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Exploring the mechanism of 18F-Fluorodopa uptake in recurrent high-grade gliomas : a comprehensive histomolecular-PET analysis.

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ABSTRACT

Background 18F-FDOPA PET is a valuable tool for managing high-grade gliomas (HGGs), but there is a lack of literature on its relationship with glioma subtypes since the 2021 reclassification of brain tumors. There is also debate surrounding the mechanism of 18F-FDOPA uptake, particularly after chemo-radiation therapy. This study aimed to investigate the correlation between 18F-FDOPA uptake and histo-molecular characteristics, particularly LAT1 expression, in recurrent gliomas, and examine their impact on survival in HGGs.

Methods Thirty-nine patients with recurrent HGGs (14 IDH-mutant, 25 IDH-wildtype) who underwent a brain 18F-FDOPA PET/CT or PET/MRI followed by surgical resection of the 18F-FDOPA-avid lesion within 6 months, were retrospectively reviewed. PET results were compared with histological examination and for SCL7A5/LAT1 immunostaining. The study also examined the relationship between PET parameters, LAT1 expression, and survival outcomes.

Results Astrocytoma IDH-mutant G4 had higher 18F-FDOPA uptake than glioblastoma IDH-wildtype G4 (TBRmax: 5 [3.4-9] vs 3.8 [2.8-5.9], $p=0.02$). IDH-mutant gliomas had higher LAT1 expression than IDH-wildtype gliomas (100 [14-273] vs 15.5 [0-137] $p<0.05$) as well as higher TBRmax (5 [2.4-9] vs 3.8 [2.8-6], $p<0.05$). In survival analysis, LAT1 score > 100 was a predictor for longer progression-free survival in IDH-mutant HGGs.

Conclusion To our knowledge, our study is the first to suggest a link between LAT1 expression and IDH mutation status. We showed that higher TBRmax was associated with higher LAT1 expression and IDH mutation status. Further studies are needed to better understand the mechanisms underlying amino-acid PET tracers uptake, especially in the post-radiation and chemotherapy settings.

1. Introduction

Adult-type diffuse high-grade gliomas (HGGs), which include grade 3 and 4 gliomas, are the most frequently diagnosed malignant primary brain tumors. Magnetic resonance imaging (MRI) has long been the gold standard exam for the management of gliomas tumors. In addition to MRI, the use of amino-acid PET tracers for the management of gliomas has been well established by the joint EANM/EANO/RANO guidelines in 2019 (1). In particular, 18F-fluoro-ethyl-L-tyrosine (18F-FET) and 3,4-Dihydroxy-6-[18F]fluoro-L-phenylalanine (18F-FDOPA) PET can be used for the differential diagnosis between post-therapeutic changes and true progression after radiotherapy in HGGs, with a high impact on multidisciplinary brain tumor board decisions and patients treatments (2). However, the accuracies of these techniques are not fully satisfactory. In a recent meta-analysis from Cui et al, pooled values of sensitivity and specificity were 0.85 (95% CI: 0.80, 0.89) and 0.70 (95% CI: 0.60, 0.79) for 18F-FDOPA (3).

18F-FDOPA uptake has long been thought to be related to LAT1 expression, a large sodium-independent neutral amino acid transporter, which is overexpressed in gliomas both in vitro and in vivo (4–7). Furthermore, because LAT1 is overexpressed on the blood-brain-barrier, tracer uptake is not dependent on the blood-brain barrier breakdown, unlike contrast media (8). However, in recurrent glioma patient, others mechanisms such as post-treatment inflammation may also be involved in 18F-FDOPA uptake (9). Clarification of the actual relationship between amino-acid tracers uptake and LAT1 expression is therefore needed, in order to better understand the biochemical factors that influence amino acid analog PET performance in brain tumors, in particular after chemotherapy and radiation therapy. Furthermore, LAT1 expression has been shown to correlate with survival but

immunohistochemical staining for LAT1 is not routinely performed in the management of glioma patients.

Literature data on the correlation between amino acid PET uptake and glioma tumors with current molecular biomarkers are lacking, as the World Health Organization (WHO) classification of central nervous system tumors changed recently in 2021 (10). Adult-type HGG are now classified into three groups: astrocytoma IDH-mutant, oligodendroglioma IDH-mutant and 1p/19q codeleted and glioblastoma IDH-wildtype (11). Thus, astrocytoma IDH-mutant grade 4 have now replaced glioblastoma IDH-mutant and astrocytoma IDH-wildtype with molecular alterations (such as +7/-10 chromosomes, *EGFR* amplification, *TERT* promoter mutation) are now reclassified as glioblastoma IDH-wildtype. In addition, the new classification takes into account molecular findings such as the presence of *CDKN2A/B* homozygous deletion to define astrocytoma IDH-mutant grade 4.

The aim of our study was therefore twofold: 1- to investigate the correlation between PET uptake of 18F-FDOPA and histomolecular characteristics, particularly LAT1 expression, in a homogeneous population of recurrent HGGs patients; 2- to investigate the impact of 18F-FDOPA uptake and LAT1 expression on survival of patients with HGGs previously treated with chemotherapy and radiation therapy.

2. Materials and Methods

2.1 Patient selection

We retrospectively included patients with suspected glioma recurrence, who underwent 18F-FDOPA PET followed by brain surgery within 6 months following PET, between February 2016 and October 2020, at the Pitié- Salpêtrière Hospital. For all patients, PET was performed

at least three months after the end of radiotherapy to reduce the risk of false positives. Patients for whom the therapeutic regimen was changed between PET and surgery were excluded. All included individuals gave informed consent to participate in the study. Patients' data use was approved by the French authority for the protection of privacy and personal data in clinical research (Commission Nationale de l'Informatique et des Libertés, approval No. 2111722). The study abided to the principles of the Declaration of Helsinki.

2.2 PET imaging protocols

¹⁸F-FDOPA PET were performed on two systems: Biograph mCT Flow PET/CT (Siemens Healthineers, USA) and Signa 3T PET/MR (General Electric Healthcare, Waukesha, WI, USA). Patients fasted for four hours before the injection of 2 MBq/kg of ¹⁸F-FDOPA. Images analysis were performed on static acquisitions, reconstructed from the list mode data ranging between the 10th and 30th minute post-injection. PET images were reconstructed using OSEM type iterative algorithms including point-spread function. Attenuation correction was performed using a 2-point Dixon MR sequence supplemented by a single-atlas to capture bone information for PET/MR, and using CT for PET/CT.

2.3 ¹⁸F-FDOPA PET analysis

PET images analysis was performed by two nuclear medicine physicians (NC, LR). Metabolic tumor volume (MTV) was automatically delineated on the SyngoVia® software using a threshold of 1,6 x contralateral cortex SUV_{mean}, as previously described (12). Reference regions were delineated in the unaffected contralateral parietal cortex (ROI of 3cm³) and in the contralateral striatum as previously described (13). We then calculated the ratios of SUV_{max} or SUV_{mean} of the tumor to the SUV_{mean} of the contralateral cortex (TBR_{max}

and TBRmean, respectively) and the ratios of SUVmax or SUVmean of the tumor to the SUVmean of the contralateral striatum (TSRmax and TSRmean, respectively).

2.4. Histomolecular analysis

Two neuropathologists (FB, ST) independently reviewed the histological slides (hematoxylin&eosin/HE staining and SCL7A5/LAT1 immunostaining) for the integrated diagnosis according to WHO classification 2021 and for SCL7A5/LAT1 immunostaining. Four micrometres-thick formalin-fixed paraffin-embedded tissue sections were processed for deparaffinization and immunolabeling by a fully automatic Ventana benchmark Ultra System (Roche, Basel, Switzerland), using a streptavidin-peroxidase complex with diaminobenzidine as the chromogen and the following primary antibodies: SCL7A5/LAT1 (Rabbit monoclonal, clone EPR17573, Abcam, 1/40). The SCL7A5/LAT1 H-score was assessed with a score as followed: staining intensity was evaluated between 0 (no staining) to 4 (highest intensity) and the tumor cells having the same staining intensity were evaluated in percentage of total tumor cells. The score spanned from 0 to 400. A mean score was rendered from the two scores obtained independently by FB and ST.

2.5 Survival time

Progression-free survival (PFS) and overall survival (OS) were defined as the time, in months, from PET to progression according to the RANO group, respectively. OS was measured from the date of PET to death or last follow-up during in the patient was recorded as alive. To avoid any survival bias related to surgical extension, all MRIs performed within 24 hours after surgery were reviewed by a neurosurgeon (B.M.) and a neuroradiologist (L.N.) and the extent of resection was classified as complete resection (100%), subtotal resection

(80-100%) or partial resection (under 80%) (Table 1). The final date for reporting any event for PFS or OS was 06/01/22.

2.6 Statistical analysis

Continuous variables were expressed as medians (minimum – maximum). The Mann-Whitney test was used to compare quantitative data. Expression of LAT and PET parameters in relation to tumor histology was evaluated using ANOVA comparisons. Correlations between 18F-FDOPA parameters and LAT1 expression were analyzed using the non-parametric Spearman test. Patients were classified in two groups according to the respective median split of the above described LAT1 overall score and TBRmax in order to perform Kaplan–Meier analyses with log-rank test. Statistical significance was defined for 2-tailed p values below 0.05. Statistical analyses were performed with the JMP Pro 16® software.

3. Results

3.1 Patient characteristics

Forty-one patients were selected according to our inclusion criteria, but two patients were excluded, because of a histologic diagnosis of radionecrosis, and insufficient histological specimen for reclassification according to the WHO 2021. Details of the clinical data of the remaining thirty-nine patients are listed in Table 1. Nineteen patients underwent a PET/CT and twenty a PET/MRI. Mean time from PET to surgery was 1.4 ± 1.3 months. According to the WHO 2021, classification of recurrence surgical specimens, 25 patients had glioblastoma IDH-wildtype, 7 astrocytoma IDH-mutant and 7 oligodendroglioma IDH-mutant. Thirty-five (90%) patients had a second recurrence and thirty-one (79%) patients died during the follow-up period.

3.2 PET parameters

In our cohort of recurrent HGGs, all patients showed significant uptake of 18F-FDOPA on PET.

Median values were 4.1 [2.4-9] for TBRmax and 2.8 [1.9-6.5] for TSRmax. Among grade 4 gliomas, astrocytoma IDH-mutant had a significantly higher TBRmax than glioblastoma IDH-wildtype (5 [3.4-9] vs 3.8 [2.8-6], $p < 0.05$). TBRmax also tended to be higher in oligodendroglioma compared with glioblastoma, but without reaching significance. No significant difference was found within IDH-mutant gliomas (i.e., astrocytoma vs oligodendroglioma). Details of 18F-FDOPA PET parameters in IDH-mutant and IDH-wildtype gliomas can be found in Table 2.

3.3 LAT1 parameter

The median LAT1 score of all patients was 42, ranging from 0 to 273/400 from low to high. Based on surgical findings following 18F-FDOPA PET, LAT1 expression varied by glioma subtype: median [range] were 134 [18-203] for oligodendroglioma IDH-mutant and 1p/19q codeleted, 64 [14-273] for astrocytoma IDH-mutant and 15.5 [0-137] for glioblastoma IDH-wildtype. The mean H-score was higher in IDH-mutant than in IDH-wildtype glioma: 100 [14-273] vs 15.5 [0-137] ($p < 0.005$) (Table 3).

To obtain external validation of this result, we analyzed the relationship between LAT1 mRNA expression and IDH mutant status in the public Glass Consortium diffuse glioma database, Nature 2019, freely available at <https://www.cbioportal.org/>. Similar to our study, data from the diffuse glioma cohort showed a significant correlation between IDH status and LAT1 with higher expression in IDH mutant gliomas than in IDH wild-type gliomas (supplementary information Fig 1 and Table 1).

3.4 Correlation of 18-FDOPA uptake with LAT1 expression

A significant association was found between the 18F-FDOPA uptake and the LAT1 expression: a high H-score (above median 42) was associated with a higher TBRmax (4.4 [2.9-9] vs 3.7 [2.4-5.6], $p < 0.05$) (Figure 1). However, no significant linear correlation was found between LAT1 expression (as assessed by the H-Score) and the 18F-FDOPA PET quantitative indexes, in the overall population of HGGs or in populations separated according to their histological subtypes or IDH mutation status.

3.4 Outcome analysis

The median follow-up time was 16 months (range, 4- 58 months). Univariate analysis revealed no statistical difference in survival based on the extent of surgery following the 18F-FDOPA PET exam, IDH status, or LAT1 expression split by median value. However, in the IDH-mutant gliomas subgroup, a threshold > 100 (median) for the LAT1 score was a predictor of longer PFS (19 vs 7 months, $p < 0.005$). The analysis of OS showed a persistent trend, although statistical significance was not achieved ($p = 0.06$). Kaplan-Meier survival curve for the prediction of PFS in the whole population and of IDH-mutant gliomas is shown in Figure 2

4. Discussion

Our study reports the results of a systematic correlation between 18F-FDOPA uptake and histo-molecular analysis according to the WHO 2021 classification of brain tumors, and LAT1 immunostaining, in 39 recurrent HGGs. We found that IDH-mutant tumors had higher 18F-FDOPA uptake than IDH-wildtype gliomas, and demonstrated, for the first time to our knowledge, that IDH-mutant status was also associated with higher expression of LAT1.

Recent literature showed that IDH-mutant astrocytoma and IDH-wildtype glioblastoma had different recurrence pattern following chemoradiation ; therefore *in-vivo* identification of IDH mutation among grade 4 glioma could be of great interest in the future (14). Our work including 39 histologically confirmed recurrent HGGs, showed that IDH mutant gliomas (astrocytoma grade 4 and oligodendroglioma grade 3) had higher 18F-FDOPA uptake (TBRmax) than IDH wildtype HGGs. Similar results were found when comparing astrocytoma IDH-mutant grade 4 and glioblastoma IDH-wildtype. Our results are in line with Verger et al. who found higher 18F-FDOPA uptake in 43 newly diagnosed grade 2 and 3 gliomas with IDH mutation compared with those without IDH mutation (15,16). However, other PET parameters, such as the SUVmax or the TBRmean were not associated with IDH mutation status in our study, as previously described in another cohort which evaluated ¹¹C-methionine PET uptake in WHO 2016 de novo glioblastoma with and without IDH-mutation (which may reflect our comparison of grade 4 astrocytoma and glioblastoma) (16). In our study, we did not observe any significant difference within IDH-mutant gliomas when comparing astrocytomas and oligodendrogliomas. While several studies have reported a higher level of amino acid uptake in IDH-mutant oligodendrogliomas compared to IDH-mutant astrocytomas, it is important to note that these studies exclusively involved newly diagnosed cases and have not been corroborated by other studies (15–21).

To the best of our knowledge, our study is the first to report that IDH-mutant gliomas had higher LAT1 expression than IDH-wildtype gliomas. By further examining the public database of diffuse glioma (GLASS cohort, Nature 2019) we showed that a significant relationship between LAT1 mRNA expression and IDH mutant status could have already been noticed (22). It is noteworthy that two patients with IDH-wildtype glioma in the GLASS cohort exhibited very high LAT1 levels. These unexpected findings might be explained by a

sampling bias or possibly by epileptogenic foci. Indeed, Hutterer et al. showed in a study on 10 patients that LAT1 was strongly expressed in neurons and endothelium of seizure-affected brain (23).

IDH mutation results in 2-hydroxyglutarate (2HG) accumulation which has been described to be linked to a lower hypoxia (24). On the other hand, hypoxia has been reported to be associated with a down-regulation LAT1 gene expression in blood-brain barrier, resulting in decreased amino acid availability in the brain (25). We may therefore suggest that under-expression of LAT1 in IDH-wildtype tumors may result from a more profound hypoxia in these tumors. In this regard, Wang et al. recently demonstrated that IDH-wildtype gliomas exhibited higher 18F-FMISO uptake, a radiotracer reflecting hypoxia within the tumor, when compared to IDH-mutant gliomas (26).

Although we did not report a linear correlation between LAT1 expression and 18F-FDOPA uptake, we showed that higher TBRmax was associated with higher LAT1 expression. These results aligned with those of several studies with 18F-FDOPA or 18F-FET (27–29). Others, found a linear correlation between the tracer uptake and LAT expression but their study population consisted only of de novo HGGs (4,30). Recurrent tumors may not depend on the same amino acid uptake mechanisms as de novo gliomas; and LAT1 expression may only partly explain tracer uptake when post-therapeutic changes are involved. Stockhammer et al. have suggested that key uptake mechanisms may be located in the endothelium rather than in tumor cells (29). Others transporters, such as the glutamine transporter sodium-coupled neutral amino-acid transporter (SNAT) 1 have also been proposed (31).

In our study, we observed that in IDH-mutant gliomas, a LAT1 score exceeding 100 was predictive of improved survival. This finding contrasts with prior studies by Vetterman et al.

and Nawashiro et al., which demonstrated an association between higher LAT1 expression and shorter PFS ; however, it's important to note that their studied population solely consisted of de novo grade 2 and 3 gliomas (28,32). A notable limitation of our survival analyses is the absence of a larger cohort to perform multivariate survival analyses, which would strengthen the validity of our findings. Consequently, further studies with larger sample sizes are needed to confirm or refute our observations regarding the correlation between LAT1 expression and both PFS and OS. Concerning PET uptake, we did not find any association between 18F-FDOPA and survival, similar to several studies in homogeneous population of HGGs. Positive correlations between 18F-FDOPA uptake and survival have mostly been described in population of de novo gliomas and it can be speculated that post-treatment mechanisms may change the biology of the tumor and thus the relationship between 18F-FDOPA uptake and survival parameters (33,34).

Although it provides new data regarding 18F-FDOPA related to LAT1 expression in glioma patients, our study has several limitations. Firstly, our sample size was restricted to 39 patients, a consequence of the infrequent use of surgery as a second-line treatment for high-grade gliomas. Furthermore, our ability to explore the correlation between 18F-FDOPA and LAT1 expression in patients with radionecrosis was limited, as only two patients presented with this condition histologically. Secondly, the LAT staining analyzed may not accurately represent the maximum tumor uptake observable on the PET scan. This discrepancy arises from the fact that the staining was performed on a mere sample of the collected tissue, potentially accounting for the absence of a linear correlation in our cohort. Thirdly, the time interval between the 18F-FDOPA PET and surgery was as long as 168 days in some instances. This extended duration could lead to alterations in LAT1 expression, possibly due to the effects of prior cytotoxic treatments. However, it is important to note that for 30 out of

the 39 patients (77%), the time interval was less than two months. Moreover, no new treatments were initiated between the PET scan and the histological examination for any of the patients. Despite these limitations, our study stands as the first to establish a link between LAT1 expression and IDH-mutation status.

As LAT1 is emerging as a new target for cancer therapy, knowledge of its contribution to 18F-FDOPA uptake in glioma patients is of great interest (32,35,36). Our study revealed a significant correlation between high LAT1 expression and longer PFS in HGGs with IDH mutation, with a trend observed for OS. Further studies are needed to confirm our results in a larger population and to investigate other potential mechanisms involved in 18F-FDOPA uptake in HGGs.

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Legends for illustrations

Fig. 1 Two patients with high grade gliomas,

Upper panel : 53 y-old man with a recurrent fronto-temporo-insular IDH mutant astrocytoma (A : 3D FLAIR in the axial plane, B : 3D T1 after gadolinium injection, axial plane). 18F-FDOPA uptake was very high with a tumor-to-background ratio (TBRmax) of 5,6 (C: axial PET) LAT1 staining reveal an high expression with an H-score of 273 (D).

Lower panel : 72 y-old man with a recurrent occipito-temporal IDH-wildtype glioblastoma (E : 3D FLAIR in the axial plane, F : 3D T1 after gadolinium injection, axial plane). 18F-FDOPA uptake was high but more moderate : TBRmax 3.4 (G: axial PET) LAT1 staining reveals almost no expression (H-score =5) (H)

Fig. 2 Survival analysis of the LAT1 expression in the overall group (A) and in the IDH-mutant high-grade gliomas subgroup (B)