.

**Conflict of interest statement.** None declared.

**References**