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SHORT COMMUNICATION

A high ^{18}F-FDOPA uptake is associated with a slow growth rate in diffuse Grade II–III gliomas

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Objective: In diffuse Grade II–III gliomas, a high 3,4-dihydroxy-6-(^{18}F)-fluoro-L-phenylalanine (^{18}F-FDOPA) positron emission tomography (PET) uptake, with a standardized uptake value (SUV_{max})/contralateral brain tissue ratio greater than 1.8, was previously found to be consistently associated with the presence of an isocitrate dehydrogenase (IDH) mutation, whereas this mutation is typically associated with a better prognosis. This pilot study was aimed to ascertain the prognostic value of this high ^{18}F-FDOPA uptake in diffuse Grade II–III gliomas with regard to the velocity of diameter expansion (VDE), which represents an established landmark of better prognosis when below 4 mm per year.
Methods: 20 patients (42 ± 10 years, 10 female) with newly-diagnosed diffuse Grade II–III gliomas (17 with IDH mutation) were retrospectively included. All had a ^{18}F-FDOPA PET, quantified with SUV_{max} ratio, along with a serial MRI enabling VDE determination.
Results: SUV_{max} ratio was above 1.8 in 5 patients (25%) all of whom had a VDE <4 mm/year (100%) and IDH mutation (100%). Moreover, a SUV_{max} ratio above 1.8 was associated with higher rates of VDE <4 mm/year in the overall population (45 *vs* 0%, p = 0.04) and also in the subgroup of patients with IDH mutation (45 *vs* 0%, p = 0.10).
Conclusion: This pilot study shows that in diffuse Grade II–III gliomas, a high ^{18}F-FDOPA uptake would be predictive of low tumour growth, with a different prognostic significance than IDH mutation.
Advances in knowledge: ^{18}F-FDOPA PET in a single session imaging could have prognostic value in initial diagnosis of diffuse Grade II–III gliomas.

INTRODUCTION

The prognosis of newly-diagnosed Grade II–III gliomas is difficult to determine, according to the classification of the World Health Organization (WHO).[1] Nowadays, in clinical routine, most clinicians measure tumour growth by repeating MRI scans.[2,3]

For patient monitoring, MRI is recommended to assess tumour volume and its evolution over time (growth kinetics). In this setting, even if experience is limited in heterogeneous patient samples, a velocity of diameter expansion (VDE) of less than 4 mm per year constitutes an established landmark of good prognosis, associated with a significantly longer overall survival and longer malignant progression-free survival.[2,4]

PET using radiolabelled amino-acids was recently recommended by the Response Assessment in Neuro-Oncology working group as an additional tool in the diagnostic assessment of brain tumours.[5] Among these amino-acid radiotracers, 3,4-dihydroxy-6-(^{18}F)-fluoro-L-phenylalanine (^{18}F-FDOPA) is useful for grading tumours in newly- diagnosed gliomas,[6] although its prognostic value remains debated particularly for diffuse Grade II and III gliomas.[7–9] In a recent report and related to a subsequent analysis of data, a rather high ^{18}F-FDOPA Positron Emission Tomography (PET) uptake, with a maximal Standardized Uptake Value (SUV_{max})/contralateral brain tissue ratio greater than 1.8 in diffuse Grade II–III gliomas has been shown to be consistently associated with the presence of isocitrate dehydrogenase (IDH) mutation,[8] a

factor of better prognosis according to the new classification of the WHO in 2016.[10] However, the prognostic value of such high ^{18}F-FDOPA uptake remains unknown.

In light of the above, the aim of this pilot study was to ascertain the predictive value of this elevated level of ^{18}F-FDOPA PET uptake in histologically proven diffuse Grade II–III gliomas with regard to VDE.

METHODS AND MATERIALS

Patients

20 patients with histologically confirmed newly-diagnosed diffuse Grade II–III gliomas were retrospectively included. Patients had been referred to the Nuclear Medicine Department of the Nancy University Hospital (CHRU, Nancy) for an ^{18}F-FDOPA PET. Serial MRIs were also conducted, with PET performed less than two months after the first MRI (MRI1) and before the second MRI (MRI2). The local ethics committee approved the retrospective evaluation of the data. There was no conflict with the Declaration of Helsinki. All patients from our institution are systematically informed that their medical data can be rendered anonymous and used for scientific purposes.

PET

^{18}F-FDOPA PET examinations were performed on a Biograph 6 system (Siemens®, Erlangen, Germany) after injection of 3 MBq of ^{18}F-FDOPA per kilogram of body weight. Acquisition and reconstruction parameters have already been detailed elsewhere.[6]

PET images were analysed and quantified by a single experienced observer as detailed previously.[6] Briefly, ratios of tumour uptake to normal tissue uptake were generated by dividing Tumour SUV_{max}-derived indices with Normal contralateral brain tissue uptake (SUV_{max} T/N).

MRI

Two MRIs were performed in each patient on a GE Healthcare 1.5 or 3T magnet. All MRI examinations were analysed in this study by a single experienced radiologist in two blinded sessions to assess reproducibility in size assessment. Mean tumour diameters were determined on fluid attenuation inversion recovery (FLAIR) weighted MR images as recommended,[2] after semi-automated tumour volume contouring (ADW, GE®). VDE was calculated as the difference in mean tumour diameter measurement between the two MRI examinations divided by the interval-time between the two examinations. A VDE of less than 4 mm per year was considered to be indicative of a better prognosis.[2]

Histological and molecular analysis

All cases were reviewed and classified according to the 2016 "WHO Classification of Tumours of the Central Nervous System". Pathological confirmation was conducted by resection (n = 15) or biopsy (n = 5). IDH mutation status was assessed by immunohistochemistry with IDH1 R132H protein expression (Dianova, clone H09), or Sanger sequencing in case of ATRX loss without IDH1 R132H staining. For oligodendroglial morphology, tumours were tested for 1p 19q codeletion using multiplex PCR analysis (loss of heterozygosity), or comparative genomic hybridization.

Statistical analysis

Quantitative variables are expressed as means ± standard deviations, and categorical variables as percentages. Two-group unpaired comparisons were performed with Mann-Whitney tests for quantitative variables and with Fischer exact tests for categorical variables. A p-value < 0.05 was determined as significant. All analyses were performed with SPSS® 20.0 software.

RESULTS

The final study population consisted of 10 males and 10 females with a mean age of 41.8 ± 10.3 years (24–62 years). According to the WHO 2016 classification, the 20 gliomas involved 3 oligodendrogliomas, IDH-mutant and 1p 19q codeleted; 1 anaplastic oligodendroglioma, IDH-mutant and 1p 19q codeleted; 8 diffuse astrocytomas, IDH-mutant; 2 diffuse astrocytomas, IDH-wild type; 5 anaplastic astrocytomas, IDH-mutant; and 1 anaplastic astrocytoma, IDH-wildtype. On average, the mean interval-time separating the first MRI from the ^{18}F-FDOPA PET was 40.9 ± 20.9 days and between the two MRI examinations was 82 ± 29 days with a minimum of 40 days. Mean delay between ^{18}F-FDOPA PET and histological diagnosis was 99.2 days ± 67.3.

A low growth rate, with a VDE <4 mm per year, was documented in 11 of the 20 patients (55%) and an IDH mutation documented in 17 (85%). Patients with VDE <4 mm showed a trend toward higher rates of IDH mutations compared to those with VDE ≥4 mm (p = 0.07, Table 1).

SUV_{max} ratio was above 1.8 in 5 patients (25%) all of whom had a VDE <4 mm/year (100%) and IDH mutation (100%). In contrast, patients with a SUV_{max} ratio below 1.8 had a VDE <4 mm/year in 40% of cases (6/15) and IDH mutation in 80% of cases (12/15). Examples of PET images of gliomas with SUV_{max} T/N > 1.8 and < 1.8 are shown in Figures 1–3.

As detailed in Table 1, the rates of high SUV_{max} ratio (>1.8) were significantly higher in patients with a VDE <4 mm comparatively to those with a VDE ≥4 mm (45 *vs* 0%, p = 0.04) as well as a trend toward higher SUV_{max} ratio, analysed as a continuous variable, in patients with a VDE <4 mm than in those with VDE ≥4 mm (1.6 ± 0.9 *vs* 1.0 ± 0.3, p = 0.06). The remaining demographic and histological variables were not significantly different between the two groups (Table 1).

Of note, when the analysis was restricted to the vast majority of patients showing an IDH mutation (n = 17), the rates of high SUV_{max} ratio (>1.8) remained higher in those with a VDE <4 mm than in those with a VDE ≥4 mm although this relationship was slightly above the level of statistical significance (45 *vs* 0%, p = 0.10).

DISCUSSION

In diffuse Grade II–III gliomas, a high ^{18}F-FDOPA uptake, with a SUV_{max} ratio above 1.8, was previously found to be consistently associated with the presence of an IDH mutation. The present pilot study shows that this criterion is additionally predictive of a low tumour growth (<4 mm per year) and thus, presumably of a better prognosis.

Table 1. Patient and tumour characteristics

	Velocity of diameter expansion <4 mm/year *n* = 11 (55%)	Velocity of diameter expansion ≥4 mm/year *n* = 9 (45%)	*p*
Age (years)	42.4 ± 11.4	41.1 ± 10.3	0.80
Female gender	4 (36%)	6 (67%)	0.37
Time between MRI 1 and PET (days)	41.0 ± 23.2	40.8 ± 18.9	0.98
Time between PET and histology (days)	106.1 ± 77.6	90.7 ± 55.5	0.61
Time between MRI 1 and MRI 2 (days)	81.9 ± 24.5	82.4 ± 36.3	0.97
WHO 2016 Classification			
Diffuse astrocytoma, IDH-mutant	6 (55%)	2 (22%)	0.20
Anaplastic astrocytoma, IDH-mutant	3 (27%)	2 (22%)	1
Diffuse astrocytoma, IDH-wildtype	0	2 (22%)	0.19
Anaplastic astrocytoma, IDH-wildtype	0	1 (11%)	0.45
Oligodendroglioma, IDH-mutant and 1p 19q codeleted	2 (18%)	1 (11%)	1
Anaplastic oligodendroglioma, IDH-mutant and 1p 19q codeleted	0	1 (11%)	0.45
IDH mutation	11 (100%)	6 (66%)	0.07
Anaplastic	3 (27%)	4 (36%)	0.64
SUV_{max} T/*N*	1.6 ± 0.9	1.0 ± 0.3	0.06
SUV_{max} T/*N* > 1.8	5 (45%)	0 (0%)	0.04

IDH mutation,isocitrate deshydrogenase mutation; PET, positron emission tomography; SUV, standardized uptake value; T/N, tumour/contralateral normal brain tissue uptake; WHO, World Health Organization.

The malignant progression of diffuse Grade II/III gliomas is variable and difficult to predict non-invasively given that these gliomas represent a very heterogeneous population. As evidenced by current MRI monitoring, these tumours grow inexorably although at an unpredictable rate. Pallud and al. reported a median interval of 21 months between the radiological discovery and oncological treatment of low-grade gliomas.[2] An early non-invasive identification of prognostic factors would hence be useful in tailoring therapeutic strategy. Advanced MRI methods (perfusion, diffusion and spectroscopy) have been proposed to enhance prognostic information in this setting. However, PET imaging, especially with ^{18}F-FDOPA, was recently found to be somewhat more efficient than the aforementioned advanced MRI techniques for glioma grading and prognosis.[11,12] Moreover, these studies have confirmed that information provided by MRI and ^{18}F-FDOPA PET clearly differ.

As an illustration of this difference, gliomas with a high growth rate (VDE ≥4 mm) had a lower ^{18}F-FDOPA uptake in the current

Figure 1. Axial FLAIR MRI1 (a), MRI2 (b) and PET ^{18}F-FDOPA (c) imaging of a diffuse IDH-mutant (WHO 2016) astrocytoma, with a SUV_{max} T/N (Tumour/contralateral Normal brain tissue uptake) ratio = **5.8** (>1.8) and velocity of diameter expansion between MRI1 and MRI2 of **1.2** mm (<4 mm per year). F-FDOPA, 3,4-dihydroxy-6-(^{18}F)-fluoro-L-phenylalanine; FLAIR, fluid attenuation inversion recovery; PET, positron emission tomography; SUV, standardized uptake value.

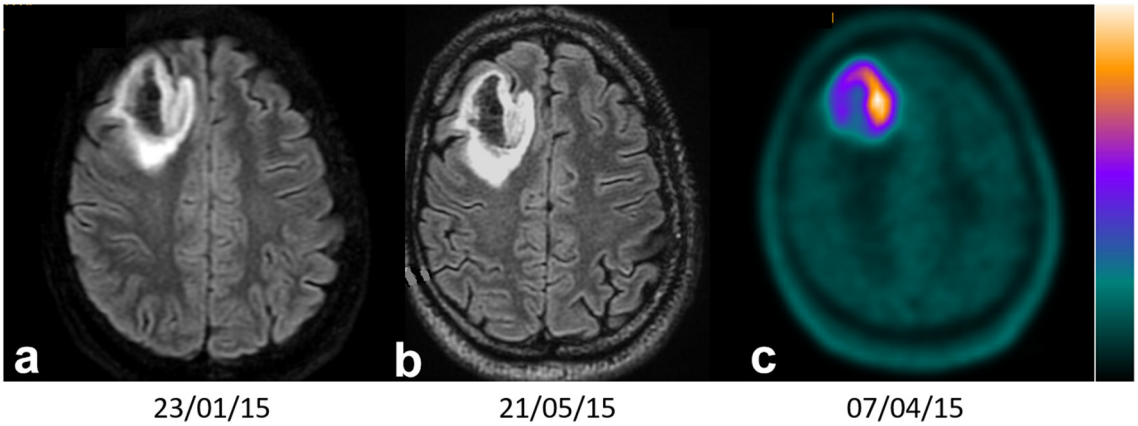
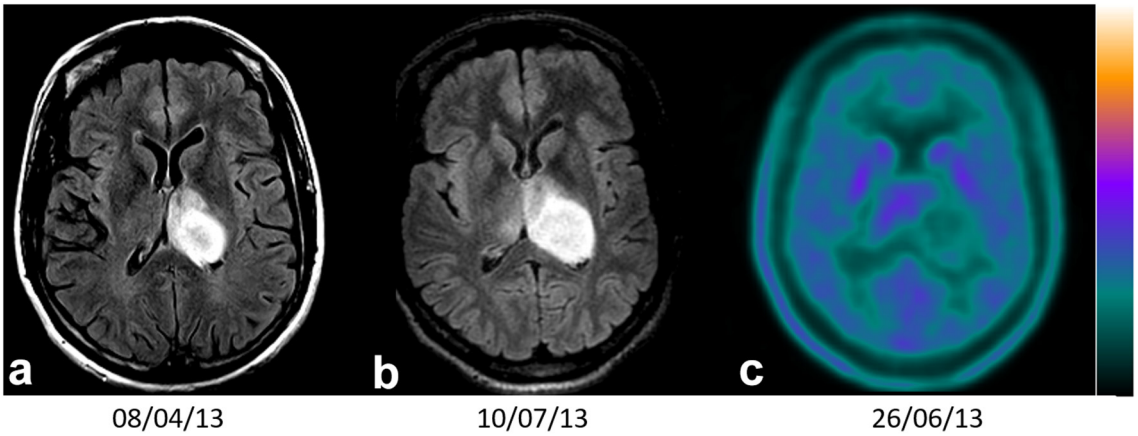


Figure 2. Axial FLAIR MRI1 (a), MRI2 (b) and PET ^{18}F-FDOPA (c) imaging of a diffuse IDH wild type (WHO 2016) astrocytoma, with a SUV_{max} T/N (Tumour/contralateral Normal brain tissue uptake) ratio = **1.1** (<1.8) and velocity of diameter expansion between MRI1 and MRI2 of **7.7** mm (>4 mm per year). F-FDOPA, 3,4-dihydroxy-6-(^{18}F)-fluoro-L-phenylalanine; FLAIR, fluid attenuation inversion recovery; IDH, isocitrate deshydrogenase; PET, positron emission tomography; SUV, standardized uptake value; WHO, World Health Organization.



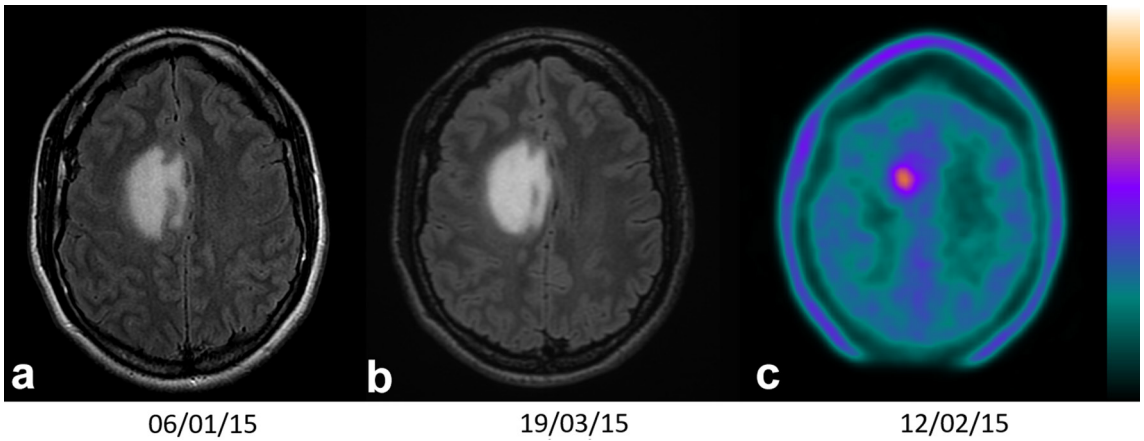
study. This observation is in agreement with the previous observation that ^{18}F-FDOPA uptake was higher in gliomas harbouring an IDH mutation, whereas this mutation is known to confer a better prognosis.[8] Finally, these results strengthen the hypothesis that a rather high ^{18}F-FDOPA uptake may confer a better prognosis in this setting. Possible explanation to this higher ^{18}F-FDOPA uptake could be the specific accumulation of 2-hydroxyglutarate in IDH mutated gliomas, which may act as an oncometabolite with alternative molecular pathways.[13] On the other hand, IDH mutation status is also associated with an elevation of intracellular free amino-acids including tyrosine,[14] which could potentially facilitate the uptake of ^{18}F-FDOPA via amino-acid transporters which act as exchangers. Another potential explanation is that ^{18}F-FDOPA uptake in IDH-mutated gliomas could also be influenced by an impairment in dopamine catabolism due to a mitochondrial dysfunction.[15]

It should also be pointed out that, when the analysis was restricted to patients with IDH mutation, the rate of SUV_{max} ratio >1.8 remained higher in patients with low growth tumour rate, even if this relationship was only at the limit of the statistical significance, presumably due to the limited sample size. This suggests that this SUV_{max} ratio provides a very different prognostic information than that provided by IDH mutation, as illustrated by the example in Figure 3.

In more practical terms, our results suggest that the criterion of a SUV_{max} ratio >1.8, in case of suspicion of low-grade glioma on standard MRI, may allow identifying a subgroup of patients with a low growth rate, independently of IDH status. For this subgroup of patients, the treatment may be delayed allowing time to tailor their management as opposed to patients for whom treatment (such as surgical removal) should not be delayed.

Interesting, the oligodendroglial component didn't influence nor MRI VDE nor ^{18}F-FDOPA PET uptake since only 1 oligodendroglioma exhibited a SUV_{max} T/*N* > 1.8. Indeed, this component may

Figure 3. Axial FLAIR MRI1 (a), MRI2 (b) and PET ^{18}F-FDOPA (c) imaging of an anaplastic IDH-mutant (WHO 2016) astrocytoma, with a SUV_{max} T/N (tumour/contralateral normal brain tissue uptake) ratio = **1.7** (<1.8) and velocity of diameter expansion between MRI1 and MRI2 of **21** mm (>4 mm per year).



positively affect the substrate metabolism of gliomas for certain amino-acid uptake.[16]

The most important limitations of the present study are its limited sample size and its retrospective and single-centre nature. Further larger-scale studies are thus required, especially for the subgroups of patients with IDH-mutant 1p/19q co-deleted oligodendrogliomas or wild-type IDH astrocytomas, in order to confirm the low growth rate as well as the good prognosis of patients showing a SUV_{max} ratio >1.8. Secondly, the average time between MRI 1 and MRI 2 (82 days ± 29) could be sometimes short to define precisely tumour growth rate. However, a minimum delay of 40 days was observed between the two investigations.[2] Finally, the growth rate of tumour was chosen as a surrogate for clinical course in this study since no overall survival could be obtained in our population owing to the long clinical course duration of diffuse low-grade gliomas.

Overall, the present pilot study shows that in histologically proven diffuse Grade II–III gliomas, a high ^{18}F-FDOPA uptake, with a SUV_{max} ratio above 1.8, would be predictive not only of an IDH mutation but also of a low tumour growth and thus, presumably of a better prognosis. This might be helpful to optimize the individualized therapeutic approach for these patients.

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COMPLIANCE WITH ETHICAL STANDARDS

There was no conflict with the Declaration of Helsinki. The research procedures were approved by the institutional committee on human experimentation, and Informed consent was obtained for human subjects.

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