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IDH mutation is paradoxically associated with higher ^{18}F -FDopa PET uptake in diffuse grade II and grade III gliomas

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Running-title: ^{18}F -FDopa PET uptake and IDH mutation status in gliomas

Abstract

Purpose: The World Health Organization (WHO) has recently updated Central Nervous System (CNS) classification by integrating diagnostic and prognostic molecular parameters, giving pivotal attention to *IDH* mutation as a favorable factor. Amino-acid PET is increasingly used in the management of gliomas, with however debated impact concerning the prognostic value. This study aims to assess relationship between *IDH* mutation and ^{18}F -FDopa PET uptake in newly diagnosed gliomas.

Methods: Forty-three patients, presenting with diffuse astrocytic and oligodendroglial tumors grade II and III gliomas and reclassified according to the 2016 WHO classification of tumors of the CNS, were retrospectively included. They all had ^{18}F -FDopa PET at initial stage, before surgery and histological diagnosis. ^{18}F -FDopa uptake values were compared between patients with and without *IDH* mutation using SUV (Standard Uptake Value) max ratios of T/N (Tumor/Normal contralateral brain) and T/S (Tumor/Striatum).

Results: Patients with *IDH* mutation exhibited higher uptake of ^{18}F -FDopa in SUVmax ratios of T/N (1.6 vs. 1.2) and T/S (0.9 vs. 0.6), in comparison to patients without *IDH* mutation ($p < 0.05$).

Conclusions: This study reveals a higher paradoxical ^{18}F -FDopa uptake in diffuse grade II and III gliomas with *IDH* mutation. Despite evident interest in the management of gliomas, and especially for post-therapeutic evaluation, our findings thus question the prognostic value of ^{18}F -FDopa PET uptake in this group of patients. This may be related to differences in amino-acid integration, metabolism, or cell differentiation.

Keywords: ^{18}F -FDopa PET, *IDH* mutation, gliomas, prognosis.

Introduction

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4 Positron Emission Tomography (PET) is widely used in the medical management of gliomas
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6 [1]. At initial stage of the diagnosis, and before the revision World Health Organization
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8 Classification of Tumors of the Central Nervous System (2016 CNS WHO) [2], many
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10 neuroimaging studies have investigated the PET value to predict glioma grade, and possibly
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12 identify, for a same histological grade, metabolic profiles of distinct prognosis. In this line,
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14 FDG has shown to provide additional prognostic information in patients with high-grade
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16 gliomas [3]. However, due to a weak tumor contrast, FDG PET is less efficient than amino-
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18 acid PET for initial assessment of brain tumors, and especially for low-grade gliomas [1]. In
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20 this context, amino-acid PET tracers have become a well-established tool [4]. Among these
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22 tracers, ^{18}F -FDopa is the most available amino-acid radiotracer in Europe, and particularly in
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24 France, despite possible less validation in literature [4]. Briefly, ^{18}F -FDopa, is mainly
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26 integrated in cells by L-Amino-acid Transporter 1 (LAT 1), which is overexpressed in
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28 gliomas [5]. ^{18}F -FDopa PET allows to distinguish glioblastoma from other gliomas but its
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30 contribution to prognosis remains debated inside a same grade, particularly to stratify newly
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32 diagnosed low-grade gliomas [4,6,7]. Up to now, only two studies have reported a prognostic
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34 value of ^{18}F -FDopa uptake in low-grade gliomas for disease progression [6,7]. Nevertheless,
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36 the relationship with molecular parameters was not evaluated; the first one did not provide
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38 semi-quantitative ratios [6], and the second one involved a weak number of patients (n=12)
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40 [7].
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51 The 2016 CNS WHO has indeed recently updated gliomas classification with the introduction
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53 of molecular parameters including *IDH* (isocitrate dehydrogenase enzyme isoform) mutation,
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55 a key-factor of good-prognosis, in order to better define entities and subsequent prognosis [2].
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58 The *IDH* mutation is associated with a better prognosis in glioma cells regardless of
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1 histological parameters [8], and leads to a longer survival in patients with low-grade-gliomas
2 [9].
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5 The aim of our study was to compare ^{18}F -FDopa PET uptake to *IDH* mutation status in newly
6 diagnosed grade II and III gliomas that were retrospectively reclassified according to the 2016
7 WHO classification of CNS tumors.
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Material and Methods

Patients

From February 2008 to August 2015, 71 patients had an ^{18}F -FDopa PET for brain lesion assessments at Timone Hospital (Marseille, France). Among them, we have retrospectively selected patients initially classified according to the 2007 WHO classification into astrocytoma, oligoastrocytoma or oligodendroglioma, for whom ^{18}F -FDopa PET was performed at an initial stage, before any treatment [10]. Patients with glioblastoma were excluded, because of weak number of cases (n=2). All the tumors were reclassified according to the 2016 WHO classification [2]. All patients included received oral information and gave their consent. The **mean** delay between ^{18}F -FDopa PET and histopathological and molecular diagnosis was 30.7 (\pm 64.2) days.

^{18}F -FDopa PET

PET-CT were performed before histological diagnosis with a Discovery ST (GE Healthcare, Waukesha, WI). Routinely PET protocols were planned with a 110 MBq of ^{18}F -FDopa injection and a 15-minute static acquisition started at 15 minutes. No carbidopa was administered before radiotracer injection. Reconstruction image parameters were iterative OSEM 3D with 5 iterations and 32 subsets. After a first-step of visual examination, image analysis was only based on SUVmax ratios of T/N (Tumor/ Normal contralateral brain) and T/S (Tumor/ Striatum) as recommended for interpretation [11,12,4]. A two-dimensional Region-of-Interest (ROI) of 10 mm in diameter was placed on the major uptake of the tumor, with association to T1-weighted-gadolinium-enhanced MRI or T2-weighted-MRI when no

1 ¹⁸F-FDopa uptake was visualized. Contralateral normal brain and striatum ROIs were defined
2 to calculate SUV_{max} ratios.
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8 *Histopathological and molecular analysis* 9

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11 In order to reclassify the glioma cohort according to the 2016 WHO classification, we
12 searched for *IDH* mutation and 1p/19q codeletion. For *IDH* mutation status, we first searched
13 for *IDH1*^{R132H} protein expression by immunohistochemistry (Dianova, H09). In case of lack
14 of immunostaining, we performed *IDH1* and *IDH2* direct sequencing using the Sanger
15 method as previously described [13]. 1p/19q codeletion status was analyzed by FISH
16 (fluorescent *in situ* hybridization) [13]. At last ATRX (alpha-thalassemia/mental retardation
17 syndrome X-linked) (Sigma, polyclonal) and Ki67 (cell marker for proliferation) (Dako,
18 Mib1) nuclear expression was searched for by immunostaining.
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31 Automated immunostaining was performed on 4- μ m-thick FFPE (formalin-fixed paraffin-
32 embedded) sections with an avidin-biotin-peroxidase complex on Bechmark XT (Ventana
33 Medical System Inc, Tucson AZ, USA) using the Ventana kit including DAB (3,3-
34 diaminobenzidine) reagent.
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45 *Statistical analysis* 46

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48 Quantitative variables are expressed as means \pm standard deviations, and categorical variables
49 as percentages. Student T-test was performed for means comparison of quantitative variables,
50 with adjustment in case of unequal variances determined by Levene's Test [14] (means
51 comparison between the two ratios and *IDH* status, and between T/S ratio and tumor grade)
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and Chi-square tests for comparison between two categorical variables. Spearman coefficients were used for correlations. A p-value <0.05 was determined as significant.

Results

Patient characteristics and follow up

The final constituted population was of 43 patients. They included 23 men and 20 women, with an age at 41.9±12.7 years. *IDH*-mutant and *IDH*-wild-type subgroups differed for age, as well for 1p/19q and ATRX status (Table 1).

Molecular analysis and integrated diagnosis

IDH mutation was recorded in 34 cases (79%) including 32 *IDH1*^{R132H} and one *IDH1*^{R132C} and one *IDH1*^{R132G}. Among *IDH*-mutated tumors 12 were associated with a 1p/19q codeletion and 16 with nuclear ATRX loss of expression. As previously reported [15], 1p/19q codeletion and ATRX loss of expression were mutually exclusive. The remaining cases (9) displayed neither *IDH* mutation, nor 1p/19q codeletion. Therefore, according to histopathological criteria and molecular data we were able to classify our cohort according to the 2016 WHO classification.

The present study includes: 19 diffuse astrocytomas, *IDH*-mutant, 3 anaplastic astrocytomas, *IDH*-mutant, 9 oligodendrogliomas, *IDH*-mutant, 1p/19q-co-deleted, 3 anaplastic oligodendrogliomas, *IDH*-mutant, 1p/19q-co-deleted, 2 diffuse astrocytomas, *IDH*-wild type and 7 anaplastic astrocytomas, *IDH*-wild type. On the whole, 13 patients had anaplastic gliomas while 30 not.

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Relationship between ¹⁸F-FDopa PET uptake and IDH mutation

Patients with *IDH* mutation exhibited higher uptake of ¹⁸F-FDopa SUVmax ratios of T/N (1.6 vs. 1.2; p = 0.046) and T/S (0.9 vs. 0.6; p = 0.024), in comparison to patients without *IDH* mutation. An illustrative case is shown in Figure 1.

Relationship between ¹⁸F-FDopa PET uptake and other histopathological and molecular parameters

Concerning histological parameters, significant differences were observed in ¹⁸F-FDopa PET uptake between non-anaplastic and anaplastic gliomas with a 2.0 T/N ratio in anaplastic gliomas vs. a 1.4 T/N ratio in non-anaplastic gliomas (p=0.02; 1.1 vs. 0.8 for T/S ratio, p=0.20).

Concerning molecular parameters, a significant positive correlation between ¹⁸F-FDopa PET uptake and Ki-67 was noticed with a 0.37 Spearman coefficient correlation for T/N ratio and 0.33 for T/S (p=0.02). No statistical differences in ¹⁸F-FDopa uptake was found for the presence/absence of 1p/19q codeletion (1.8 vs. 1.4 for T/N ratio, p=0.06; 1.0 vs 0.8 for T/S, p=0.12) or ATRX loss of expression (1.4 vs. 1.5 for T/N ratio, p=0.70; 0.8 vs 0.9 for T/S, p=0.46).

A summary of main significant results is available in Figure 2.

Discussion

This study reveals that newly diagnosed gliomas with *IDH* mutation, in particular setting of non-glioblastoma gliomas, paradoxically have higher ^{18}F -FDopa uptake than those without *IDH* mutation, despite expected better prognosis [2]. This result is obtained for both SUVmax ratios. Explanations have certainly to be searched in biological characteristics of ^{18}F -FDopa uptake and those of *IDH*-mutant tumor cells.

The first hypothesis could be linked to the biological properties conferred by *IDH* mutation to gliomas. The *IDH* mutation in fact leads to a decrease of amino-acid metabolism, including tyrosine, the dopamine precursor of ^{18}F -FDopa [10]; consequently, an elevation of free amino-acids is expected in mutant cells, and possibly of ^{18}F -FDopa. According to this statement, amino-acid tracer, in particular ^{18}F -FDopa uptake, should be enhanced in gliomas with *IDH* mutation, despite better prognosis. Indeed, *IDH* mutation induces the ability to catalyze NADPH-dependent reduction of α -keto-glutarate (α -KG) to 2-hydroxyglutarate (2-HG). It leads thus to an excess of 2-HG in the cell causing the development a of alternative molecular pathways [13]. In this line, Reitman et al. studied effects of *IDH* mutation in the cellular metabolome [16]. They showed that *IDH* mutation confers changes in metabolic pathways including elevation of free amino-acids, and particularly of tyrosine. With this elevation of amino-acids, the exchange with ^{18}F -FDopa through amino-acid transporter would be enhanced, and explain its PET accumulation. In this line, findings could be shared with ^{18}F -Fluoro-Ethyl-Tyrosine (^{18}F -FET).

In the second hypothesis, *IDH* mutation could rather confer a better differentiation to gliomas, explaining the ^{18}F -FDopa uptake enhancement. In a study of metabolic flows, Grassian et al. showed that cells with *IDH* mutation exhibited non-significant difference with non-mutant cells in context of normoxic conditions, which is a condition shared by glioma in absence of

1 necrosis. However, it is noteworthy that in hypoxic conditions, these mutant cells increased
2 oxidative tricarboxylic acid metabolism along with decreased reductive glutamine metabolism
3 [17], leading to a diminution of cellular growth and thus explain a better prognosis. This better
4 prognosis should partly be linked to a better cell differentiation, since ^{18}F -FDopa uptake has
5 been associated with tumor differentiation [18].
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12 The third hypothesis would be related to an enhanced ^{18}F -FDopa cell integration through
13 mainly LAT 1, which could be also shared by others amino-acid tracers, LAT 1 being the
14 main transport mechanism of them [5].
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21 To our knowledge, the only one amino-acid tracer PET previous study aiming to compare
22 radiotracer uptake to *IDH* mutation, found a tendency to higher ^{18}F -FET PET uptake, as
23 measured by SUVmax ratio of T/N [19]. Nevertheless, 21.5 % of ^{18}F -FET PET scans were
24 negative, without any uptake. Moreover, the study included only non-anaplastic gliomas. On
25 the other hand, *IDH* mutation has been also evaluated with FDG PET, and no association was
26 reported, certainly because of the well-known limitations of this tracer for tumor contrast,
27 especially for low-grade gliomas [13].
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38 These findings **question the prognosis value** of ^{18}F -FDopa PET uptake in particular setting of
39 newly diagnosed non-glioblastoma gliomas, but of course do not question its value for
40 diagnosis and follow-up [1]. Future studies involving dynamic acquisitions equivalent to
41 those related to FET-PET [20] could however modify this statement and further investigate
42 ^{18}F -FDopa uptake by differentiating integration and metabolism steps.
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51 Concerning the other studied histopathological and molecular parameters, results are in
52 accordance with previous reports. Patients presented *IDH* mutation were significantly younger
53 than those without mutation [13] and presented a 1p/19q codeletion [13] and a loss of ATRX
54 mutation [21]. Moreover, as previously reported [22], all 1p/19q codeleted tumors were *IDH*-
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1 mutated. We confirm significant correlations between anaplastic status and ^{18}F -FDopa PET
2 uptake using SUVmax ratio of T/N [4]. Moreover, we found significant associations between
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4 Ki-67 expression, a marker of cellular proliferation, and ^{18}F -FDopa PET uptake as previously
5 reported [1].
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10 Otherwise, no other molecular associations with ^{18}F -FDopa uptake was noticed, excluding
11 potential molecular interference in our results, especially for 1p/19q codeletion, or ATRX loss
12 of expression, highly intertwined with *IDH* mutation [2,13,21].
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17 Our study has several limitations. In addition to its retrospective design, these findings will
18 need to be compared to survival after a more prolonged follow-up. Secondly, glioblastomas
19 were here excluded, not allowing thus to extend these findings to all types of gliomas. Finally,
20 the PET methodology could be discussed since a two dimension ROI was done instead of a
21 Volume of Interest, and since no carbidopa was administered before radiotracer injection as
22 recommended [23]. Nonetheless, the two-dimension ROI was done on the maximum tumor
23 uptake, and the absence of carbidopa administration could unlikely influence results since all
24 PET data were acquired using the same procedure.
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38 On the whole, our study reveals a higher paradoxically ^{18}F -FDopa uptake in newly diagnosed
39 non-glioblastoma gliomas with *IDH* mutation, which is a key-factor of good-prognosis in the
40 2016 WHO classification [2]. This discrepancy may be related to differences in amino-acid
41 integration, metabolism, or cell differentiation. Despite evident interest in the management of
42 gliomas, and especially for post-therapeutic evaluation, our findings thus question the
43 prognostic value of ^{18}F -FDopa PET uptake in this group of patients. Investigations with
44 different amino-acid PET tracers should be performed to determine if these findings could be
45 extrapolating to others radiotracers, also using larger studies and prolonged follow-up.
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Compliance with Ethical Standards

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Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Tumor specimens were retrieved from the AP-HM tissue bank AC 2013-1786.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Table 1. Clinical, histopathological and molecular characteristics of included patients

	<i>IDH</i> -mutant (n=34)	<i>IDH</i> -wild-type (n=9)	p value*
Age (years)	38.8 (SD=11.3)	53.3 (SD=11.7)	0.01*
Gender (female)	15 (44%)	5 (56%)	0.54
Delay between PET and histological diagnosis (days)	25.3 (SD=65.9)	51.1 (SD=55.7)	0.29
Anaplastic gliomas	6 (18%)	2 (22%)	0.75
Ki67 (%)	6.3 (SD=4.7)	4.8 (SD=5.9)	0.41
1p/19q codeletion	12/34 (35%)	0/9 (0%)	0.04*
ATRX loss of expression	4/20 (20%)	4/4 (100%)	0.01*

*p value for difference between *IDH*-mutant and *IDH*-wild-type subgroups

Figure Legend

Figure 1. Axial slices of T2-weighted-MRI (left panel) and ^{18}F -FDopa PET (right panel). For both astrocytomas, they appear hyperintense in T2-weighted-MRI (white arrows) whereas no contrast was observed in T1-weighted-gadolinium-enhanced MRI. In panel A, no significant ^{18}F -FDopa uptake (ratio T/N=1) is observed within the astrocytoma (white arrow), in a patient with a right temporal diffuse astrocytoma glioma *IDH*-wild-type. In panel B, significant ^{18}F -FDopa uptake (ratio T/N=1.4) is noted within the astrocytoma (white arrow), in a patient with a left fronto-insular diffuse astrocytoma glioma *IDH*-mutant. *T/N: Tumor/Normal contralateral brain*

Figure 2. Summary of main significant results. Box-plots of distribution of SUVmax ratios for *IDH*-wildtype and -mutant gliomas in A, and for grade II and III gliomas in B (bars represent minimum and maximum values, except for outliers illustrating by rings). Scatter-plots of correlation between SUVmax ratios and Ki-67 index (in %) in C.



