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Permalink
https://escholarship.org/uc/item/14f194d2

Journal
Neuro-Oncology, 14(8)

ISSN
1522-8517

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Publication Date
2012-08-01

DOI
10.1093/neuonc/nos141

Peer reviewed
18F-FDOPA and 18F-FLT positron emission tomography parametric response maps predict response in recurrent malignant gliomas treated with bevacizumab

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The current study examined the use of voxel-wise changes in 18F-FDOPA and 18F-FLT PET uptake, referred to as parametric response maps (PRMs), to determine whether they were predictive of response to bevacizumab in patients with recurrent malignant gliomas. Twenty-four patients with recurrent malignant gliomas who underwent bevacizumab treatment were analyzed. Patients had MR and PET images acquired before and at 2 time points after bevacizumab treatment. PRMs were created by examining the percentage change in tracer uptake between time points in each image voxel. Voxel-wise increase in PET uptake in areas of pretreatment contrast enhancement defined by MRI stratified 3-month progression-free survival (PFS) and 6-month overall survival (OS) according to receiver-operating characteristic curve analysis. A decrease in PET tracer uptake was associated with longer PFS and OS, whereas an increase in PET uptake was associated with short PFS and OS. The volume fraction of increased 18F-FDOPA PET uptake between the 2 posttreatment time points also stratified long- and short-term PFS and OS (log-rank, P < .05); however, 18F-FLT uptake did not stratify OS. This study suggests that an increase in FDOPA or FLT PET uptake on PRMs after bevacizumab treatment may predict response to bevacizumab therapy.

Keywords: Bevacizumab, 18F-FDOPA, 18F-FLT, glioblastoma, PRMs.

Malignant gliomas (World Health Organization [WHO] grades III–IV) are primary central nervous system (CNS) tumors with a poor patient prognosis. Malignant gliomas constitute approximately 70% of all neuroepithelial tumors and approximately 23% of all primary CNS tumors. Despite new therapies, the median survival time for patients with malignant gliomas has improved only marginally. Bevacizumab, a humanized monoclonal antibody that inhibits vascular endothelial growth factor (VEGF), is now the standard of care for recurrent malignant gliomas, including glioblastoma. Treatment with bevacizumab has shown to be effective in extending progression-free survival in patients with glioblastoma; however, only a few biomarkers are available for predicting the response of recurrent malignant gliomas to bevacizumab therapy.

Positron emission tomography (PET) imaging using [18F]-fluorodeoxyglucose (FDG) is the most commonly used radiotracer method for examining metabolic activity of malignant tumors. Despite its widespread use, in
between tumor and normal tissue is higher for $^{18}$F-FLT than for $^{18}$F-FDG for evaluating recurrent high-grade gliomas.\textsuperscript{11} 3,4-dihydroxy-6-$^{18}$F-fluoro-L-phenylalanine ($^{18}$F-FDOPA) is an amino acid analog. Similar to $^{18}$F-FLT, $^{18}$F-FDOPA has also shown improved contrast between tumor and normal brain tissue in patients with high-grade glioma because of elevated amino acid transport in malignant tumor cells.\textsuperscript{12} We hypothesized that voxel-wise changes in $^{18}$F-FDOPA and $^{18}$F-FLT uptake, or parametric response maps (PRMs), in the same patient across multiple time points would be predictive of response in patients with recurrent glioblastoma treated with bevacizumab, as measured by progression-free (PFS) and overall survival (OS). Furthermore, we hypothesized that the combination of $^{18}$F-FDOPA and $^{18}$F-FLT would be synergistically prognostic, because the biological mechanisms of tracer uptake are fundamentally different.

To test these hypotheses, PET PRMs were constructed for both $^{18}$F-FDOPA and $^{18}$F-FLT for each patient in regions of contrast enhancement defined by magnetic resonance imaging (MRI). PRMs were calculated by examining the change in PET uptake before and after initial bevacizumab treatment, along with the change in PET uptake between the 2 time points after initiation of bevacizumab treatment.

### Materials and Methods

#### Patients

All patients in this study signed institutional review board–approved informed consent to have their data collected and stored in our institution’s neuro-oncology database. Data from 24 patients with malignant gliomas (WHO grade IV, $n = 18$; WHO grade III, $n = 6$) who were previously examined in separate studies using circular regions of interest and placed in the highest tumor standard uptake value (SUV)\textsuperscript{13,14} were retrospectively analyzed for the current study. All patients were treated with bevacizumab, and all but 2 received a supplemental chemotherapeutic agent (irinotecan). Of the 24 patients in the study, $^{18}$F-FDOPA data was acquired for 23, $^{18}$F-FLT data was acquired for 21, and 20 received both $^{18}$F-FDOPA and $^{18}$F-FLT scans. PET time points were taken within 1 week before the start of bevacizumab treatment, 1–2 weeks after treatment, and 5–7 weeks after the start of treatment (Fig. 1). $^{18}$F-FDOPA and $^{18}$F-FLT scans were obtained within 1–2 days at each time point in patients with both scans, and the order of PET scan acquisition was randomized at each follow-up time.

#### PET

$^{18}$F-FDOPA images were acquired and processed using methods similar to those previously described.\textsuperscript{13–19} $^{18}$F-FDOPA was synthesized according to standard procedures\textsuperscript{18,19} and injected at a dose of 1.1–6.6 MBq/kg body weight. $^{18}$F-FLT was synthesized locally using previously described methods,\textsuperscript{20} and $^{18}$F-FLT images were acquired and processed using techniques similar to those previously described.\textsuperscript{13} For both $^{18}$F-FDOPA and $^{18}$F-FLT images, a transmission scan was obtained for attenuation correction.\textsuperscript{21} $^{18}$F-FDOPA emission data were acquired in 3-dimensional mode 10 min after injection for a total of 30 min. Data collected at 10–30 min were summed to obtain a 20-min static $^{18}$F-FDOPA image after reconstruction as previously described. $^{18}$F-FLT emission data were collected in 3-dimensional mode immediately after injection for a total of 60 min. Data collected at 30–60 min were summed to obtain a 30-min static $^{18}$F-FLT image and reconstructed as previously described. All images for both $^{18}$F-FDOPA and $^{18}$F-FLT were obtained using a high-resolution full-ring PET scanner (ECAT HR+; Siemens/CTI).

#### MRI

Data were collected on a 1.5T MR system (General Electric Medical Systems or Siemens Medical) using pulse sequences supplied by the scanner manufacturer. Standard anatomical MRI sequences included axial T1 weighted (TE/TR = 15 ms/400 ms, slice thickness = 5 mm with 1 mm interslice distance, NEX = 2, matrix size = 256 $\times$ 256, and FOV = 24 cm), T2 weighted FSE (TE/TR = 126–130 ms/4000 ms, slice thickness = 5 mm with 1 mm interslice distance, NEX = 2, matrix size = 256 $\times$ 256, and FOV = 24 cm), and fluid-attenuated inversion recovery (FLAIR) images (TI = 2200 ms, TE/TR = 120 ms/4000 ms, slice thickness = 5 mm with 1 mm interslice distance, NEX = 2, matrix size = 256 $\times$ 256, and FOV = 24 cm).
size = 256 × 256, and FOV = 24 cm). In addition, gado-
pentetate dimeglumine enhanced (Magnevist; Berlex;
0.1 mmol/kg) axial and coronal T1-weighted images
(T1 + C; coronal: TE/TR = 15 ms/400 ms, slice thick-
ness 3 mm with 1 mm interslice distance, NEX = 2,
a matrix size of 256 × 256, and FOV = 24 cm) were
acquired after contrast injection.

Image Registration

All images for each patient at each time point were
registered to a high resolution (1.0 mm isotropic),
T1-weighted brain atlas (MN152; Montreal
Neurological Institute) using a mutual information algo-
rithm and a 12-degree of freedom transformation using
FSL (FMRI3, Oxford, UK; http://www.fmrib.ox.ac.uk/
fsil/). Manual adjustment, if necessary, was performed
using the trkregister2 routine available from Freesurfer
(surfer.nmr.mgh.harvard.edu; Massachusetts General
Hospital, Harvard Medical School).

PET PRM Generation

PET SUV images for each patient and time point were
normalized separately to an area of contralateral
normal-appearing white matter (NAWM) for each
patient. Areas of contralateral NAWM were selected
from the corresponding aligned MR image acquired
closest to the time of that PET image. PRMs of the rela-
tive percentage change in normalized voxel SUV values
from one time point to the next were calculated for the
pretreatment and first posttreatment time point
([Post1-Pre]/Pre) and the 2 posttreatment time points
([Post2-Post1]/Post1). After calculating the 2 sets of
PRMs for each PET tracer, a histogram of PRM values
in NAWM regions were calculated using values from
all available patients. A 95% confidence interval of
normal tissue PRM variability across time was calculated
from these data, similar to other voxel-wise
techniques. Any PRM voxel value outside of the
95% confidence interval was classified as a significant
increase or decrease in PET tracer uptake.

Region of Interest (ROI) Selection

The current study focused on using contrast enhancing
regions on pretreatment, postcontrast T1-weighted
images for subsequent PRM analysis. Regions of T2 or
FLAIR signal abnormality are thought to encompass
the largest extent of malignant infiltrating tumor.23–27
radiographic assessment (i.e., Macdonald criteria34)
and the new Response Assessment in Neuro-Oncology
assessment.35 A semiautomated thresholding technique
described previously was used to mask the pretreatment
contrast-enhancing lesion for each patient.6 For each
PET PRM (4 per patient consisting of a Pre/Post
18F-FDOPA PRM, Post1/Post2 18F-FDOPA PRM,
Pre/Post 18F-FLT PRM, and a Post1/Post2 18F-FLT
PRM), the total volume of increasing [Vol(+)], decreasing
[Vol(−)], or changing (increasing or decreasing
[Vol(+/−)]) uptake, and the percentage of contrast-
enhancing tumor significantly increasing [%Vol(+)],
decreasing [%Vol(−)], or changing [%Vol(+/−)] was
calculated. Of note, Pre/Post PRMs were defined only
with respect to the pretreatment and first posttreatment
time point and not between pretreatment and the second
posttreatment time point.

Definition of Disease Progression

Progression was defined prospectively by the treating
neuro-oncologists. If subsequent scans showed definite
increase in imaging-evaluable tumor (≥25% increase
in the sum of enhancing lesions, new enhancing lesions
> 1 cm², or an unequivocal qualitative increase in non-
enhancing tumor or unequivocal new area of noncon-
trast enhancing tumor), progression was declared at
that time. Change in steroid dosage was taken into con-
sideration while defining progression. Patients who did
not meet these imaging criteria for progression but had
significant neurologic decline were declared to have pro-
gressed at the time of irreversible decline. Patients who
died before evidence of imaging progression were
defined to have progressed on the date of death. PFS
was defined as the time from the start of bevacizumab
treatment to radiographic and/or clinical progression.
OS was defined as the interval from the start of beva-
cizumab treatment to patient death.

Hypothesis Testing

Receiver-operating characteristic (ROC) analysis was
performed on PET PRM measurements and change in
the volume of contrast enhancement on post-contrast
T1-weighted images to determine the sensitivity and
specificity of detecting 3-month PFS and 6-month OS.
Area under the curve (AUC) was used as a measure of
PET PRM performance. In addition, survival analysis
was performed using log-rank statistical analysis of
Kaplan-Meier data. All statistical tests were performed
NAWM was 2.14% to +14.5% between the pre- and posttreatment time points and 2.13.5% to +14.5% between the 2 posttreatment time points (Fig. 2A), whereas the 95% confidence interval for voxel-wise changes in normalized $^{18}$F-FLT was 2.29.6% to +34.6% between the pre- and posttreatment time points and 2.28.6% to +38.7% between the 2 posttreatment time points (Fig. 2B). These confidence intervals were then used for production of $^{18}$F-FDOPA and $^{18}$F-FLT PET PRMs. (Note that the confidence intervals for $^{18}$F-FLT PRMs were slightly asymmetric, biased slightly to a subtle decrease in tracer uptake between the different time points.)

Qualitatively, initial administration with bevacizumab resulted in reduction of both contrast enhancement and T2-weighted signal abnormality for most patients. Similarly, $^{18}$F-FDOPA and $^{18}$F-FLT showed a significant decrease in uptake for the same patients after initial administration of bevacizumab. Between the 2 posttreatment time points, the change in $^{18}$F-FDOPA and $^{18}$F-FLT uptake varied, with some patients showing stable or further decreasing levels of uptake, whereas other patients had increased uptake between the 2 posttreatment time points. Patients exhibiting continued or increasing uptake were classified as responders, whereas patients with decreasing uptake were classified as non-responders.

**Fig. 3.** $^{18}$F-FDOPA and $^{18}$F-FLT PET PRM responder showing decreased PET uptake after administration of bevacizumab. PFS = 10.6 months, OS = 15 months.

**Fig. 4.** $^{18}$F-FDOPA and $^{18}$F-FLT PET PRM non-responder showing increased PET uptake after administration of bevacizumab. PFS = 1.6 months, OS = 3.3 months.
enhancement on postcontrast T1-weighted MR images, to determine sensitivity and specificity for predicting 3-month PFS and 6-month OS. Performance of each PET PRM metric for each end point is summarized in Tables 1–4. In general, ROC analysis suggested that a decrease in contrast enhancement of .5 cc on MRI before and after treatment was a good predictor of both longer time to progression and overall survival.

Table 1. ¹⁸F-FDOPA PET PRMs ROC analysis for 3-month progression-free survival (PFS)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Threshold</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>AUC</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vol(2) y^Pre/Post_FDOPA [mL]</td>
<td>7 cc</td>
<td>66</td>
<td>45</td>
<td>0.59</td>
<td>0.4884</td>
</tr>
<tr>
<td>Vol(+1/2) y^Pre/Post_FDOPA [mL]</td>
<td>3 cc</td>
<td>66</td>
<td>93</td>
<td>0.70</td>
<td>0.1154</td>
</tr>
<tr>
<td>Vol(1/2) y^Pre/Post_FDOPA [mL]</td>
<td>15 cc</td>
<td>75</td>
<td>70</td>
<td>0.82</td>
<td>0.0110*</td>
</tr>
<tr>
<td>%Vol(2) y^Pre/Post_FDOPA</td>
<td>38%</td>
<td>56</td>
<td>79</td>
<td>0.54</td>
<td>0.7528</td>
</tr>
<tr>
<td>%Vol(+1/2) y^Pre/Post_FDOPA</td>
<td>5%</td>
<td>66</td>
<td>79</td>
<td>0.67</td>
<td>0.1859</td>
</tr>
<tr>
<td>%Vol(+/2) y^Pre/Post_FDOPA</td>
<td>67%</td>
<td>66</td>
<td>57</td>
<td>0.62</td>
<td>0.3447</td>
</tr>
<tr>
<td>Vol(2) y^Post1/Post2_FDOPA [mL]</td>
<td>3.5 cc</td>
<td>75</td>
<td>44</td>
<td>0.56</td>
<td>0.7003</td>
</tr>
<tr>
<td>Vol(+1/2) y^Post1/Post2_FDOPA [mL]</td>
<td>3 cc</td>
<td>56</td>
<td>75</td>
<td>0.54</td>
<td>0.7728</td>
</tr>
<tr>
<td>%Vol(2) y^Post1/Post2_FDOPA</td>
<td>28%</td>
<td>44</td>
<td>89</td>
<td>0.53</td>
<td>0.8253</td>
</tr>
<tr>
<td>%Vol(+1/2) y^Post1/Post2_FDOPA</td>
<td>50%</td>
<td>78</td>
<td>50</td>
<td>0.53</td>
<td>0.8474</td>
</tr>
<tr>
<td>%Vol(+/2) y^Post1/Post2_FDOPA</td>
<td>3%</td>
<td>78</td>
<td>50</td>
<td>0.61</td>
<td>0.4415</td>
</tr>
<tr>
<td>%Vol(+/2) y^Post1/Post2_FDOPA</td>
<td>27%</td>
<td>100</td>
<td>33</td>
<td>0.56</td>
<td>0.6511</td>
</tr>
</tbody>
</table>

*P , .05.

Table 2. ¹⁸F-FDOPA PET PRMs ROC analysis for 6-month overall survival (OS)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Threshold</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>AUC</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vol(2) y^Pre/Post_FDOPA [mL]</td>
<td>20 cc</td>
<td>80</td>
<td>50</td>
<td>0.57</td>
<td>0.6056</td>
</tr>
<tr>
<td>Vol(+1/2) y^Pre/Post_FDOPA [mL]</td>
<td>0.2 cc</td>
<td>71</td>
<td>67</td>
<td>0.76</td>
<td>0.0588</td>
</tr>
<tr>
<td>Vol(1/2) y^Pre/Post_FDOPA [mL]</td>
<td>16 cc</td>
<td>67</td>
<td>75</td>
<td>0.65</td>
<td>0.2453</td>
</tr>
<tr>
<td>%Vol(2) y^Pre/Post_FDOPA</td>
<td>38%</td>
<td>40</td>
<td>75</td>
<td>0.53</td>
<td>0.8465</td>
</tr>
<tr>
<td>%Vol(+1/2) y^Pre/Post_FDOPA</td>
<td>2%</td>
<td>60</td>
<td>75</td>
<td>0.63</td>
<td>0.3017</td>
</tr>
<tr>
<td>%Vol(+/2) y^Pre/Post_FDOPA</td>
<td>77%</td>
<td>67</td>
<td>50</td>
<td>0.53</td>
<td>0.8465</td>
</tr>
<tr>
<td>Vol(2) y^Post1/Post2_FDOPA [mL]</td>
<td>5 cc</td>
<td>58</td>
<td>83</td>
<td>0.72</td>
<td>0.1341</td>
</tr>
<tr>
<td>Vol(+1/2) y^Post1/Post2_FDOPA [mL]</td>
<td>1.5 cc</td>
<td>60</td>
<td>67</td>
<td>0.60</td>
<td>0.5121</td>
</tr>
<tr>
<td>Vol(1/2) y^Post1/Post2_FDOPA [mL]</td>
<td>15 cc</td>
<td>67</td>
<td>83</td>
<td>0.71</td>
<td>0.1601</td>
</tr>
<tr>
<td>%Vol(2) y^Post1/Post2_FDOPA</td>
<td>50%</td>
<td>83</td>
<td>67</td>
<td>0.61</td>
<td>0.4537</td>
</tr>
<tr>
<td>%Vol(1/2) y^Post1/Post2_FDOPA</td>
<td>2.5%</td>
<td>91</td>
<td>83</td>
<td>0.83</td>
<td>0.0271*</td>
</tr>
<tr>
<td>%Vol(+/2) y^Post1/Post2_FDOPA</td>
<td>6%</td>
<td>67</td>
<td>83</td>
<td>0.58</td>
<td>0.5742</td>
</tr>
</tbody>
</table>

*P , .05.

Table 3. ¹⁸F-FLT PET PRMs ROC analysis for 3-month progression-free survival (PFS)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Threshold</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>AUC</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vol(2) y^Pre/Post_FLT [mL]</td>
<td>7 cc</td>
<td>60</td>
<td>40</td>
<td>0.62</td>
<td>0.3211</td>
</tr>
<tr>
<td>Vol(+1/2) y^Pre/Post_FLT [mL]</td>
<td>0.1 cc</td>
<td>70</td>
<td>63</td>
<td>0.60</td>
<td>0.4386</td>
</tr>
<tr>
<td>Vol(1/2) y^Pre/Post_FLT [mL]</td>
<td>7.5 cc</td>
<td>70</td>
<td>35</td>
<td>0.59</td>
<td>0.4568</td>
</tr>
<tr>
<td>%Vol(2) y^Pre/Post_FLT</td>
<td>70%</td>
<td>90</td>
<td>67</td>
<td>0.70</td>
<td>0.1069</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Threshold</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>AUC</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vol(+1/2) y^Pre/Post_FLT [mL]</td>
<td>70%</td>
<td>90</td>
<td>67</td>
<td>0.70</td>
<td>0.1069</td>
</tr>
</tbody>
</table>

*P , .05.
Table 4. $^{18}$F-FLT PET PRMs ROC analysis for 6-month overall survival (OS)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Threshold</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>AUC</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vol(2) $Y_{pre/post}^{FLT}$ [mL]</td>
<td>7.5cc</td>
<td>54</td>
<td>67</td>
<td>0.51</td>
<td>0.9380</td>
</tr>
<tr>
<td>Vol(+/-) $Y_{pre/post}^{FLT}$ [mL]</td>
<td>0.3cc</td>
<td>75</td>
<td>80</td>
<td>0.81</td>
<td>0.0390*</td>
</tr>
<tr>
<td>Vol(+/-) $Y_{pre/post}^{FLT}$ [mL]</td>
<td>8cc</td>
<td>67</td>
<td>63</td>
<td>0.55</td>
<td>0.6986</td>
</tr>
<tr>
<td>%Vol(2) $Y_{pre/post}^{FLT}$</td>
<td>22%</td>
<td>88</td>
<td>43</td>
<td>0.53</td>
<td>0.8411</td>
</tr>
<tr>
<td>%Vol(+/-) $Y_{pre/post}^{FLT}$</td>
<td>1%</td>
<td>73</td>
<td>67</td>
<td>0.70</td>
<td>0.1612</td>
</tr>
<tr>
<td>%Vol(+/-) $Y_{pre/post}^{FLT}$</td>
<td>68%</td>
<td>73</td>
<td>75</td>
<td>0.67</td>
<td>0.1968</td>
</tr>
<tr>
<td>Vol(2) $Y_{post1/post2}^{FLT}$ [mL]</td>
<td>6cc</td>
<td>71</td>
<td>50</td>
<td>0.57</td>
<td>0.6710</td>
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<tr>
<td>Vol(+/-) $Y_{post1/post2}^{FLT}$ [mL]</td>
<td>3cc</td>
<td>58</td>
<td>75</td>
<td>0.54</td>
<td>0.7906</td>
</tr>
<tr>
<td>Vol(+/-) $Y_{post1/post2}^{FLT}$ [mL]</td>
<td>9cc</td>
<td>64</td>
<td>75</td>
<td>0.64</td>
<td>0.3956</td>
</tr>
<tr>
<td>%Vol(2) $Y_{post1/post2}^{FLT}$</td>
<td>1%</td>
<td>60</td>
<td>50</td>
<td>0.55</td>
<td>0.7500</td>
</tr>
<tr>
<td>%Vol(+/-) $Y_{post1/post2}^{FLT}$</td>
<td>1%</td>
<td>55</td>
<td>50</td>
<td>0.56</td>
<td>0.6971</td>
</tr>
<tr>
<td>%Vol(+/-) $Y_{post1/post2}^{FLT}$</td>
<td>48%</td>
<td>74</td>
<td>50</td>
<td>0.52</td>
<td>0.8763</td>
</tr>
</tbody>
</table>

*P < .05.

(Fig. 5A and B; contrast enhancement, 3-month PFS, Sensitivity = 80%, Specificity = 78%, AUC = 0.77, P = .025; 6-month OS, Sensitivity = 80%, Specificity = 78%, AUC = 0.78, P = .033); however, failure of bevacizumab was at least partially defined by MRI justifying further inquiry into the predictive nature of PET PRMs.

ROC analysis suggested that a large volume (or volume fraction) of decreased $^{18}$F-FDOPA PET uptake was associated with longer PFS and OS. Decreased $^{18}$F-FDOPA uptake had a high sensitivity to 3-month PFS and 6-month OS but relatively low specificity. Conversely, the volume (or volume fraction) of increased $^{18}$F-FDOPA PET uptake had higher specificity and lower sensitivity for shorter 3-month PFS and 6-month OS. A large volume of voxels with changing $^{18}$F-FDOPA uptake within areas of contrast enhancement between pre- and posttreatment time points $[Vol(+/-) Y_{pre/post}^{FDOPA}]$ was a statistically significant predictor for 3-month PFS (Table 1; Fig. 5A; Threshold = 15cc, Sensitivity = 75%, Specificity = 70%, AUC = 0.82, P = .0110). A volume fraction of increasing $^{18}$F-FDOPA uptake within areas of contrast enhancement between the 2 posttreatment time points $[% Vol(+/-) Y_{post1/post2}^{FDOPA}]$ was a statistically significant predictor of 6-month OS (Table 2; Fig. 5B; Threshold = 2.5%; Sensitivity = 91%; Specificity = 83%, AUC = 0.83, P = .0271).

$^{18}$F-FLT had slightly less specificity for 3-month PFS and 6-month OS than did $^{18}$F-DOPA, although overall ROC performance suggested similar trends. Of importance, the volume (and volume fraction) required for $^{18}$F-FLT PRMs to predict response was much lower than for $^{18}$F-DOPA, providing an opportunity to improve on $^{18}$F-DOPA PRMs by using $^{18}$F-FLT.
Log-rank analysis on Kaplan-Meier data suggested a volume fraction of increasing $^{18}$F-FLT uptake on PRMs evaluated between the 2 follow-up posttreatment time points. 10% resulted in a statistically shorter PFS (Fig. 6C; % Vol$(+)^{\text{Post}/\text{Post}^2}$ FLT; Log-rank, $P = .0035$); however, there was no significant difference in OS between these groups. Combined response of $^{18}$F-FDOPA and $^{18}$F-FLT PET PRMs allowed for significant separation of PFS using a threshold of 15% (Fig. 6D; % Vol$(+)^{\text{Pre}/\text{Post}}_{\text{FDOPA}}$ or %Vol$(+)^{\text{Pre}/\text{Post}}_{\text{FLT}}$, Log-rank, $P = .0010$). This same criterion was not predictive of OS.

**Discussion**

Results from the current study suggest that a large volume (or volume fraction) of increased $^{18}$F-FDOPA or $^{18}$F-FLT uptake on PRMs evaluated between the 2 follow-up time points after initial administration of bevacizumab treatment were associated with a shortened PFS, compared with patients with a sustained decrease in uptake after treatment. Decreased uptake in both tracers appeared to provide a high sensitivity but low specificity for predicting 3-month PFS and 6-month OS; conversely, increased uptake was associated with a high specificity and low sensitivity for predicting these same end points. Log-rank analysis revealed, however, that only $^{18}$F-FDOPA PRM measurements taken using the 2 posttreatment time points were a statistically significant predictor of OS.

Of note, test-retest reliability of PET tracers in the current study were consistent with previous studies examining PET uptake in normal structures, suggesting that results obtained in the current study may be applicable at other clinical sites. For example, $^{18}$F-FDOPA PET uptake in normal individuals has been estimated at approximately 8%.$^{56}$ Assuming that $^{18}$F-FDOPA SUVs follow a normal distribution, this 8% standard deviation results in a 95% confidence interval for change in $^{18}$F-FDOPA SUV of approximately 15%, consistent with estimates in the current study of approximately 14.5%. Standard deviation in $^{18}$F-FLT SUV uptake, however, has been estimated to be as high as 15%.$^{37,58}$ A standard deviation this high results in a 95% confidence interval for $^{18}$F-FLT of nearly 30%, consistent with the voxel-wise 95% confidence interval for NAWM of approximately 30%. Together, these results suggest that the inherent variability in $^{18}$F-FDOPA uptake may be slightly less than that of $^{18}$F-FLT PET, which may explain the superior performance of
Fig. 6. Best performing $^{18}$F-FDOPA and $^{18}$F-FLT PET PRM metrics according to Log-rank analysis on Kaplan-Meier survival data. (A) Stratification of short- and long-term PFS using $^{18}$F-FDOPA PET PRMs. (B) Stratification of short- and long-term OS using $^{18}$F-FDOPA PET PRMs. (C) Stratification of short- and long-term PFS using $^{18}$F-FLT PET PRMs. (D) Further stratification of short- and long-term PFS using the combined $^{18}$F-FDOPA and $^{18}$F-FLT PET PRM response. All PET PRM metrics shown had statistically significant separation according to Log-rank analysis ($P < .05$).

T2 (DQT2) maps. Studies examining fDMs and DQT2 demonstrated significant changes in the apparent diffusion coefficient (ADC) and T2 relaxation rate, which was largely attributed to changes in vascular permeability and edema. CIMP maps, which were evaluated after administration of bevacizumab, were thought to more closely reflect changes in cell proliferation rate rather than changes in edema. It is conceivable that the large decrease in tracer uptake observed before and after initial administration of bevacizumab in the current study was attributable to the change in vascular permeability or perfusion, whereas the change in tumor uptake between the 2 posttreatment follow-up time points more closely reflected changes in tumor metabolism and proliferation. Muzi et al. clearly demonstrated the dependence of $^{18}$F-FLT uptake rate (i.e., $K_T$) on vascular permeability; however, studies have shown that $^{18}$F-FDOPA uptake rate may not reflect simple tracer diffusion because of disruption of T2 relaxation and other factors. Although both MRI and PET may be predictive of response to therapy, they provide dramatically different information about tumor biology. Although a change in contrast-enhancing volume as a result of therapy was predictive of PFS and OS, a change in PET uptake on subsequent time points (excluding the potential confounds from vascular permeability) was a better predictor of PFS. These results suggest that MRI and PET features are distinctly different and are both potentially valuable. Of note, although change in contrast-enhancing volume before and after bevacizumab treatment was predictive of 3-month PFS, progression was at least partially defined by contrast enhancement via MRI, potentially introducing bias into this type of analysis. Furthermore, the study performed by Schwarzberner et al. which used the same patients but evaluated using ROI analysis, also found that MRI was predictive of PFS and OS; however, PET analysis provided increased predictive power, compared with MRI alone.
between \(^{18}\text{F}-\text{FLT}\) uptake and OS when using the Kaplan-Meier analysis. This is likely to be attributable to the relatively wide confidence intervals for voxel-wise change in \(^{18}\text{F}-\text{FLT}\) uptake in NAWM, compared with \(^{18}\text{F}-\text{FDOPA}\) uptake (Fig. 2). This high variability resulted in fewer voxels being categorized as significantly increasing or decreasing and may have lowered the overall sensitivity of this biomarker for stratifying OS. Future studies aimed at either reducing this variability or using a different confidence interval for \(^{18}\text{F}-\text{FLT}\) PRMs may be necessary for improving performance of this biomarker.

In addition to \(^{18}\text{F}-\text{FDOPA}\), kinetic parameters and uptake measured by SUVs of \(^{18}\text{F}-\text{FDOPA}\) have been previously studied for the prediction of tumor grade and proliferative activity in glioblastoma. However, to our knowledge, \(^{18}\text{F}-\text{FDOPA}\) has not previously been tested for predictive capabilities of PFS and OS among patients with recurrent malignant gliomas treated with bevacizumab. The current study demonstrates that voxel-wise changes in \(^{18}\text{F}-\text{FDOPA}\) provided higher sensitivity and specificity for predicting 3-month PFS and 6-month OS and allowed statistically significant separation of short- and long-term PFS and OS using log-rank analysis.

Although the current study used \(^{18}\text{F}-\text{FDOPA}\) and \(^{18}\text{F}-\text{FLT}\) PET images to predict the response to recurrent malignant gliomas treated with bevacizumab, other PET tracers have also shown promise for predicting response to anti-angiogenic therapy. For example, a recent study by Colavolpe et al. clearly demonstrated the prognostic ability of baseline, pretreatment \(^{18}\text{F}-\text{FDG}\) maximum SUV to predict the response to bevacizumab and irinotecan therapy in malignant gliomas, supporting the hypothesis that \(^{18}\text{F}-\text{FDG}\) uptake is strongly correlated with angiogenesis markers in gliomas.

\(^{18}\text{F}-\text{FDG}\) SUV in contrast-enhancing regions, normalized to gray matter, at 4 weeks posttreatment has also been shown to be a significant prognostic factor in anaplastic gliomas treated with single-agent bevacizumab. However, this study did not find baseline or change in \(^{18}\text{F}-\text{FDG}\) PET uptake to be particularly predictive of patient response. On the basis of these somewhat conflicting results, which are likely to be attributable to different definitions of \(^{18}\text{F}-\text{FDG}\) uptake and slightly different patient populations, we hypothesize that \(^{18}\text{F}-\text{FDG}\) PET PRMs may also be useful for assessing malignant glioma response to bevacizumab.

**Conclusion**

The current study examined retrospective \(^{18}\text{F}-\text{FDOPA}\) and \(^{18}\text{F}-\text{FLT}\) PET data collected from 24 patients with recurrent malignant gliomas treated with bevacizumab to construct voxel-wise PET PRMs. PRMs provided a visual and quantitative assessment of regional changes in PET uptake and prognostic information about PFS based on change in tracer uptake during the weeks after treatment. Despite these promising findings, we observed only a weak relationship between PRM response and OS. These results suggest that \(^{18}\text{F}-\text{FDOPA}\) and \(^{18}\text{F}-\text{FLT}\) PET PRM may be valuable imaging biomarkers for predicting PFS in recurrent malignant gliomas treated with bevacizumab.

**Acknowledgments**

Authors Wei Chen and Benjamin M. Ellingson contributed equally to this work.

Conflict of interest statement. None declared.