

The Role of PET [^{18}F]FDOPA in Evaluating Low-grade Glioma

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Abstract. *Aim: The aim of the present study was to evaluate the prognostic value of 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine ([^{18}F]-FDOPA) positron-emission tomography (PET) in predicting the risk of radiological progression of disease in patients affected by low-grade glioma. Patients and Methods: Patients affected by grade II glioma were consecutively enrolled in a prospective observational study at the Department of Neurology of Regina Elena National Cancer Institute in Rome, Italy. At enrolment, all patients underwent PET [^{18}F]-FDOPA and Magnetic Resonance Imaging (MRI), and clinical and radiological assessments with MRI every six months to evaluate the progression of disease. Results: A total of 50 patients affected by grade II glioma (30 males and 20 females) were included in the study. The multivariate analysis showed that standardized uptake value greater than 1.75 and disease duration were independent predictors of disease progression. Conclusion: These findings suggest that the PET [^{18}F]-FDOPA may play an important prognostic role in evaluation of low-grade glioma.*

Low-grade gliomas (LGGs) are slow-growing tumors including grade II oligodendrogliomas, astrocytomas and mixed oligo-astrocytomas according to the classification of the World Health Organization (WHO) (1). LGGs are clinically, histologically, and molecularly diverse (2). The natural history of LGGs results in transformation into high-grade tumors. This transformation is the main determinant of

a patient's survival, but the timing of change into a high-grade tumor is still not predictable. Today, magnetic resonance imaging (MRI) provides excellent morphological information on the localization of this kind of tumor (3), but is inadequate in providing the exact delineation of tumor volumes, treatment-induced changes, and recurrence (4, 5). LGG growth does not follow an exponential evolution because newly-produced tumor cells diffuse into the surrounding parenchyma, and their density does not reach the minimal threshold required to be detected on MRI (6, 7).

Given the limitations of morphological imaging for low-grade tumor assessment, metabolic imaging using positron-emission tomography (PET) with radiolabelled aminoacids may help overcome the aforementioned drawbacks. The most popular amino acid utilized for PET study of LGG is PET with L-[methyl- ^{11}C]-methionine ([^{11}C]-methionine). PET [^{11}C]-methionine exhibits a sensitivity of 76%-95% in the diagnosis of gliomas, and is more efficient than FDG in delineating the tumor extent and detecting tumor progression and recurrence (8-13). However, its use is restricted to PET centers with an in-house cyclotron facility (8).

Another ^{18}F -labelled amino acid which has been used in PET studies is 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine ([^{18}F]-FDOPA), with a longer half-life (110 min). [^{18}F]-FDOPA is brought into tumor cells *via* amino acid transporters and recent studies have established the diagnostic value of PET [^{18}F]-FDOPA in heterogeneous population affected by LGG and high-grade gliomas (14-28). The aim of the present study was to evaluate the prognostic value of PET [^{18}F]-FDOPA in predicting the risk of radiological progression of disease in patients affected by LGG.

Patients and Methods

Between December 2012 and February 2014, patients with histologically confirmed (grade II) newly diagnosed and progressive glioma, who were more than 18 years of age and had a Karnofsky

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Key Words: Low-grade glioma, PET ^{18}F -FDOPA, prognostic factors, progressive disease.

Table I. Demographic and clinical features of patients.

Characteristic	N	%
Total sample	50	
Sex		
Male	30	60
Female	20	40
Age, years		
Mean (SD)	43.8 (14.0)	
Median (range)	41 (19-77)	
≤50 Years	36	72
>50 Years	14	28
KPS score, %		
Median (range)	100 (70-100)	
>90	45	90
70-80	5	10
Diagnosis		
Astrocytoma	34	68
Oligodendroglioma	16	32
Mean (SD) disease duration, years	5.7 (6.0)	
Radiotherapy	25	50
Type of patient		
Newly diagnosis	12	24
In chemotherapy treatment	21	42
Follow-up after chemotherapy treatment	17	34

Karnofsky Performance Status (KPS); Standard Deviation (SD).

Performance Scale (KPS) score of 60 or more, were consecutively enrolled in a prospective observational study at the Department of Neurology of the Regina Elena National Cancer Institute in Rome. The local Institutional Review Board approved the study (N. 4314) and each patient provided their valid informed consent before enrolment in the study. Clinical and demographic characteristics, including age, sex, histological diagnosis, grade of tumor, disease duration, symptoms at onset, surgery or biopsy, radiotherapy and chemotherapy (type and duration), were collected at enrolment.

At enrolment, all patients underwent PET[¹⁸F]-FDOPA and MRI examination over a 4-week span. All patients underwent clinical and radiological assessments with MRI every six months to evaluate the progression of disease, defined on the basis of the Response Assessment in Neuro-Oncology (RANO) criteria (29).

Study procedures. MRI scans were carried out at the Department of Neuro-radiology of the Regina Elena National Cancer Institute, Rome. MRI scans were performed with a 1.5T superconductive system (OptimaTM MR450w; GE Medical System, Waukesha, WI, USA). We used a head-coil. All patients were scanned with the following sequences: fast spin-echo (FSE) T2 on coronal plane, FSE T1, T2 and fluid attenuated inversion recovery images (FLAIR) in axial plane with 3-mm thick slices. After gadolinium infusion (Gd-DTPA; 0.1mmol/kg), volumetric T1 fast-sequences (3D FSPGR) were acquired.

Both FLAIR and contrast-enhanced weighted sequences were considered for evaluating the tumor volume, as well as assessing the response to treatment, according to the RANO criteria (29). According to RANO criteria, we considered: complete response (CR) as requiring all of the following: complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks; no new lesions; stable or improved non-enhancing (T2/FLAIR)

Table II. Receiver operating characteristic (ROC) analysis between contrast enhancement and maximum standardized uptake value (SUV max); diagnostic values were calculated on the total sample (n=50).

Contrast-enhancement/SUV max*	Value	SE	95% CI
Area under the curve	0.819	0.063	0.696-0.942
Sensitivity	0.769	0.01365	0.477-1.061
Specificity	0.842	0.05915	0.694-0.990
Accuracy	0.824	0.05338	0.690-0.957
Positive predictive value	0.625	0.12103	0.322-0.928
Negative predictive value	0.914	0.04732	0.796-1.033

*SUV max cut-off value was obtained with Youden's index (J) where J=Sensitivity+ Specificity-1. Standard error (SE); maximum standardized uptake value (SUV max); 95% Confidence Interval (95% CI)

lesions; and no corticosteroids or on physiological replacement doses only, and stable or improved clinical condition. In the absence of a confirming scan 4 weeks later, this response was considered only stable disease. Partial response (PR) required all of the following: ≥50% decrease, compared with baseline, in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of non-measurable disease; no new lesions; stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan and clinically stable status. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging showed that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease was that obtained when the corticosteroid dose was equivalent to the baseline dose. Progression was defined by any of the following: ≥25% increase in sum of the products of perpendicular diameters of enhancing lesions (compared with baseline if no decrease) on stable or increasing doses of corticosteroids; a significant increase in T2/FLAIR non-enhancing lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not due to comorbid events; the appearance of any new lesions; clear progression of non-measurable lesions; or definite clinical deterioration not attributable to other causes apart from the tumor, or to decrease in corticosteroid dose. Failure to return for evaluation as a result of death or deteriorating condition was also considered as progression.

The PET scans were carried out at the Department of Biomedicine and Prevention, University Tor Vergata, Rome. The PET-computerized tomography (CT) was performed using a PET-CT Discovery VCT (GE Medical Systems, TN, USA) using a standard technique in 3D mode in 256x256 matrix. The images were reconstructed by using a OSEM algorithm (4 iterations, 20 subsets). The system combines a high-speed ultra 16-detector-row (912detectors per row) CT unit and a PET

Table III. Cox regression analyses for disease progression: Univariate and multivariate analyses-

Parameter	Univariate analyses			Multivariate analyses		
	HR	95% CI	p-Value	HR	95%CI	p-Value
MRI response						
NED	1.00					
FLAIR with CE	6.12	0.77-48.42	0.09			
FLAIR without CE	3.39	0.41-27.80	0.26			
Histology						
Astrocytoma	1					
Oligodendroglioma	0.55	0.17-1.82	0.331			
Basal KPS (each point increase)	0.97	0.92-1.03	0.347			
Basal KPS						
>90	1.00					
70-80	0.63	0.2-1.98	0.427			
Age (each year)	0.99	0.95-1.03	0.626			
Age						
<50 Years	1.00					
≥50 Years	1.06	0.28-4.03	0.928			
Residual tumour(cc)	1.00	0.99-1.02	0.465			
SUV max (each unit increase)	2.92	1.38-6.15	0.005			
SUV max						
<1.75	1.00			1.00		
≥1.75	8.26	1.82-37.5	0.006	9.10	1.92-42.96	0.005
Years of disease (each year)	0.67	0.47-0.95	0.025	0.66	0.45-0.95	0.025
[¹⁸ F]-FDOPA uptake						
Positive	1.00					
Negative	0.20	0.03-1.58	0.128			

95% Confidence Interval (95% CI); Contrast-enhancement (CE); Fluid attenuated inversion recovery (FLAIR); 3,4-dihydroxy-6-[¹⁸F]-fluoro-L-phenylalanine ([¹⁸F]-FDOPA); Hazard Ratio (HR); Karnofsky Performance status (KPS); Magnetic resonance imaging (MRI); Not evidence of disease (NED); Maximum Standardized Uptake Value (SUV max).

scanner with 13440 bismuth germanate crystals in 24 rings (axial full width at half-maximum 1-cm radius, 5.2 mm in 3D mode, axial field of view 157 mm). A low-amperage CT scan of the head for attenuation correction (40 mA;120 kV) was performed before PET image acquisition. All the patients fasted for at least 5 hours before intravenous injection of [¹⁸F]-FDOPA. The dose administered was 185-210 MBq. After the injection, the patients were hydrated with 500 ml of saline (0.9% sodium chloride). PET-CT acquisition started at least 15 minutes after [¹⁸F]-FDOPA injection. The PET-CT images were interpreted as positive when the lesion definitely showed increased [¹⁸F]-FDOPA accumulation, taking into consideration the background and the contralateral site. The slices with a maximal [¹⁸F]-FDOPA uptake in the region of interest (ROI) were chosen for quantitative measurement of metabolic activity of the tracer [standardized uptake value]. From the volume of interest (VOI), the standardized uptake value was calculated using standard body weight method.

Statistical analysis. Descriptive statistics were used to summarize pertinent study information. Categorical variables are reported as frequencies and percentage values, while continuous variables are summarized through mean values and the relative standard deviation (SD), or median (range), as appropriate.

To determine the optimal maximum standardized uptake value ratio cut-off value, we used the receiver operating characteristics (ROC) curve analysis. Across various cut-off points, Youden's index maximized the differences between real-positive and false-positive

subjects; thus, the optimal cut-off value was calculated. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were then obtained in order to evaluate the diagnostic performance of the contrast enhancement.

The prognostic value of PET [¹⁸F]-FDOPA in predicting the risk of radiological progression of disease was evaluated using a Cox proportional hazards univariate model, where disease progression was the dependent variable, while age, disease duration, Karnofsky Performance Status, residual volume, maximum standardized uptake value, and qualitative [¹⁸F]-FDOPA uptake were inserted as covariates. A multivariate Cox model was also carried out using a stepwise approach (forward selection; enter limit and remove limit $p=0.10$ and $p=0.15$, respectively), with predictive variables that were significant in the univariate analyses being inserted into the final multivariate model as covariates.

Two-sided p -values of less than 0.05 denote statistically significant associations. Statistical analyses were carried out using SPSS software (SPSS version 21.0; SPSS Inc., Chicago, IL, USA).

Results

Characteristic of patients, MRI and PET [¹⁸F]-FDOPA at enrolment. Fifty patients (30 males and 20 females) with LGG were enrolled in the study. In Table I, we report on the demographic and clinical data of the whole sample cohort.

The mean \pm SD age at diagnosis was 43.8 \pm 14 years; the mean \pm SD of disease duration was 5.7 \pm 6.0 years. Out of the 50 patients recruited in this study, 12 (24%) were newly-diagnosed, 17 (34%) were in follow-up after previous treatment and 21 (42%) were receiving chemotherapy treatment. The majority of patients (n=34, 68%) were affected by astrocytoma, while 16 patients (32%) were affected by oligodendroglioma.

At enrolment, MRI features were: nine (18%) patients had a negative scan (without evidence of disease); 26 (52%) had residual disease without contrast enhancement, and 15 (30%) patients had residual disease with areas of contrast enhancement. PET [18 F]-FDOPA showed increased uptake in 35 (70%) patients, and was negative in the remaining 15 (30%), based on interpretation criteria mentioned in the Patients and Methods section. The mean standardized uptake value was 1.55 (0.62).

Follow-up data. All patients had a median of 16 (range=8-29) months of follow-up after entering the study with MRI examination. At the end of follow-up, 18 (36%) patients showed disease progression, according to the RANO criteria. The median time from PET examination to radiological progression disease was six months.

Prognostic value of PET [18 F]-FDOPA. The area under the ROC curve for the maximum standardized uptake value predicting the presence of contrast enhancement at baseline (*i.e.* at study entry) was 0.819. According to the ROC analysis, the best possible predictive cut-off value for maximum standardized uptake value was 1.75. The diagnostic values, expressed as sensitivity, specificity, positive predictive value, negative predictive value and overall accuracy are reported in Table II.

Table III shows the findings of the Cox regression model. The univariate analysis demonstrates that the variables useful in predicting disease progression were: the disease duration [(Hazard Ratio-HR)=0.67, 95% confidence interval (CI)=0.47-0.95; $p=0.025$], and the maximum standardized uptake value with cut-off value of 1.75 found by means of the ROC analysis (HR=8.26, 95%CI=1.82-37.5; $p=0.006$). No significant difference was observed between patients with and those without contrast enhancement. The multivariate analysis confirmed that a maximum standardized uptake value greater than 1.75 (HR=9.1095% CI=1.92-42.96; $p=0.005$), and the disease duration (HR=0.66 for each year, 95% CI=0.45-0.95; $p=0.025$) were independent predictors of disease progression. This implies that a patient with a maximum standardized uptake value higher than 1.75 had an almost 9-fold increased risk of disease progression, regardless of clinical and basal MRI features.

Discussion

Early identification of anaplastic modifications in the management of glioma may drive different clinical and

therapeutical approaches. Today, MRI is inadequate in exactly delineating tumor volumes, treatment-induced changes, and recurrence, especially in LGG (4, 5). Given these limitations regarding the use of MRI, PET has been advocated for evaluating LGG in clinical practice. Previous studies using [11 C]-methionine PET have shown that the intensity of amino acid uptake correlates, in general, with the grade of malignancy (30).

Several studies have shown that PET [18 F]-FDOPA has a higher sensitivity and specificity for identifying gliomas compared to other tracers, mainly in evaluating the recurrence of LGG or high-grade malignant gliomas (16-19, 23, 25). Becherer *et al.* also demonstrated that [18 F]-FDOPA gave similar values to [11 C]-methionine and concluded that [18 F]-FDOPA might therefore be applied as a substitute for [11 C]-methionine in the diagnosis of residual or recurrent tumors, particularly in PET centers without a cyclotron (26).

Ledezema *et al.* observed that the metabolic alteration observed with PET [18 F]-FDOPA preceded the tumor modifications detected by MRI (24). A more recent study on glioma recurrence reported that the results of MRI and PET [18 F]-FDOPA were concordant in 74.3% and discordant in 17.1% of cases (16). The authors also concluded that this diagnostic tool is more accurate than MRI for high and LGGs (16).

Our results confirm that PET [18 F]-FDOPA has a high sensitivity and specificity in the prospective evaluation of LGG. PET [18 F]-FDOPA provides a linear quantification of tumor activity, whereas the maximum standardized uptake value can provide useful information. In our cohort, an maximum standardized uptake value of 1.75 exhibited sufficient sensitivity (81%) and excellent specificity (85%) in early prediction of radiological progression.

Fueger *et al.* demonstrated that in patients with newly-diagnosed tumors, an [18 F]-FDOPA maximum standardized uptake value of 2.72 discriminated between LGG and high-grade tumors, with sensitivity and specificity of 85% and 89%, respectively (22). Overall sensitivity of [18 F]-FDOPA ranges from 85% to 100%, and specificity varies from 89% to 100% (26-27). All these findings suggest that the value of maximum standardized uptake value of the PET [18 F]-FDOPA may help in the early detection of risk of progression in patients with LGG.

In our study, the univariate analysis showed that the duration of disease and a maximum standardized uptake value cut-off >1.75 were predictors of progression in patients with glioma.

Only few studies evaluated the potential prognostic role of PET in recurrent glioma (21, 31-35). Nyazi *et al.* found that uptake kinetics of [18 F]-Fluoroethyltyrosine PET is an independent determinant of overall and progression-free survival (34). [11 C]-Methionine PET has not only been used for diagnosis, but also as a prognostic tool in recurrent glioma (35).

In a retrospective analysis on patients treated with bevacizumab, the authors concluded that the voxel-wise changes

in [¹⁸F]-FDOPA uptake may be a predictor for progression-free survival and overall survival in recurrent malignant glioma (21). Our study confirms the role of PET [¹⁸F]-FDOPA as a useful diagnostic tool in predicting progression. In the multivariate analysis, the presence of an maximum standardized uptake value >1.75 and disease duration were independent predictors of disease progression, irrespective of other clinical characteristics and MRI findings. In our study, we did not observe any statistically significant differences in terms of disease progression between patients presenting contrast enhancement areas at basal MRI compared to those without contrast enhancement. Recently, it was demonstrated that the contralateral normal hemispheric brain tissue ratio of PET [¹⁸F]-FDOPA is an independent predictor of survival in patients with suspected recurrent glioma. A contralateral normal hemispheric brain tissue ratio greater than 1.5 or size exceeding 2.5 cm of recurrent tumor on contrast enhancement sequences were predictors of poor survival (14). Walter *et al.* found that patients with a positive PET [¹⁸F]-FDOPA had significantly shorter survival than those with negative [¹⁸F]-FDOPA imaging (36). We have not considered survival in our study because the number of patients who died was low.

The present study has some limitations, including the heterogeneity of patients who presented histologically-different tumors, with different stages and history of disease. Moreover, a longer follow-up is warranted to explore whether imaging by PET [¹⁸F]-FDOPA may predict survival. Lastly, our findings need to be replicated in larger patient samples. Despite these limitations, the present study may provide further insights into the role of PET [¹⁸F]-FDOPA in glioma, encompassing both its diagnostic and prognostic value.

Conclusion

We suggest that neuro-oncologists should rely not only on clinical, biomolecular and MRI radiological features, but also on PET [¹⁸F]-FDOPA for the assessment of patients with LGG.

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