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Treatment Response Evaluation using ^{18}F-FDOPA PET in Patients with Recurrent Malignant Glioma on Bevacizumab Therapy

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Abstract

Purpose—This study compares the value of 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine (^{18}F-FDOPA) PET and MRI in assessing outcome during antiangiogenic treatment in patients with recurrent high-grade gliomas.

Experimental Design—Thirty patients were prospectively studied with ^{18}F-FDOPA PET scans immediately before, and two and six weeks after start of bevacizumab therapy. ^{18}F-FDOPA metabolic tumor volumes (MTV) as well as max and mean SUVs within this MTV were obtained. MRI treatment response was assessed at 6 weeks. The predictive ability of ^{18}F-FDOPA PET and MRI response assessment were evaluated with regard to progression-free survival (PFS) and overall survival (OS).

Results—30, 28, and 24 ^{18}F-FDOPA PET scans at baseline, 2 weeks, and 6 weeks, were available for analysis, respectively. ^{18}F-FDOPA PET SUVs as well as their changes through therapy were not predictive of outcome. However, metabolic tumor volume (MTV) parameters such as MTV changes were highly prognostic. Interestingly, absolute MTV at the first follow up scan provides the most significant prediction for increased OS ($P < 0.0001$) as well as PFS ($P =$

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0.001). This surprising result was scrutinized with cross-validation and simulation analysis. Responders based on ^{18}F-FDOPA PET data survived 3.5 times longer (12.1 vs. 3.5 months median OS, $P < 0.001$) than non-responders (17 vs. 11 patients, respectively). In comparison, responders based on MRI data lived 1.5 times longer (11.4 vs 7.7 mo, $P = 0.03$) than non-responders (22 vs. 7 patients, respectively).

Conclusions—^{18}F-FDOPA PET identifies treatment responders to antiangiogenic therapy as early as two weeks after treatment initiation.

Introduction

High-grade gliomas carry a very poor prognosis (1). Patients when initially diagnosed are treated typically by the combination of surgery, chemo and radiation therapy. Inevitably, tumors will recur. The disease status in patients with high-grade gliomas is routinely evaluated clinically and radiographically by contrast-enhanced MRI. However, due to the highly heterogeneous nature of these tumors and the complexity of changes induced by the treatment, the structural information derived from these images does not always adequately reflect both the extent of the actual lesion as well as its malignant potential (2, 3). Biomarkers that are surrogates of proliferative and malignant properties of the tumor and thus can predict treatment responses early and reliably, are under active investigation (4, 5),

Amino acid analogues (6–14) have been studied for brain tumor imaging. ^{18}F-labeled amino acid analogues have the advantage of easy clinical application because of the favorable half life (110 min) of the ^{18}F-PET tracer (7). Preliminary studies with ^{18}F-Fluoroethyl-L-Tyrosine PET in twenty-one patients with recurrent high-grade glioma on antiangiogenic treatment have shown promising results (15,16). The amino-acid-analogue L-3,4-dihydroxy-6-^{18}F-fluorophenyl-alanine (^{18}F-FDOPA) has recently also been under investigation in the evaluation of brain tumors (17–24). ^{18}F-FDOPA uptake in brain tumors is increased compared to normal brain tissue due to the up-regulation of amino acid transport across the blood brain barrier (BBB) by the neutral amino acid transporter. It has been shown previously that ^{18}F-FDOPA provides excellent visualization of high-grade as well as low-grade brain tumors (17–20). Furthermore, its uptake in tumor tissue correlates with tumor grade as well as Ki-67 proliferation index in newly diagnosed gliomas, allowing for a quantitative assessment of malignancy (23).

This study examines the tumor staging potential and predictive power of ^{18}F-FDOPA-PET in the assessment of treatment response for patients with recurrent high-grade glioma undergoing bevacizumab therapy. First, tumor uptake of ^{18}F-FDOPA as well as tumor volumes was obtained. Second, the predictive power of ^{18}F-FDOPA for progression-free (PFS) and overall survival (OS) in patients with recurrent high-grade gliomas was assessed. Last, the predictive power of ^{18}F-FDOPA was compared with MRI and other survival predictors.

PATIENTS AND METHODS

Patients

Thirty patients with recurrent high-grade gliomas were enrolled prospectively in this study (Table 1). There were 18 males and 12 females with median age of 57.5 (range: 26–78) years. All patients met the following inclusion criteria: they had a histologically confirmed diagnosis of glioblastoma (GBM) or anaplastic astrocytoma (AA) (GBM: N = 24; AA: N = 6) and had previously undergone surgical resection and chemoradiation therapy. All patients had MRI-confirmed recurrent disease by the time bevacizumab treatment was started. Further criteria included a Karnofsky Performance Score (KPS) ≥70, adequate hematological values, and sufficient hepatic and renal function. Patients were excluded if there was a bleeding disorder, a recent history of intracranial bleeding or thromboembolism.

All patients gave written consent to participate in this study, which had been approved by the University of California, Los Angeles, Office for Protection of Research Subjects.

Treatment

All Patients were treated with bevacizumab and irinotecan except for 3 patients who were treated with bevacizumab alone (patient no. 23, 26, and 28, Table 2). Co-administration of corticosteroids was closely monitored. While 12 patients did not require corticosteroids, 9 patients were maintained on stable or tapering doses of dexamethasone, and 9 patients needed a dose increase after the baseline MRI and PET studies were obtained.

Patient’s disease status was evaluated and monitored using gadolinium enhanced as well as non-enhanced MRI obtained within one week before and at approximately six-week intervals after starting bevacizumab therapy. Patients were followed until death with no subjects lost to follow up. The overall survival (OS) was defined as the interval between treatment initiation and death while progression-free survival (PFS) was defined as the interval between treatment initiation and radiographic and/or clinical progression.

PET Imaging

PET imaging was performed on a dedicated PET system (ECAT HR or HR^{+}) (25, 26). Patients were asked to fast for at least 4 hours before image acquisition. ^{18}F-FDOPA was synthesized according to a previously reported procedure (27, 28) and was injected intravenously at a mean dose of 1.89±0.37 MBq/kg. Data were acquired in the 3-dimensional mode. The emission scan was started 10 minutes after tracer injection. To correct for photon attenuation, 5-min transmission scans were acquired after the emission scans for all patients. Images were acquired for 30 minutes in the 3-dimensional mode. Image data acquired between 10 and 30 minutes were summed to obtain a 20 minute static image. PET images were reconstructed using iterative techniques with ordered-subset expectation maximization consisting of 6 iterations with 8 subsets (29, 30). A Gaussian filter with a full width at half maximum of 4 mm was applied.

Image Analysis

Images were first inspected visually with the axial PET image slice displaying the maximum tumor ^{18}F-FDOPA uptake selected. The radiotracer concentration in the regions of interest (ROIs) was normalized to the injected dose per kilogram of patient's body weight to derive the standardized uptake values (SUVs).

Tumor ROIs were defined on summed images in two ways. First, a standardized 10 mm circular region was placed over the area with the maximum activity. This was used to derive SUV_{max} and SUV_{peak}. Then, metabolic tumor volume (MTV) was obtained by including all voxels that fall within an SUV threshold determined by the mean SUV of the contralateral striatum (19). In cases where the tumor involved the striatum bilaterally, a threshold of 1.5 mean SUV of normal hemispheric background was used (19). Mean ^{18}F-FDOPA uptake within this volume (SUV_{mean}) was determined. Absolute MTVs and SUVs as well as their changes were correlated with clinical outcome.

Magnetic Resonance Imaging

Data were collected on a 1.5T MRI system (General Electric Medical Systems, Waukesha, WI) using pulse sequences supplied by the scanner manufacturer. Standard anatomical MRI sequences included axial proton density, T1, and T2 weighted fast spin-echo images, along with fluid-attenuated inversion recovery (FLAIR) images, all obtained with a 5mm slice thickness with 1mm inter-slice distance, two excitations, matrix size of 256×256, and a field-of-view of 24cm. Additionally, gadopentetate dimeglumine enhanced (Magnevist; Berlex, Wayne, NJ) axial and coronal T1 weighted images were acquired after contrast injection.

Regions of FLAIR abnormality were chosen based on Response Assessment in Neuro-Oncology (RANO) recommendations (31). The regions of post-contrast T1-weighted image (T1+C) hyperintensity were defined on post-contrast T1-weighted images, excluding any T1 shortening from blood products on pre-contrast T1-weighted images as well as cystic and surgical resection cavities. The volumes of FLAIR and T1+C were calculated using a semi-automated procedure as described previously (32).

MRI based response at 6 weeks was defined according to the RANO criteria. However, the 4 week sustained response requirement for complete and partial response was not considered since the goal of the study was to compare the predictive values of MRI and PET at 6 weeks after starting treatment (31). Progressive disease (PD) was defined as more than a 25% increase in the sum of the products of perpendicular diameters, a significant increase in non-enhancing tumor, or neurologic decline. Complete response (CR) was defined as neither enhancing- nor non-enhancing-tumor, without steroid use. Partial response (PR) was defined as more than a 50% decrease in the sum of the products of perpendicular diameters on stable steroids, without new lesions. Non-enhancing tumor was identified by mass effect and/or architectural distortion including blurring of the gray-white boundary. All scans that did not qualify above were considered stable disease (SD). MRI assessment was performed by a board certified neuroradiologist (W.B.P.).

In addition to assessment using the standard MRI response criteria, tumor volumes by MRI at baseline and follow up scans were also evaluated for response predication.

Statistical Analysis

^{18}F-FDOPA PET uptake threshold values for treatment response were established by receiver-operating-characteristic (ROC) curve analysis. Threshold values derived from this method were scrutinized by leave-one-out cross-validation analysis to assess how robust and sensitive these cutpoints were to individual values. The differences between groups of patients were established by the Student *t* test. Kaplan-Meier (KM) curves were subsequently generated to obtain survival estimates (33).

Univariate and multivariate Cox proportional-hazards models were constructed to test the relationship between ^{18}F-FDOPA metabolic response and other predictors with regard to survival (OS and PFS). The forward stepwise selection technique was utilized to reduce the multivariate models ($P < 0.10$). Harrell's c-index was used to compare the strength of predictive performance for each model. Furthermore, a permutation simulation study was performed to evaluate the effect of cut-point selection bias on the strength of the association between FDOPA and survival. Survival outcomes were randomly permuted and we recomputed the optimal cut-point for F-FDOPA for prediction of survival. For each of these cut-points we computed the c-statistic. This was done 10,000 times to form an empirical distribution for the optimal c-statistic. The p-value for the observed c-statistic was computed based on the proportion of the simulated c-statistics that were larger than the observed c-statistic. Statistical analyses were performed in SAS (version 9.2; SAS Institute. Cary, NC) and R (version 2.14.2 www.rproject.org).

RESULTS

^{18}F-FDOPA-PET Uptake Changes

Thirty patients were enrolled for the ^{18}F-FDOPA PET study (Table 1). All 30 patients completed the baseline ^{18}F-FDOPA PET scan while 28 patients completed the second scan two weeks later and 24 patients were able to complete the third ^{18}F-FDOPA PET scan six weeks after starting treatment.

Tumor ^{18}F-FDOPA SUVs for all scans were obtained. Tumor SUV_{max} on baseline scans varied between 1.32 and 4.14. Following therapy, no significant changes of SUVs were seen (Figure 1; SUV_{max} 2 weeks: -4.3% ± 15%; 6 weeks: −2.7% ± 19%; 2 – 6 weeks: +3.5% ± 22%).

Metabolic tumor volumes, as delineated by ^{18}F-FDOPA uptake, were determined and are listed in Table 2. Patients' median MTVs were 24.4 (range 1.6 to 272.3 ml) at baseline, 11.3 (range 1.0 to 181.0 ml) at 2 weeks, and 7.6 (range 0.83 to 115.5) at 6 weeks (Table 2). Significant changes of ^{18}F-FDOPA-PET MTV were found (mean values: −40% ± 27% at 2 weeks and −47% ± 42% at 6 weeks (Figure 1).

Optimal ^{18}F-FDOPA-PET Criteria for Survival Prediction

^{18}F-FDOPA uptake values (at baseline, two weeks or six weeks) both as SUV_{max} as well as SUV_{peak} were initially analyzed but were found not to be predictive of survival. Changes of SUV over the course of therapy were not indicative of treatment success, either.

However, ^{18}F-FDOPA MTV changes were predictive of treatment response. Using receiver-operating-characteristic curve (ROC) analysis, threshold values for MTV changes between baseline and 2 weeks, and baseline and 6 weeks, were obtained. Subsequently, Kaplan-Meier analysis was performed to assess their predictive power for PFS and OS.

When comparing ^{18}F-FDOPA MTV changes from baseline to 2 weeks using the ROC derived threshold value of ≥ 35% reduction, 16 responders and 12 non-responders were identified with ^{18}F-FDOPA MTV changes of −58% ± 16% for responders and −15% ± 17% for non-responders, respectively ($P < 0.001$). The mean OS was 13.7 months for responders versus 7.0 months for non-responders ($P = 0.02$). At 6 weeks, 17 responders and 7 non-responders were identified with ^{18}F-FDOPA MTV changes of −67% ± 18% for responders and +0.4% ± 48% non-responders, respectively ($P = 0.01$). Mean OS was 14.1 months for responders and 7.6 months for non-responders ($P = 0.02$). ^{18}F-FDOPA MTV change at 6 weeks is a stronger predictor of overall survival ($P < 0.001$) than MTV change at 2 weeks ($P = 0.001$), whereas ^{18}F-FDOPA MTV change at 2 weeks ($P < 0.001$) is a stronger predictor for progression free survival than ^{18}F-FDOPA MTV change at 6 weeks ($P = 0.003$).

Next, absolute MTVs at baseline and follow up scans were assessed for their predictive performance. As expected, baseline MTVs do not correlate with survival (PFS and OS). Interestingly, MTVs at follow up scans do correlate with survival and ROC analysis identifies an optimal threshold tumor volume of 18 ml. This surprising result was scrutinized by performing a leave-one-out cross-validation analysis to assess how robust and sensitive this cut point was to individual values. 28 of 30 cut point result thus derived generate a value of 18 ml, with the remaining two being 16.55 ml and 18.89 ml. When applying the optimal threshold value ^{18}F-FDOPA MTV ≤ 18 ml at 2 weeks, 17 responders and 11 non-responders are indentified. Examples of individual responses are shown in Figure 2. The median survival for the responders was 12.1 versus 3.5 months for non-responders, a 3.5 fold survival advantage ($P < 0.001$). ^{18}F-FDOPA MTV at two weeks is the most significant predictor of overall survival as well as progression free survival by Kaplan Meier analysis ($P < 0.001$ and $P = 0.001$ respectively; Figure 3). ^{18}F-FDOPA MTV at 6 weeks is also predictive of overall survival and progression free survival ($P = 0.03$ and $P = 0.02$ respectively).

Response assessment by MRI

Response by MRI was evaluated at approximately 6 weeks (5.9 ± 2.7) after starting treatment based on RANO criteria and was available for twenty-nine patients. By MRI criteria, 22 patients were classified as responders (76%), these include two complete response (CR), seven partial response (PR), and thirteen patients with stable disease (SD). The remaining 7 patients (24%) had progressive disease (PD) and were considered non-responders. MRI response was predictive of overall survival as well as progression-free

survival ($P = 0.01$ and $P < 0.001$ respectively). Median overall survival for responders based on MRI criteria was 1.5 times longer than for non-responders (11.4 vs 7.7 mo, $P = 0.03$). Comparing responders by PET and MRI criteria, eight discrepant cases were identified. Of these, six patients showed a response by MRI (5 SDs, 1 PR), but no treatment response by ^{18}F-FDOPA. As these patients had a median survival of only 3.4 months, ^{18}F-FDOPA predicted treatment failure earlier than MRI. A median time benefit of 7.2 weeks (range 2 – 20 weeks) for earlier detection of treatment failure with ^{18}F-FDOPA was demonstrated. The remaining two discrepant cases were classified as non-responders (PD) by MRI but showed response with ^{18}F-FDOPA. These two patients lived for 9.5 and 12 mo.

Contrary to the PET study, MRI derived absolute tumor volumes did not show survival correlation.

^{18}F-FDOPA-PET Changes Compared with other Predictors

Multiple clinical variables were tested by univariate and multivariate analyses (Table 3, 4). Measurements of MTV at baseline, two weeks, and six weeks in addition to changes between these time points were modeled. Baseline characteristics such as age, number of prior recurrences, and RANO response at 6 weeks were considered in the multivariate models. Modeling all MTV measurement combinations at each time point would induce a survival bias because those who died after two weeks would not have had 6 week measurements (and thus be excluded from the model). Therefore models were run with baseline data, data up through 2 weeks, and data up through 6 weeks separately (Table 4). By univariate analysis, OS was better if patients had fewer recurrences. Patients' age, baseline KPS, dexamethasone treatment, did not predict survival (Table 3). ^{18}F-FDOPA MTVs at 2 weeks and 6 weeks, as well as their changes from baseline to 2 weeks and baseline to 6 weeks were all predictive of OS ($P < 0.001$, $P = 0.04$, $P = 0.01$, $P = 0.01$, Table 3). However, ^{18}F-FDOPA absolute MTV at 2 weeks and ^{18}F-FDOPA MTV changes at 2 or at 6 weeks provided the highest hazard ratios (HR = 9.05, 2.94 and 4.02 respectively). Response by MRI was also predictive of survival ($P = 0.016$).

By multivariate analysis, ^{18}F-FDOPA MTV at 2 weeks ($P < 0.05$; HR = 7.79) and MTV changes at 6 weeks ($P < 0.05$; HR = 4.09) were the most significant predictors of OS. Interestingly, no apparent added value of 6-week ^{18}F-FDOPA MTV for survival prediction was seen with HR of 10.71 ($P < 0.01$) for 2 week ^{18}F-FDOPA MTV response and HR of 4.09 ($P <0.05$) for 6-week ^{18}F-FDOPA MTV response (Table 4).

Similarly, longer PFS was predicted if patients had fewer prior recurrences. ^{18}F-FDOPA MTV at 2 weeks, 6 weeks, and their changes from baseline to 2 weeks and 6 weeks, as well as MRI response were all predictive of PFS ($P = 0.004$, $P = 0.02$, $P < 0.001$, $P = 0.002$, $P = 0.01$). By multivariate analysis, ^{18}F-FDOPA MTV change at 2 weeks ($P < 0.01$; HR, 4.38) is the most significant predictor of PFS.

DISCUSSION

This study examines the value of ^{18}F-FDOPA PET in assessing treatment response in patients with recurrent high-grade gliomas on bevacizumab therapy. First, this study

demonstrates that MTV measured by ^{18}F-FDOPA uptake is predictive of OS in patients with recurrent high-grade glioma. Absolute MTV as measured by ^{18}F-FDOPA uptake as early as 2 weeks after starting treatment is the best predictor of OS ($P < 0.001$). Evaluation of ^{18}F-FDOPA MTV at 2 weeks stratifies patients into 2 subgroups, ^{18}F-FDOPA responders (17/28, 61%) and non-responders (11/28, 39%). ^{18}F-FDOPA responders survived for 12.1 mo, which is 3.5 times longer than the 3.5 mo survival for non-responders ($P < 0.001$). Second, this study shows that change of ^{18}F-FDOPA MTV at 2 weeks and at 6 weeks ($P = 0.002$ and $P = 0.02$) is also predictive of OS, albeit being not as strong a predictor as the absolute MTV at 2 weeks. Third, ^{18}F-FDOPA MTV as well as MTV change at two weeks after treatment initiation are predictive of PFS ($P < 0.001$ and $P = 0.001$ respectively). Fourth, ^{18}F-FDOPA SUV values as well as their changes at any time point are not predictive of survival. Finally, this study compared metabolic responses by ^{18}F-FDOPA with MRI response based on RANO criteria. MRI identifies 22 responders (76%; 2 CR, 7 PR, and 13 SD), and 7 patients with PD (24%) and is predictive of OS. Median OS is 1.5 times longer for MRI responders than for MRI non-responders (11.4 vs. 7.7 mo, $P = 0.03$).

MRI contrast enhancement primarily reflects a disrupted blood–brain barrier (BBB), which can be influenced by changes in corticosteroid dose as well as other treatment effects such as inflammation, radiation necrosis, and postsurgical change (3). In addition, non-enhancing T2-weighted and fluid-attenuated inversion recovery sequence changes can reflect tumor recurrence as well, especially in patients on antiangiogenic therapy (31, 32). Thus, it has been proposed by the recently published Response Assessment in Neurooncology (RANO) that changes in both enhancing and non-enhancing areas should be considered in evaluating treatment response by MRI (31, 32).

All patients in this study had also undergone ^{18}F-fluoro-thymidine (FLT) PET scans as previously reported (5). Current result showed while resonse criteria is different with ^{18}F-FLT PET (maximum tumor SUV changes rather than tumor volume), both ^{18}F-FDOPA PET and ^{18}F-FLT PET have similar predictive value in treatment response in this group of patients. OS for responders and non-responders by ^{18} F-FLT PET is 12.5 *vs* 3.8 months ($P < 0.001$) and OS by ^{18} F-FDOPA PET is 12.1 *vs* 3.5 months ($P < 0.001$).

As amino acid uptake in tumors is not limited to the disruption of BBB, amino acid PET imaging is particularly advantageous in evaluating non-contrast enhancing infiltrating tumors. Amino acid imaging with ^{18}F-FET PET in monitoring treatment in 11 and 10 glioma patients were reported previously (15,16). In was shown ^{18}F-FET PET generally demonstrated treatment failure earlier than MRI. However, follow up ^{18}F-FET-PET was done at 6 – 8 weeks after starting treatment in that study, much later than our study (15,16). Similar to our study, it was shown that ^{18}F-FET PET tumor volume change, but not the SUV change, was predictive of progression free survival. Interestingly, it was noted in our study that not only ^{18}F-FDOPA tumor volume changes but also the ^{18}F-FDOPA tumor volumes at follow up study are predictive of treatment response. As this finding has not been previously reported, rigorous statistical analyses were performed using a leave one out cross-validation analysis to assess how robust and sensitive the cut point to individual values. In addition, a simulation to assess whether this finding was likely a function of selection bias was performed. The process involves breaking up the relationship between ^{18}F-FDOPA MTV

and survival variable by randomly permuting the observations and then optimizing a cut point to create an empirical distribution of c-statistics to compare our result to.

In our study, baseline ^{18}F-FDOPA MTV is not predictive of OS ($P = 0.08$) or PFS ($P = 0.31$) but the MTVs in the follow up studies are. This is probably due to the fact that while tumor amino acid uptake is not dependent on a permeable BBB, it is enhanced by a broken BBB (34–37). High grade gliomas have pronounced tumor neovascularization through the VEGF pathway and anti-VEGF therapy results in an apparent normalization of the highly permeable BBB (38, 39). It is likely that baseline ^{18}F-FDOPA uptake is in part due to this disturbance of the BBB, thus reflecting a larger than actual tumor volume and therefore is not prognostic of survival. After "normalization" of the disturbed BBB with bevacizumab, ^{18}F-FDOPA uptake in the follow-up studies becomes more reflective of tumor metabolism and outlines an effective tumor volume. Both the decrease of the tumor volume after treatment initiation as well as the resultant tumor size are prognosticators of survival. The fact that only the follow-up ^{18}F-FDOPA MTVs but not the baseline ^{18}F-FDOPA MTV are prognostic, must to some extent reflect the effects of anti-VEGF therapy irrespective of the therapy's actual mechanism.

The current study has several limitations: First, the study population was small, thus these result need to be validated in a larger prospective study. Second, the patient population is relatively heterogeneous. There was a mix of grade III (N = 6) and grade IV (N = 24) patients. Patients also had a various number of recurrences (median 1.77, range 1 – 5). One could argue that with a patient population at different stages of disease, one would see different prognosis at baseline. Indeed, the number of recurrences before starting treatment is predictive of OS and PFS. However, it is not as strong a predictor as ^{18}F-FDOPA metabolic response, so a significant added predictive value of ^{18}F-FDOPA metabolic response is seen (Table 4).

CONCLUSION

The current study demonstrates that metabolic imaging with ^{18}F-FDOPA PET provides a powerful prognostic tool in assessing treatment response in recurrent high-grade glioma patients on bevacizumab therapy. This response already becomes apparent two weeks after starting treatment. As absolute MTV can be used for assessment, one ^{18}F-FDOPA PET at two weeks suffices to assess treatment response, thus potentially making treatment response assessment with ^{18}F-FDOPA PET both early and cost effective. A further and larger validation study is needed to test the potential of ^{18}F-FDOPA PET in guiding treatment decisions.

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References

1. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol. 2007; 114:97–109. [PubMed: 17618441]
2. Daumas-Duport C, Scheithauer BW, Kelly PJ. A histologic and cytologic method for the spatial definition of gliomas. Mayo Clin Proc. 1987; 62:435–49. [PubMed: 2437411]
3. Scott JN, Brasher PM, Sevick RJ, Rewcastle NB, Forsyth PA. How often are nonenhancing supratentorial gliomas malignant? A population study. Neurology. 2002; 59:947–9. [PubMed: 12297589]
4. Chen W, Delaloye S, Silverman DH, Geist C, Czernin J, Sayre J, et al. Predicting treatment response of malignant gliomas to bevacizumab and irinotecan by imaging proliferation with [18F] fluorothymidine positron emission tomography: a pilot study. J Clin Oncol. 2007; 25:4714–21. [PubMed: 17947718]
5. Schwarzenberg J, Czernin J, Cloughesy TF, Ellingson BM, Pope WB, Geist C, et al. 3′-deoxy-3′-18F-fluorothymidine PET and MRI for early survival predictions in patients with recurrent malignant glioma treated with bevacizumab. J Nucl Med. 2012; 53:29–36. [PubMed: 22159180]
6. Jager PL, Vaalburg W, Pruim J, de Vries EG, Langen KJ, Piers DA. Radiolabeled amino acids: basic aspects and clinical applications in oncology. J Nucl Med. 2001; 42:432–45. [PubMed: 11337520]
7. Laverman P, Boerman OC, Corstens FH, Oyen WJ. Fluorinated amino acids for tumour imaging with positron emission tomography. Eur J Nucl Med Mol Imaging. 2002; 29:681–90. [PubMed: 11976809]
8. Herholz K, Holzer T, Bauer B, Schroder R, Voges J, Ernestus RI, et al. 11C-methionine PET for differential diagnosis of low-grade gliomas. Neurology. 1998; 50:1316–22. [PubMed: 9595980]
9. Bergstrom M, Collins VP, Ehrin E, Ericson K, Eriksson L, Greitz T, et al. Discrepancies in brain tumor extent as shown by computed tomography and positron emission tomography using [68Ga]EDTA, [11C]glucose, and [11C]methionine. J Comput Assist Tomogr. 1983; 7:1062–6. [PubMed: 6415134]
10. Mosskin M, von Holst H, Bergstrom M, Collins VP, Eriksson L, Johnstrom P, et al. Positron emission tomography with 11C-methionine and computed tomography of intracranial tumours compared with histopathologic examination of multiple biopsies. Acta Radiol. 1987; 28:673–81. [PubMed: 2962599]
11. Chung JK, Kim YK, Kim SK, Lee YJ, Paek S, Yeo JS, et al. Usefulness of 11C-methionine PET in the evaluation of brain lesions that are hypo- or isometabolic on 18F-FDG PET. Eur J Nucl Med Mol Imaging. 2002; 29:176–82. [PubMed: 11926379]
12. Huang MC, Shih YH, Chen MH, Chung WY, Ho DM, Liu RS, et al. Malignancy of intracerebral lesions evaluated with 11C-methionine-PET. J Clin Neurosci. 2005; 12:775–80. [PubMed: 16198917]
13. Kim S, Chung JK, Im SH, Jeong JM, Lee DS, Kim DG, et al. 11C-methionine PET as a prognostic marker in patients with glioma: comparison with 18F-FDG PET. Eur J Nucl Med Mol Imaging. 2005; 32:52–9. [PubMed: 15309332]
14. Popperl G, Kreth FW, Mehrkens JH, Herms J, Seelos K, Koch W, et al. FET PET for the evaluation of untreated gliomas: correlation of FET uptake and uptake kinetics with tumour grading. Eur J Nucl Med Mol Imaging. 2007; 34:1933–42. [PubMed: 17763848]
15. Hutterer M, Nowosielski M, Putzer D, Waitz D, Tinkhauser G, Kostron H, et al. O-(2-18F-fluoroethyl)-L-tyrosine PET predicts failure of antiangiogenic treatment in patients with recurrent high-grade glioma. J Nucl Med. 2011; 52:856–64. [PubMed: 21622893]
16. Galldiks N, Rapp M, Stoffels G, Fink GR, Shah NJ, Goenen HH, et al. Response assessment of bevacizumab in patients with recurrent malignant glioma using [^{18}F]Fluoroethyl-L-tyrosine PET in comparison to MRI. Eur J Nucl Med Mol Imaging. 2013; 40:22–23. [PubMed: 23053325]
17. Heiss WD, Wienhard K, Wagner R, Lanfermann H, Thiel A, Herholz K, et al. F-Dopa as an amino acid tracer to detect brain tumors. J Nucl Med. 1996; 37:1180–2. [PubMed: 8965194]

18. Becherer A, Karanikas G, Szabo M, Zettinig G, Asenbaum S, Marosi C, et al. Brain tumour imaging with PET: a comparison between [18F]fluorodopa and [11C]methionine. Eur J Nucl Med Mol Imaging. 2003; 30:1561–7. [PubMed: 14579097]
19. Chen W, Silverman DH, Delaloye S, Czernin J, Kamdar N, Pope W, et al. 18F-FDOPA PET imaging of brain tumors: comparison study with 18F-FDG PET and evaluation of diagnostic accuracy. J Nucl Med. 2006; 47:904–11. [PubMed: 16741298]
20. Tripathi M, Sharma R, D'Souza M, Jaimini A, Panwar P, Varshney R, et al. Comparative evaluation of F-18 FDOPA, F-18 FDG, and F-18 FLT-PET/CT for metabolic imaging of low grade gliomas. Clin Nucl Med. 2009; 34:878–83. [PubMed: 20139821]
21. Ledezma CJ, Chen W, Sai V, Freitas B, Cloughesy T, Czernin J, et al. 18F-FDOPA PET/MRI fusion in patients with primary/recurrent gliomas: initial experience. Eur J Radiol. 2009; 71:242–8. [PubMed: 18511228]
22. Schiepers C, Chen W, Cloughesy T, Dahlbom M, Huang SC. 18F-FDOPA kinetics in brain tumors. J Nucl Med. 2007; 48:1651–61. [PubMed: 17873130]
23. Fueger BJ, Czernin J, Cloughesy T, Silverman DH, Geist CL, Walter MA, et al. Correlation of 6-18F-fluoro-L-dopa PET uptake with proliferation and tumor grade in newly diagnosed and recurrent gliomas. J Nucl Med. 2010; 51:1532–8. [PubMed: 20847166]
24. Walter F, Cloughesy T, Walter MA, Lai A, Nghiemphu P, Wagle N, et al. Impact of 3,4-dihydroxy-6-18F-fluoro-L-phenylalanine PET/CT on managing patients with brain tumors: the referring physician's perspective. J Nucl Med. 2012; 53:393–8. [PubMed: 22323780]
25. Brix G, Zaers J, Adam LE, Bellemann ME, Ostertag H, Trojan H, et al. Performance evaluation of a whole-body PET scanner using the NEMA protocol. National Electrical Manufacturers Association. J Nucl Med. 1997; 38:1614–23. [PubMed: 9379202]
26. Lartizien C, Comtat C, Kinahan PE, Ferreira N, Bendriem B, Trebossen R. Optimization of injected dose based on noise equivalent count rates for 2- and 3-dimensional whole-body PET. J Nucl Med. 2002; 43:1268–78. [PubMed: 12215569]
27. Namavari M, Bishop A, Satyamurthy N, Bida G, Barrio JR. Regioselective radiofluorodestannylation with [18F]F2 and [18F]CH3COOF: a high yield synthesis of 6-[18F]Fluoro-L-dopa. Int J Rad Appl Instrum A. 1992; 43:989–96. [PubMed: 1330984]
28. Bishop A, Satyamurthy N, Bida G, Hendry G, Phelps M, Barrio JR. Proton irradiation of [18O]O2: production of [18F]F2 and [18F]F2 + [18F] OF2. Nucl Med Biol. 1996; 23:189–99. [PubMed: 8782226]
29. Kinahan PE, Townsend DW, Beyer T, Sashin D. Attenuation correction for a combined 3D PET/CT scanner. Med Phys. 1998; 25:2046–53. [PubMed: 9800714]
30. Nuyts J, Michel C, Dupont P. Maximum-likelihood expectation-maximization reconstruction of sinograms with arbitrary noise distribution using NEC-transformations. IEEE Trans Med Imaging. 2001; 20:365–75. [PubMed: 11403196]
31. Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol. 2010; 28:1963–72. [PubMed: 20231676]
32. Ellingson BM, Cloughesy TF, Lai A, Nghiemphu PL, Mischel PS, Pope WB. Quantitative volumetric analysis of conventional MRI response in recurrent glioblastoma treated with bevacizumab. Neuro Oncol. 2011; 13:401–9. [PubMed: 21324937]
33. Kaplan E, Meier P. Nonparametric-estimation from incolmplete observations. J Am Stat Association. 1958; 53:457–81.
34. Langen KJ, Muhlensiepen H, Holschbach M, Hautzel H, Jansen P, Coenen HH. Transport mechanisms of 3-[123I]iodo-alpha-methyl-L-tyrosine in a human glioma cell line: comparison with [3H]methyl]-L-methionine. J Nucl Med. 2000; 41:1250–5. [PubMed: 10914918]
35. Roelcke U, Radu EW, von Ammon K, Hausmann O, Maguire RP, Leenders KL. Alteration of blood-brain barrier in human brain tumors: comparison of [18F]fluorodeoxyglucose, [11C]methionine and rubidium-82 using PET. J Neurol Sci. 1995; 132:20–7. [PubMed: 8523026]
36. Spaeth N, Wyss MT, Weber B, Scheidegger S, Lutz A, Verwey J, et al. Uptake of 18F-fluorocholine, 18F-fluoroethyl-L-tyrosine, and 18F-FDG in acute cerebral radiation injury in the

rat: implications for separation of radiation necrosis from tumor recurrence. J Nucl Med. 2004; 45:1931–8. [PubMed: 15534065]

37. Sasajima T, Miyagawa T, Oku T, Gelovani JG, Finn R, Blasberg R. Proliferation-dependent changes in amino acid transport and glucose metabolism in glioma cell lines. Eur J Nucl Med Mol Imaging. 2004; 31:1244–56. [PubMed: 15141325]
38. Jain RK. Molecular regulation of vessel maturation. Nat Med. 2003; 9:685–93. [PubMed: 12778167]
39. Folkman J. Tumor angiogenesis: therapeutic implications. N Engl J Med. 1971; 285:1182–6. [PubMed: 4938153]

Translational Relevance

Recurrent malignant gliomas carry a very poor prognosis and targeted therapy is an area of active investigation. A non-invasive biomarker that accurately evaluates the disease status and assesses the treatment response with prognostic value (outcome) is critically needed. This study examines the application of ^{18}F-FDOPA PET, a metabolic imaging modality, for monitoring treatment response and for providing prognostic information in patients with recurrent high-grade malignant gliomas on antiangiogenic treatment with bevacizumab. The results of the study can guide the selection of treatment for these patients by identifying responders from non-responders at an early time point after starting therapy. Responders identified by this method live an average of 3.5 times longer than non-responders. Use of this approach would facilitate accrual to clinical trials of targeted therapy in patients with recurrent malignant gliomas.

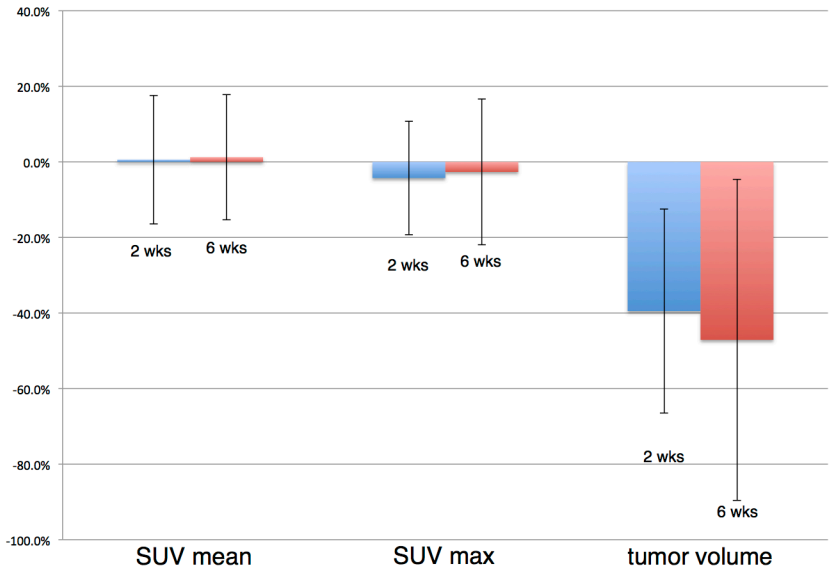

Figure 1.

Changes in ^{18}F-FDOPA SUVmean, SUVmax, and MTV from baseline to 2-weeks and baseline to 6 weeks as measured from bevacizumab treatment initiation.

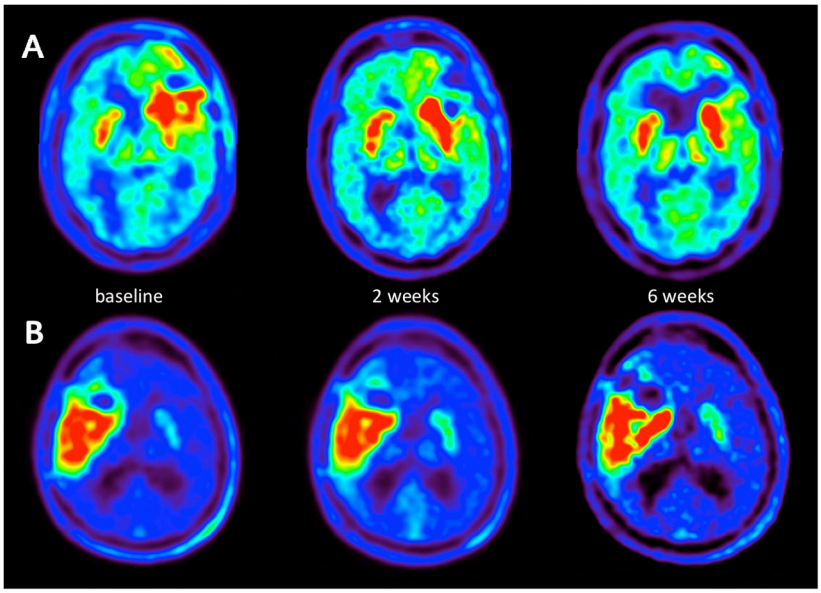

Figure 2.
^{18}F-FDOPA PET at baseline, 2 weeks, and 6 weeks of a responding patient (A, patient 25, Table 2) and a non-responding patient (B, patient 18, Table 2).

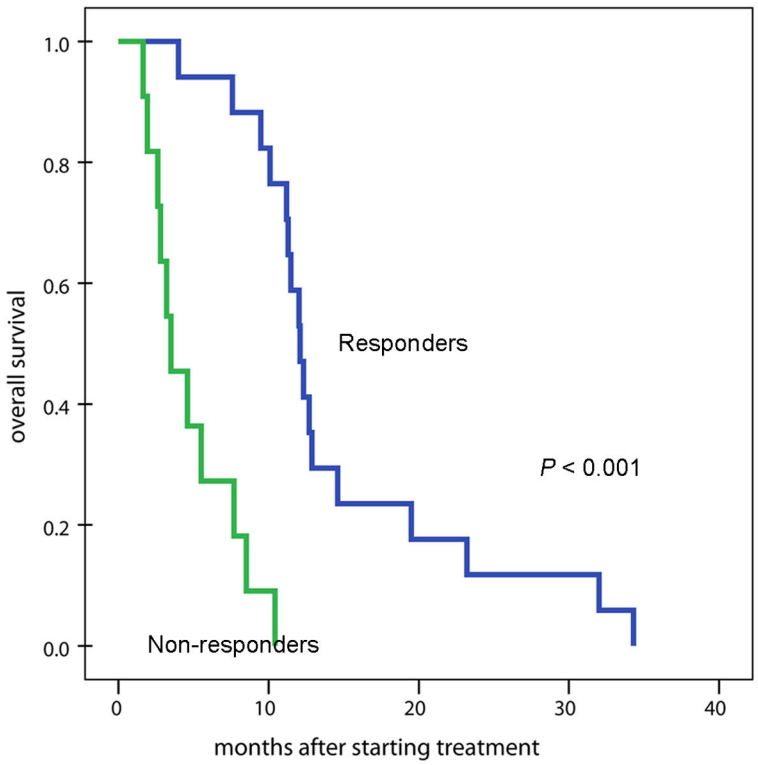

Figure 3.
Kaplan-Meier OS curve separated by ^{18}F-FDOPA PET MTV at 2 weeks after treatment initiation.

Table 1

Patient Characteristics

Characteristic	No.
Median age, years	57.5
Range	26–78
Tumor grade	
Grade III	6
Grade IV	24
Number of recurrences	
Median	2
1–2 recurrences	24
3–4 recurrences	5
5 recurrences	1
Median prior treatment regimen	3.07
Range	0–9
1–2 regimens	18
3–5 regimens	6
6–9 regimens	6
Dexamethasone treatment	
Absence	12
Presence	18
Karnofsky Performance Score (KPS)	
70–80	13
90–100	17

Table 2

Patient Characteristics, Tumor ^{18}F- FDOPA uptake, and OS

Pt No	Sex/Age	Dx	^{18}F-FDOPA baseline MTV	^{18}F-FDOPA MTV 2 wk after treatment start	^{18}F-FDOPA ΔMTV 2 wk after treatment start	^{18}F-FDOPA MTV 6 wk after treatment start	^{18}F-FDOPA ΔMTV 6 wk after treatment start	^{18}F-FDOPA response (MTV 2 wk)[b]	^{18}F-FDOPA response (ΔMTV 2 wk)[b]	MRI respone (6 wk)[c]	PFS (mon)	OS (mon)
1	F/38	AA	30.02	20.56	−32%	ND	NA	No	No	SD‡	5.0	8.5
2	M/78	GBM	22.12	ND	NA	ND	NA	NA	NA	PD	0.5	0.8
3	M/64	GBM	3.27	3.38	3%	2.64	−19%	Yes	No	PR	2.2	7.6
4	F/45	GBM	15.00	12.60	−16%	8.16	−46%	Yes	No	SD	1.7	11.3
5	M/37	GBM	32.77	10.84	−67%	11.71	−64%	Yes	Yes	SD	3.8	4.0
6	M/65	AA	272.35	138.63	−49%	115.51	−58%	No	Yes	NA*	3.6	4.6
7	M/65	AMG	34.50	23.08	−33%	ND	NA	No	No	PD	0.7	2.6
8	F/61	GBM	104.27	ND	NA	19.00	−82%	NA	NA	SD	4.5	13.1
9	M/69	GBM	87.42	18.43	−79%	2.62	−97%	No	Yes	PR‡	2.8	2.8
10	M/26	GBM	17.16	11.47	−33%	12.33	−28%	Yes	No	SD	3.2	11.5
11	F/65	GBM	26.71	30.13	13%	54.05	102%	No	No	SD‡	2.5	3.5
12	F/35	GBM	54.86	33.82	−38%	24.02	−56%	No	Yes	PD	2.1	10.4
13	F/62	GBM	3.75	0.81	−78%	0.77	−79%	Yes	Yes	PR	8.9	23.2
14	M/28	AA	185.06	181.03	−2%	ND	NA	No	No	PD	1.5	7.7
15	F/68	GBM	34.12	25.68	−25%	ND	NA	No	No	PD	1.1	1.6
16	F/47	GBM	16.18	17.22	6%	7.86	−51%	Yes	No	SD	5.6	12.7
17	F/54	GBM	29.67	7.03	−76%	7.60	−74%	Yes	Yes	PR	7.3	12.1
18	M/58	GBM	43.83	40.77	−7%	36.94	−16%	No	No	SD‡	1.6	3.2
19	M/46	GBM	10.23	5.48	−46%	5.84	−43%	Yes	Yes	SD	2.4	11.2
20	M/50	AA	15.36	10.42 [a]	−32%	ND	NA	No [a]	NA [a]	SD‡	0.9	1.9
21	M/70	GBM	9.41	4.05	−57%	3.30	−65%	Yes	Yes	PR	6.7	12.9
22	M/66	GBM	17.29	3.71	−79%	3.06	−82%	Yes	Yes	SD	11.1	12.3
23	M/47	GBM	2.76	1.79	−35%	1.65	−40%	Yes	Yes	CR	18.2	34.3
24	F/58	GBM	56.36	30.41	−46%	37.75	−33%	No	Yes	SD‡	1.3	5.5
25	M/76	GBM	36.00	11.10	−69%	3.56	−90%	Yes	Yes	CR	24.0	32.0

Pt No	Sex/Age	Dx	^{18}F-FDOPA baseline MTV	^{18}F-FDOPA MTV 2 wk after treatment start	^{18}F-FDOPA ΔMTV 2 wk after treatment start	^{18}F-FDOPA MTV 6 wk after treatment start	^{18}F-FDOPA ΔMTV 6 wk after treatment start	^{18}F-FDOPA response (MTV 2 wk)[b]	^{18}F-FDOPA response (ΔMTV 2 wk)[b]	MRI respone (6 wk)[c]	PFS (mon)	OS (mon)
26	M/68	GBM	5.17	3.01	−42%	3.93	−24%	Yes	Yes	PR	6.9	10.1
27	F/37	GBM	34.29	14.66	−57%	12.02	−65%	Yes	Yes	PR	10.6	14.6
28	M/37	AA	18.82	6.28	−67%	1.73	−91%	Yes	Yes	PD‡	1.9	9.5
29	M/57	GBM	1.64	0.97	−41%	0.83	−49%	Yes	Yes	SD	4.2	19.5
30	F/41	GBM	6.28	4.94	−21%	7.59	21%	Yes	No	PD‡	1.4	12.0

Annotations:

[a] Patient developed a second lesion after 2 weeks.

[b] according to PET criteria derived from ROC statistical analysis.

[c] As this was MRI evaluation at 6 weeks, no 4 week sustained response requirement for responders based on RANO (14) was taken into consideration for this evaluation.

‡ Mismatch between MRI and best PET response assessment, SD, PR, and CR are considered treatment responders

Abbreviations: Pt: patient; Dx: diagnosis; AA: anaplastic astrocytoma; GBM: glioblastoma multiforme; AMG: anaplastic mixed glioma; ND: not done; NA: not applicable; PFS: progression-free survival and OS: overall survival from begin of bevacizumab treatment. PD: progressive disease; SD: stable disease; PR: partial response; CR: complete response.

Table 3

Univariate Cox Regression Analysis of OS and PFS

	OS			PFS		
Predictive factor	**HR (95% CI)**	***P***	**C**	**HR (95% CI)**	**P**	**C**
Age	1.00 (0.97, 1.03)	0.97	0.50	0.99 (0.96, 1.01)	0.33	0.56
No. of recurrences	2.24 (1.44, 3.51)	0.001	0.67	2.04 (1.35, 3.10)	0.001	0.66
Dexamethasone treatment	1.79 (0.77, 4.17)	0.18	0.56	1.16 (0.51, 2.67)	0.73	0.52
Tumor size change by MRI	3.22 (1.25, 8.32)	0.02	0.62	4.15 (1.65, 10.45)	0.003	0.64
^{18}F-FDOPA baseline MTV	1.93 (0.90, 4.13)	0.09	0.58	1.27 (0.60, 2.68)	0.53	0.53
^{18}F-FDOPA MTV at 2 wk	9.05 (2.90, 28.28)	<0.001	0.71	3.91 (1.54, 9.94)	0.004	0.66
^{18}F-FDOPA MTV at 6 wk	2.84 (1.06, 7.62)	0.04	0.59	3.39 (1.19, 9.68)	0.02	0.61
^{18}F-FDOPA MTV reduction 0–2 wk	2.94 (1.24, 6.97)	0.01	0.63	4.34 (1.73, 10.88)	0.002	0.66
^{18}F-FDOPA MTV reduction 0–6 wk	4.02 (1.38, 11.72)	0.01	0.63	3.37 (1.28, 8.89)	0.01	0.62

HR: Hazard ratio. *P*: Significance. C: Harrell's C statistic.

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Table 4

Multivariate COX Regression Analysis of OS

	Inclusion of F-FDOPA measure (# cases in model)	Predictors	HR (95% CI)	P-Value	C-Statistic
Baseline factors only	without ^{18}F-FDOPA PET	Recurrences* (30)	2.24 (1.44, 3.51)	0.001	0.67
	with ^{18}F-FDOPA PET	Baseline ^{18}F-FDOPA MTV (30)	1.01(1.00, 1.01)	0.21	0.70
		Recurrences (30)	2.32(1.44, 3.74)	0.001	
Baseline and 2 week factors	without ^{18}F-FDOPA PET	Recurrences* (30)	2.24 (1.44, 3.51)	0.001	0.67
	with ^{18}F-FDOPA PET	2 week ^{18}F-FDOPA MTV	7.79 (2.18, 27.77)	0.002	0.76
		Recurrences (28)	1.74(1.04, 2.91)	0.036	
Baseline, 2 and 6 week factors	without ^{18}F-FDOPA PET	Recurrences* (29)	2.33 (1.44, 3.67)	0.01	0.68
	with ^{18}F-FDOPA PET	2 week ^{18}F-FDOPA MTV	10.71(2.44, 47.09)	0.002	0.73
		6 week ^{18}F-FDOPA MTV reduction	4.09(1.23, 13.59)	0.02	