



HAL
open science

Hybrid [18F]-F-DOPA PET/MRI Interpretation Criteria and Scores for Glioma Follow-up After Radiotherapy

Marc Bertaux, Arnaud Berenbaum, Anna-Luisa Di Stefano, Laura Rozenblum, Marine Soret, Sebastien Bergeret, Khé Hoang-Xuan, Laure-Eugenie Tainturier, Brian Sgard, Marie-Odile Habert, et al.

► **To cite this version:**

Marc Bertaux, Arnaud Berenbaum, Anna-Luisa Di Stefano, Laura Rozenblum, Marine Soret, et al.. Hybrid [18F]-F-DOPA PET/MRI Interpretation Criteria and Scores for Glioma Follow-up After Radiotherapy. *Clinical Neuroradiology*, 2022, 10.1007/s00062-022-01139-0 . hal-03573129v2

HAL Id: hal-03573129

<https://hal.sorbonne-universite.fr/hal-03573129v2>

Submitted on 14 Feb 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Clinical Neuroradiology

Hybrid [18F]-F-DOPA PET/MRI interpretation criteria and scores for glioma follow-up after radiation therapy --Manuscript Draft--

Manuscript Number:	KLNE-D-21-00514R2
Full Title:	Hybrid [18F]-F-DOPA PET/MRI interpretation criteria and scores for glioma follow-up after radiation therapy
Short Title:	F-DOPA PET/MRI hybrid interpretation
Article Type:	Original Article
Keywords:	PET FDOPA GLIOMA MRI ASL
Corresponding Author:	Marc BERTAUX, Ph. D Hôpital Foch: Hopital Foch Suresnes, France FRANCE
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Hôpital Foch: Hopital Foch
Corresponding Author's Secondary Institution:	
First Author:	Marc BERTAUX, Ph. D
First Author Secondary Information:	
Order of Authors:	Marc BERTAUX, Ph. D Arnaud BERENBAUM, MD Anna Luisa Di Stefano, MD Laura ROZENBLUM, MD Marine SORET, PHD Sebastien BERGERET Khé HOANG-XUAN, MD, PHD Laure-Eugenie TAINURIER Brian SGARD Marie-Odile HABERT Jean-Yves DELATTRE, MD, PHD Caroline DEHAIS, MD Ahmed IDBAIH, MD, PHD Nadya PYATIGORSKAYA, MD, PHD Aurelie KAS, MD, PHD
Order of Authors Secondary Information:	
Funding Information:	
Abstract:	Objectives: F-DOPA PET is used in glioma follow-up after radiotherapy to discriminate treatment-related changes (TRC) from tumour progression (TP). We compared the performances of a combined PET and MRI analysis with F-DOPA current standard of

	<p>interpretation.</p> <p>Methods : We included 76 consecutive patients showing at least one gadolinium-enhancing lesion on T1-w MRI sequence (T1G). Two nuclear medicine physicians blindly analysed PET/MRI images. In addition to the conventional PET analysis, they looked for F-DOPA uptake(s) outside T1G-enhancing areas (T1G-/PET), in the white matter (WM/PET), for T1G-enhancing lesion(s) without sufficiently concordant F-DOPA uptake (T1G+/PET), and for F-DOPA uptake(s) away from haemorrhagic changes as shown with a Susceptibility Weighted Imaging sequence (SWI/PET). We measured lesions' F-DOPA uptake using healthy brain background (TBR) and striatum (T/S) as references, and lesions' perfusion with arterial spin labelling cerebral blood flow maps (rCBF). Scores were determined by logistic regression.</p> <p>Results: 53 and 23 patients were diagnosed with TP and TRC, respectively. The accuracies were 74% for T/S, 76% for TBR, and 84% for rCBF, with best cut-off values of 1.3, 3.7 and 1.25, respectively. For hybrid variables, best accuracies were obtained with conventional analysis (82%), T1G+/PET (82%) and SWI/PET (81%). T1G+/PET, SWI/PET and rCBF ≥ 1.25 were selected to construct a 3-point score. It outperformed conventional analysis and rCBF with an AUC of 0.94 and an accuracy of 87%.</p> <p>Conclusions : Our scoring approach combining F-DOPA PET and MRI provided better accuracy than conventional PET analyses for distinguishing TP from TRC in our patients after radiation therapy.</p>
<p>Response to Reviewers:</p>	<p>Once again, we would like to thank the reviewers and the editorial team for their work. As requested, the manuscript was fully checked with the Grammarly software and modified accordingly.</p>

Hybrid [¹⁸F]-F-DOPA PET/MRI interpretation criteria and scores for glioma follow-up after radiation therapy

Marc BERTAUX¹, Arnaud BERENBAUM¹, Anna-Luisa DI STEFANO², Laura ROZENBLUM¹, Marine SORET^{1,3}, Sebastien BERGERET¹, Khé HOANG-XUAN², Laure-Eugenie TAINTURIER¹, Brian SGARD¹, Marie-Odile HABERT^{1,3}, Jean-Yves DELATTRE², Caroline DEHAIS², Ahmed IDBAIH², Nadya PYATIGORSKAYA^{4,5}, Aurelie KAS^{1,3}

¹ AP-HP, Hôpitaux Universitaires La Pitié Salpêtrière - Charles Foix, Service de médecine nucléaire, F-75013, Paris, France

² Sorbonne Université, Inserm, CNRS, UMR S 1127, Institut du Cerveau et de la Moelle épinière, ICM, AP-HP, Hôpitaux Universitaires La Pitié Salpêtrière - Charles Foix, Service de Neurologie 2-Mazarin, F-75013, Paris, France

³ Sorbonne Université, LIB, INSERM U1146, 75013, Paris, France.

⁴ AP-HP, Hôpitaux Universitaires La Pitié Salpêtrière - Charles Foix, Service de neuroradiologie, F-75013, Paris, France

⁵ Institut du Cerveau et de la Moelle épinière-ICM, INSERM U 1127, CNRS UMR 7225, Sorbonne Université, UPMC Univ Paris 06, UMRS 1127, CNRS UMR 7225, Paris, France

Author's contribution: All the authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Marc BERTAUX, Caroline DEHAIS, Laura ROZENBLUM, Laure-Eugenie TAINTURIER, and Aurelie KAS. Blind examination of images was performed by Arnaud BERENBAUM and Marc BERTAUX. The first draft of the manuscript was written by Marc BERTAUX and all the authors have commented on the previous versions of the manuscript. All the authors read and approved the final manuscript.

Corresponding author:

Marc Bertaux

marc.beraux@gmail.com

ORCID: <https://orcid.org/0000-0001-9954-8866>

Cover letter

Paris, October (revised in December) 2021

To the Editor of Clinical Neuroradiology

Please find enclosed the manuscript entitled “Hybrid (18)F-FDOPA PET and MRI interpretation criteria and scores for glioma follow-up after radiation therapy” to be considered for publication in the Clinical Neuroradiology journal, as an original research article.

In this study, we have developed, tested, and combined into scores new hybrid PET and MRI parameters by blindly reviewing the examinations of 76 patients seen in F-DOPA PET/MRI during the follow-up after radiotherapy of their infiltrative glioma. For our patients, these scores performed better than F-DOPA PET conventional interpretation criteria and MRI perfusion sequences. If the good performance and robustness of these scores were to be confirmed prospectively, they could be used as a framework to go beyond the current usual interpretation criteria of F-DOPA PET in clinical routine.

Yours sincerely,

Marc BERTAUX, MD, head of the nuclear medicine department at the Foch hospital (40 rue Worth, Suresnes), and previously working at AP-HP, Pitié-Salpêtrière hospital (47-83 Boulevard de l'Hôpital, Paris), where the study was conducted.

marc.beraux@gmail.com

ORCID: <https://orcid.org/0000-0001-9954-8866>,

phone number: +33 6 88 99 57 47

Hybrid [¹⁸F]-F-DOPA PET/MRI interpretation criteria and scores for glioma follow-up after radiation therapy

Abstract:

Objectives: F-DOPA PET is used in glioma follow-up after radiotherapy to discriminate treatment-related changes (TRC) from tumour progression (TP). We compared the performances of a combined PET and MRI analysis with F-DOPA current standard of interpretation.

Methods: We included 76 consecutive patients showing at least one gadolinium-enhancing lesion on the T1-w MRI sequence (T1G). Two nuclear medicine physicians blindly analysed PET/MRI images. In addition to the conventional PET analysis, they looked for F-DOPA uptake(s) outside T1G-enhancing areas (T1G-/PET), in the white matter (WM/PET), for T1G-enhancing lesion(s) without sufficiently concordant F-DOPA uptake (T1G+/PET), and F-DOPA uptake(s) away from haemorrhagic changes as shown with a Susceptibility Weighted Imaging sequence (SWI/PET). We measured lesions' F-DOPA uptake using healthy brain background (TBR) and striatum (T/S) as references, and lesions' perfusion with arterial spin labelling cerebral blood flow maps (rCBF). Scores were determined by logistic regression.

Results: 53 and 23 patients were diagnosed with TP and TRC, respectively. The accuracies were 74% for T/S, 76% for TBR, and 84% for rCBF, with best cut-off values of 1.3, 3.7 and 1.25, respectively. For hybrid variables, best accuracies were obtained with conventional analysis (82%), T1G+/PET (82%) and SWI/PET (81%). T1G+/PET, SWI/PET and rCBF ≥ 1.25 were selected to construct a 3-point score. It outperformed conventional analysis and rCBF with an AUC of 0.94 and an accuracy of 87%.

Conclusions: Our scoring approach combining F-DOPA PET and MRI provided better accuracy than conventional PET analyses for distinguishing TP from TRC in our patients after radiation therapy.

Keywords:

PET

F-DOPA

GLIOMA

MRI

ASL

Funding: No funding was received for conducting this study.

Conflicts of interest/Competing interests: The authors have no relevant financial or non-financial interests to disclose.

1
2 **Abbreviations:**

3
4 **TRC:** Treatment-Related Changes

5
6 **TP:** Tumour Progression

7
8 **T1G:** MRI T1-weighted sequences after gadolinium contrast agent injection

9
10 **DSC:** Dynamic Susceptibility Contrast

11
12 **ASL:** Arterial Spin-Labeling

13
14 **F-DOPA:** ¹⁸F-fluoro-L-3,4-dihydroxyphenylalanine

15
16 **PET:** Positron Emission Tomography

17
18 **ROI:** region-of-interest

19
20 **FET:** ¹⁸F-fluoroethyl-tyrosine

21
22 **SWI:** susceptibility-weighted imaging MRI sequence

23
24 **IDH:** Isocitrate Dehydrogenase

25
26 **rCBF:** regional cerebral blood flow

27
28 **FLAIR:** Fluid-attenuated inversion recovery (FLAIR) T2 sequence

29
30 **TBR:** tumour-to-background ratio

31
32 **SUVmax:** maximum standard uptake value

33
34 **T/S:** tumour-to-striatum ratio

35
36 **ROC:** receiver operating characteristic

37
38 **OS:** overall survival

Introduction:

1 Treatment-related changes (TRC), i.e. pseudoprogression and radionecrosis, can occur during the follow-up of
2 patients with a diffuse glioma after radiation therapy. TRC and Tumour progression (TP) may have a similar
3 aspect in MRI T1-weighted sequences after gadolinium contrast agent injection (T1G) as both can lead to an
4 increased blood-brain barrier permeability. The most widely used technique to differentiate them is MRI
5 perfusion-weighted imaging using the dynamic susceptibility contrast (DSC) technique. In patients with high-
6 grade glioma, the calculation of the normalized regional cerebral blood volume ratio with DSC shows an overall
7 good performance in this setting, with sensitivity and specificity ranging from 0.81 to 0.94 and from 0.78 to
8 0.95, respectively. However, proposed cut-off values are highly variable across studies [1]. Moreover, the
9 haemorrhagic changes that frequently occur in patients with glioma can lead to magnetic susceptibility artefacts
10 and be responsible for false-negative results. Arterial spin-labelling (ASL) perfusion sequence is an alternative to
11 DSC. It also showed good performances in differentiating TP from TRC [2] and should be less prone to
12 susceptibility artefacts, as frequently seen in this setting.

13 ¹⁸F-fluoro-L-3,4-dihydroxyphenylalanine (F-DOPA) Positron emission tomography (PET) imaging can be used
14 during the follow-up of patients with glioma, when morphological and advanced MRI results remain equivocal
15 [3]. F-DOPA PET sensitivity to diagnose recurrence is good in both high- and low-grade gliomas, ranging from
16 81% to 95 %, but its specificity remains suboptimal, ranging from 66% to 85% [4-7]. The conventional F-DOPA
17 PET method of interpretation is purely based on lesion(s) intensity of uptake. Whether by visual analysis or a
18 region-of-interest (ROI) based method, F-DOPA uptakes are considered suggestive of TP when their intensity is
19 greater than that of contralateral striatum or twice that of the normal cortex, and suggestive of TRC when it's not
20 [8]. Unlike ¹⁸F-fluoroethyl-tyrosine (FET), the diagnostic value of kinetic analysis has not been shown for F-
21 DOPA in this setting. [9-11].

22 Current European practice guidelines state that amino-acid PET images should be fused and interpreted in
23 conjunction with most recent T1G and T2-weighted sequences [12]. However, the guidelines do not specify how
24 lesion characteristics on MRI may or may not influence PET images interpretation and how to implement it in
25 clinical practice, as data on the subject are scarce [13,14]. Yet, misleading F-DOPA PET uptake can occur in
26 inflammatory [15], infectious [16], epileptic [17] and haemorrhagic processes [18]. Some of these features can
27 be specified on MRI. For example, the extracortical localization of an uptake excludes its epileptic origin and
28 massive inflammatory changes in the brain are rarely seen without concordant enhancement in T1G sequences.
29 In addition, susceptibility-weighted imaging MRI sequences (SWI) make it possible to delineate brain regions
30 where bleeding has occurred. Thus, it can be assumed that F-DOPA uptakes are more specific for viable tumour
31 tissue when they are located in the white matter, and/or outside enhancing areas in T1G, and/or outside of
32 haemorrhagic areas on SWI sequences. Conversely, we believed that the presence of a T1G enhancing lesion
33 incompletely matched by an F-DOPA PET uptake could be a good indicator of TRC even when it co-exists with
34 abnormal uptakes elsewhere in the brain.

35 Based on these hypotheses, the purpose of this exploratory work was to create hybrid parameters and scores
36 combining MRI and PET features to use for clinical routine interpretation of F-DOPA PET scans in glioma
37 patients after radiation therapy, which would outperform the current standard interpretation.

Material and method:

Patients

All patients who underwent an F-DOPA PET/MRI in the nuclear medicine department of the Pitié-Salpêtrière Hospital, Paris, France, for post-radiation therapy follow-up of a histologically proven infiltrating glioma between 1 January 2016 and 31 December 2018 were retrospectively included in our study. Patients were excluded from the analysis if they had no enhancing lesion on MRI. For patients who underwent multiple PET/MRI scans, only the first was analysed.

All gliomas were classified according to the WHO 2016 classification based on the status of isocitrate dehydrogenase (IDH) genes (mutated versus none mutated) and on 1p19q co-deletion (co-deleted or non-co-deleted). Three subgroups were identified: IDH mutated without 1p-19q co-deletion (IDH_{m-non-codel}), IDH mutated and 1p-19q co-deleted (IDH_{m-codel}), and IDH wild-type (IDH_{WT}).

When available, the definitive diagnosis of TRC or TP was based on histology. In all the other cases, it was the result of an expert consensus based on the RANO criteria and current glioma monitoring guidelines. The latter indicates that a new tumour or brain lesion observed on MRI and/or an obvious increase in the size of the tumour or an increase in contrast enhancement, and/or a significant clinical deterioration, provided that these modifications are not attributable to non-tumour causes, correspond to a recurrence/progression [19, 20]. For the diagnosis to be considered as TP, a new progression had to occur within 3 months following PET/MRI for IDH_{WT}, within 6 months for IDH_{m-non-codel}, and within 12 months for IDH_{m-codel} gliomas. In patients for whom a new treatment had been started after F-DOPA PET/MRI, the time limit was extended to 6 months for IDH_{WT} and to 9 months for IDH_{m-non-codel} gliomas.

The use of patients' data 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). This study was carried out in accordance with the principles of the Declaration of Helsinki.

Image acquisition and post-processing

The images were acquired with a Signa PET/MR camera (General Electric Healthcare®, Milwaukee, WI, USA) combining a 3T MR and a SiPM-PET, using an 8-channel head coil. Patients had to fast for at least 4 hours before the examination and were not given any premedication. PET images were acquired 10 minutes after the intravenous injection of 2 MBq/kg of F-DOPA for 20 minutes. They were reconstructed with an iterative algorithm (OSEM-3D, 28 subsets, 8 iterations, 4 mm transaxial Gaussian post-filtering, matrix 256 x 256) using time of flight and point spread function modelling. Attenuation correction was done using a 2-point Dixon MR sequence that was segmented into three components and supplemented by the use of a single-atlas to capture bone information [21].

For this study, we used native and contrast-enhanced (injection of 0,2 ml/kg of Dotarem® 90 seconds before acquisition) sagittal 3D T1 spin-echo sequences (TR = 602 ms, TE = 16.7 ms, voxel size 0.5 x 0.5 x 1.2 mm), axial 3D SWAN sequence (TR = 68.5 ms, TE = 28.1 ms, voxel size 0.39 x 0.39 x 3.2 mm), and the 3D pseudo-continuous ASL sequence (post-label delay = 2025 ms, TR = 4833 ms, TE = 10.7 ms, bandwidth 976.6 Hz/pixel, flip angle = 111,1°, voxel size 1.875 x 1.875 x 4 mm). ASL sequences were post-processed with the dedicated software using the advantage windows server version 3.2 solution (General Electric Healthcare®) to obtain cerebral blood flow (rCBF) maps. Fluid-attenuated inversion recovery (FLAIR) T2 sequences that are routinely performed for our neuro-oncological patients were not used in this study.

Blind image analysis

Two nuclear medicine physicians reviewed the images using the VB 30 version of the imaging software Syngo.via (Siemens Healthcare®, Munich, Germany). They performed a blind examination where the patients' diagnoses and results, as well as their clinical parameters, previous MRI, and request for examination, were not known.

A "conventional" PET analysis was performed first, using only PET images. Patients were visually classified as positive or negative depending on whether or not there was an encephalic area with an "intense" F-DOPA uptake. "Intense" uptake was visually defined as higher than twice the background cortex intensity. This was performed using the SUV100 manufacturer's colour scale, adjusted so that the healthy cortex maximum intensity was in the middle of the colour range (dark green). Thus, "intense" uptake areas appeared in the upper colour of the range (pink).

For hybrid PET and MRI combined analysis we defined the notion of "valid" PET uptake as follows: when situated in any T1G enhancing or cortical areas, an F-DOPA uptake had to be "intense" to be considered "valid". In the non-enhancing white matter, any visible F-DOPA uptake was considered "valid". Then, we defined four binary morpho-metabolic parameters to be visually classified by reviewers (Table 1). After T1 and T1G sequences were fused with PET images, the first parameter, T1G+/PET, was defined as positive if each gadolinium-enhancing lesion of at least 20 mm was matched with a PET "intense" uptake in more than 60% of its volume (T1G+/PET (+)). As such, this parameter was negative *if any* enhancing lesion of this size was not matched with this type of PET uptake (T1G+/PET (-)). Lesions of less than 20 mm were not considered here as PET poor spatial resolution may impact quantification and visual semi-quantification too much in such small objects. The second parameter, T1G-/PET, was classified as positive when any "valid" F-DOPA uptake was found outside MRI enhancing areas (T1G-/PET (+)), and as negative when none was found outside MRI enhancing areas (T1G-/PET (-)). The third parameter, WM/PET, was classified as positive when any "valid" F-DOPA uptake could be seen in the white matter (WM/PET (+)), and as negative when none could be found in the white matter (WM/PET (-)). Then, a fusion between PET images and SWI sequence was performed to define the fourth parameter, SWI/PET, and reviewers searched for the presence (SWI/PET (+)) or absence (SWI/PET (-)) of any "valid" PET uptake outside of susceptibility artefact-induced hypointensities, i.e. not related to haemorrhagic changes. Figure 1 examples illustrate these morpho-metabolic parameters.

Quantitative analysis

For PET, we measured the maximum standard uptake value (SUV_{max}) of the most intense lesion in each patient. Its ratios to the contralateral striatal SUV_{max} (T/S) and the healthy brain SUV_{mean} (TBR) were then calculated. The latter was measured using a spherical peripheral 3 cm³ volume of interest drawn in the periphery of the contralateral parietal lobe.

For MRI, the size of the enhancing lesion was measured by the product of axial perpendicular short and long axes of the greatest enhancing lesion. A lesion rCBF mean value was obtained for each patient, using a 0.6 cm² circular ROI located on the abnormal area showing the highest perfusion. PET images were used to distinguish relevant hot spots from physiological cortex perfusion and vessels. When there was no obvious abnormal perfusion hot spot, the ROI was positioned on the most intense PET uptake. The normalization of these rCBF

1 values to the contralateral semi-oval white matter rCBF mean value was performed to obtain rCBF ratios, except
2 for purely cortical lesions, in which case the normalization was based on cortical contralateral mirrored ROIs.
3

4 **Statistical analysis**

5 Kappa inter-rater reliability coefficients were calculated for morpho-metabolic binary variables and PET analysis
6 alone. In the event of divergent results between the two reviewers, a consensus was reached after a joint blind
7 examination of the images which was used for the statistical analyses.
8

9 A binary logistic regression using bootstrap analysis (1,000 samples) and the enter method was then performed,
10 based on morpho-metabolic variables, TBR and rCBF ratio as predictors, and diagnosis as the target. A second
11 regression analysis was carried out, using only the parameters that remained statistically significant predictors in
12 the first analysis. The third regression was conducted without rCBF. Multicollinearity between predictive
13 variables was assessed by calculating variance inflation factors. The regression coefficient values finally
14 obtained were used to create morpho-metabolic scores by rounding off their relative value to the nearest whole
15 number.
16

17 Variables are presented as mean \pm standard deviation unless otherwise specified. Subgroups variable values were
18 compared using a non-parametric Mann-Whitney. The performances of scores as well as those of rCBF ratio and
19 PET quantitative parameters were compared with receiver operating characteristic (ROC) curve analysis. The
20 best cut-offs were chosen to maximize Youden's index [22]. Accuracies of binary variables were compared with
21 the McNemar test for paired samples and with the χ^2 test for independent samples.
22

23 The patient overall survival (OS) rate was calculated from the date of PET/MRI to the date of death. Kaplan-
24 Meier survival curves were compared with the log-Rank method. A multivariate analysis using the strongest
25 prognostic factors was carried out with the Cox survival model after quantitative variables were dichotomized.
26 To this purpose, optimal cut-offs were identified using X-Tile software (3.6.1, Yale University), as well as a
27 follow-up cut-off at 3 years.
28

29 All statistical analyses were performed using SPSS 26 software (IBM®). A p-value of 0.05 or less was
30 considered significant for all the analyses performed.
31

32 **Results:**

33 **Patients**

34 Eighty-six consecutive patients referred between January 2016 and December 2018 for an F-DOPA PET/MRI
35 examination were initially included. Five patients were excluded from the study because of the absence of any
36 enhancing lesion in T1G. Five additional patients, for whom a new treatment line had been started after
37 PET/MRI and who had no tumour progression within the given time frame, were also excluded as a retrospective
38 diagnosis of TP or TRC could not be asserted. Consequently, 76 patients were included in our analysis (Figure
39 [S1](#) in supplementary materials), of which 23 (30%) were finally diagnosed with TRC and 53 (70%) with TP. The
40 final diagnosis was based on histology in 15 cases (20%) and clinical-radiological follow-up in 61 cases (80%).
41 Gliomas were classified as IDH_{WT} for 36 patients (42%), as IDH_{m-non-codel} for 20 patients (26%) and as IDH_{m-codel}
42 for 18 patients (24%). The molecular profile was not known for 6 patients (8%). Seventeen
43 patients (22%) underwent PET/MRI within 6 months after radiotherapy, and 59 (78%) after these 6 months. The
44 proportion of TRC (29% and 35%, respectively) was not significantly different between these two subgroups.
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1 Also, 31 patients (41%) received chemotherapy in the 6 months before the PET/MRI scan. For them, there was a
2 trend towards a higher proportion of TRC than in other patients, but it did not reach statistical significance (42 %
3 versus 22%, $p = 0.07$). No significant differences were found in the performances of the diagnostic parameters
4 within these sub-groups. Patients' characteristics are presented in Table 2.
5
6

7 **Conventional PET analysis and hybrid parameters performances**

8 The accuracies to distinguish between TP and TRC were 82% for conventional analysis, 82% for T1G+/PET, 64
9 % for T1G-/PET, 68% for WM/PET, and 80% for SWI/PET. Kappa measures of inter-rater reliability were 0.81
10 for conventional analysis, 0.87 for T1G+/PET, 0.66 for T1G-/PET, 0.77 for WM/PET, and 0.66 for SWI/PET.
11 Qualitative parameters are summarized in Table 3.
12
13
14
15

16 **Quantitative parameters results**

17 Mean T/S (1.6 ± 0.3 vs 1 ± 0.3), TBR (4.5 ± 1.4 vs 2.9 ± 1) and rCBF ratio (2.6 ± 1.5 vs 1.2 ± 0.4) were higher
18 in patients with TP than in those with TRC ($p < 0.001$). The best cut-offs of 1.35 for T/S, 3.7 for TBR and 1.25 for
19 rCBF ratio led to accuracies to differentiate TP from TRC of 74%, 76% and 84%, respectively. These were not
20 significantly different from each other ($p = 0.134$ in between T/S and rCBF). Quantitative parameters are
21 summarized in Table 4.
22
23
24
25
26

27 **Scores construction and performances**

28 The multicollinearity between variables in the logistic regressions was low or moderate with variance inflation
29 factors lower than 3 in all cases (Table S1). In the first regression analysis, only T1G+/PET, SWI/PET and rCBF
30 ratio were shown to contribute significantly to the model ($p = 0.006$, 0.027 and 0.011 respectively). Using only
31 T1G+/PET, SWI/PET, and a dichotomized version of rCBF ratio with a cut-off of 1.25, the second logistic
32 regression model was able to correctly classify patients in 86% of the cases, with similar Beta coefficient values
33 for the 3 parameters (2.3, 1.8, and 2.4, respectively). Using only T1G+/PET and SWI/PET, a model without ASL
34 allowed to correctly classify 83% of the patients, with similar Beta coefficient values for both parameters (2.3
35 and 2.5, respectively).
36
37
38
39
40

41 A 3-point score, with 1 point each for T1G+/PET, SWI/PET and $rCBF \geq 1.25$ was built. With an AUC of 0.93 in
42 ROC analysis, it performed better than T/S (AUC 0.81; $p = 0.001$), TBR (AUC 0.82; $p = 0.003$), rCBF (AUC
43 0.85; $p = 0.016$) and conventional visual analysis (AUC 0.75 $p < 0.001$) to discriminate between TP and TRC
44 (Figure 2). Patients presenting a 3-point score of 0 or 1 and those with a score of 2 or 3 were correctly classified
45 as TRC and TP, respectively, with an accuracy of 87%.
46
47

48 A 2-point score using only T1G+/PET and SWI/PET (1 point for each) had an AUC of 0.89, which was higher
49 than with conventional analysis ($p = 0.001$), slightly but not significantly higher than TBR ($p = 0.09$), and
50 slightly but not significantly lower than the 3-point score ($p = 0.085$). Patients with a 2-point score of 0 and those
51 with a score of 1 or 2 were correctly classified as TRC and TP, respectively, with an accuracy of 83%.
52
53

54 The logistic regression-based predicted probabilities distribution varied between both models. These
55 probabilities were comprised between 0.25 and 0.75 for 22% of the patients in the model without ASL, and for
56 only 13% of them in the model with ASL (Figures S2 and S3 in supplementary materials). In terms of scores, it
57 meant that a 2-point score of 1 was associated with major diagnostic uncertainty, as 57% of these patients had
58
59
60
61
62
63
64
65

1 TP and 43% had TRC. 3-point scores of 2 and 3 were associated with somewhat lower but still important
2 diagnostic uncertainty with a correct classification of patients in 64% and 72% of the cases, respectively. On the
3 contrary, a 2-point score of 2 and a 3-point score of 3 were both very strong predictors of TP, with positive
4 predictive values of 97% and 100%, respectively, whereas scores of 0 showed good negative predictive values
5 for TP, of 81 % and 92%, respectively.
6

7 8 9 **PET and ASL features of different glioma subgroups**

10 Among the 53 patients diagnosed with TP, both IDH_{WT} and IDH_{m-codel} gliomas showed higher T/S than IDH_{m-non-}
11 _{codel} tumours (p = 0.008 and 0.018), while only IDH_{m-codel} lesions had significantly higher TBR than IDH_{m-non-codel}
12 tumours (p = 0.036 and 0.076). No statistically significant difference was found between tumour groups for
13 rCBF ratio. IDH_{WT} gliomas were associated with enhancing lesions of greater size than other tumours (p = 0.01
14 and 0.03). These results are shown in Table 4.
15
16
17
18

19 **Survival analyses**

20 The median and mean OS in the whole cohort were respectively 22 and 30 months. OS was longer in patients
21 with TRC than in patients with TP (median not reached versus 18 months, respectively; p < 0.001; figure 3).
22 Using the Cox model, the tumour molecular profile as well as most PET, MRI and hybrid variables were
23 associated with OS in univariate analysis, with the notable exception of T1G+/PET (p = 0.15) and T1G/PET (p =
24 0.55). In multivariate analyses using best predictors of survival, only molecular profile (p = 0.02-0.03) and rCBF
25 ≥ 2.7 (p = 0.03) were found to be independently and significantly associated with OS. These results are shown in
26 Table 5. The proportional hazards assumption hypothesis was met in all cases.
27
28
29
30
31
32
33
34

35 **Discussion**

36 In our study, we found that conventional F-DOPA PET analysis based solely on lesion uptake intensity had
37 moderate performances in discriminating between TP and TRC, whether it was measured with volumes of
38 interest or assessed visually in a semi-quantitative manner. In this respect, our results are similar to those of
39 Herrmann *et al.* [8], who published the largest study on the subject. Indeed, both quantitative analysis (accuracy
40 of 76% for T/S in our study versus 78% in Herrmann's, for example) and visual semi-quantitative PET analysis
41 (accuracy of 82% but with limited specificity in both studies) had similar performances. We used point spread
42 correction in our study, which probably explains why we found slightly higher best cut-off values than them (T/S
43 = 1.35 vs 1.1 for example).
44
45
46
47

48 Some of the morpho-metabolic semi-quantitative visual parameters we designed were able to discriminate
49 between TP and TRC with fairly good accuracy. Especially, T1G+/PET had an accuracy of 82% and seemed
50 reliable (inter-observer Kappa of 0.87). This result indicates that to discriminate between TP and TRC, looking
51 for signs of radionecrosis (blood-brain barrier disruption areas, as assessed with T1G sequence, without
52 sufficiently matched "intense" F-DOPA uptake) may be as useful as looking for signs of viable tumour.
53 SWI/PET accuracy was also good (81%) but the inter-observer agreement was slightly lower (Kappa of 0.66).
54 This result indicates that carefully considering regions where haemorrhagic changes occurred, as depicted by
55 SWI MRI sequences, is useful when interpreting F-DOPA PET. By design, SWI/PET was less sensitive to
56
57
58
59
60
61
62
63
64
65

1 diagnose TP than conventional analysis (79% vs 92%) but it proved to be much more specific (83% vs 57%). It
2 should be noted that these results may not apply to FET. Indeed, macrophagic uptake of FET has been shown to
3 be weaker than that of other amino-acid radiotracers in animal models of brain injury [23]. As brain bleeding can
4 be responsible for macrophagic infiltration [24], FET-PET may be less sensitive to these phenomena. Lastly, the
5 presence of F-DOPA PET uptakes away from contrast-enhancing areas (T1G-/PET (+)) and in the white matter
6 (WM/PET (+)), which were supposed to depict respectively non-enhancing glioma infiltration and glioma tissue
7 in the white matter, was of limited value to discriminate between TP and TRC in our patients.

8
9
10 ASL rCBF ratio showed good performances in our study. With the best cut-off at 1.25, it was able to
11 discriminate between TP and TRC with an accuracy of 84%. We chose to study pseudo-continuous ASL because
12 it is known to be less sensitive to magnetic susceptibility artefacts than gradient-echo based DSC [25]. The
13 literature on the value of ASL perfusion in this setting is still scarce, but it is known to correlate well with DSC
14 [26]. In a study carried out on 32 patients treated by radio-chemotherapy for a glioblastoma, pseudo-continuous
15 ASL performed particularly well to discriminate pseudo-progression from TP, with an AUC of 0.95 for a cut-off
16 at 1.57 [27]. In another study on 33 patients treated with proton beam therapy for high-grade glioma, ASL had
17 better sensitivity (94%) than DSC, using an rCBF ratio cut-off value of 1.3 [28]. Finally, our team has recently
18 shown the good performances of an automatic and parametric analysis of ASL sequences and F-DOPA PET in
19 the differential diagnosis between progression and pseudoprogression. In this previous study, the combined
20 performance of the two techniques was excellent (sensitivity 94% and specificity 100%) but this required
21 complex pre-processing of the images and could only be applied to lesions involving only one of the two
22 cerebral hemispheres [29]. On the other hand, our use of ASL sequence in the present work was unusual because
23 both morphologic MRI sequences and F-DOPA-PET images were used to guide ROIs positioning. PET allowed
24 positioning ROIs in small metabolic tumour “hot spots” with $rCBF \geq 1.25$ despite the absence of a visually
25 obvious hyperperfused area in some patients. In others with lesions involving the cortex or near vessels, it helped
26 to discriminate physiological features from tumour-related hyperperfusion. We think ASL sequences are
27 particularly well suited for F-DOPA PET/MRI in neuro-oncology as they are less sensitive to haemorrhagic
28 changes than DSC and may help mitigate the lower specificity of F-DOPA PET in haemorrhagic lesions. DSC
29 sequences were also acquired in our patients but were deemed to be at risk of false-negative results due to
30 haemorrhagic changes in several of them. The direct comparison between ASL and DSC was beyond the scope
31 of this article and could be biased in our study. With this reservation, the accuracy of regional cerebral blood
32 volume ratios as calculated with DSC was lower, although not significantly, than that of ASL rCBF, with an
33 AUC of 0.77 and an accuracy of 71% for the best cut-off value of 1.59.

34
35
36 Having selected among our imaging parameters through logistic regression analyses, we created a 3-point score,
37 based on two morpho-metabolic parameters and ASL rCBF. It classified patients more accurately than any
38 individual parameter, with an AUC of 0.93 and an accuracy of 87%. The performance of our 3-point score is
39 similar to that found for the sequential use of DSC and FET-PET in a study by Steidl et al. on 104 patients with
40 accuracies of 87% and 83% (with leave-one-out cross-validation), respectively [30]. However, our score offers a
41 more balanced distribution between sensitivity and specificity than their algorithm, with sensitivities of 91%
42 versus 96 %, and specificities of 78% vs 25%, respectively. We also created a 2-point score that only included
43 T1G-/PET and SWI/PET, to be used when ASL perfusion is not available, whose performances appeared slightly
44 but not significantly lower than the 3-point score. Indeed, extreme values of both scores were very reliable for
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1 establishing or excluding TP. Nevertheless, a 2-point score of 1 was associated with major diagnostic uncertainty
2 and should probably be followed by further investigations,

3 In our study, IDH_{m-non-codel} gliomas exhibited significantly lower uptake than other tumour types, as previously
4 described with F-DOPA [31] and FET [32]. We found no significant impact of tumour molecular type on the
5 accuracy of PET parameters in our patients as it has been shown with FET [33], but this study is probably
6 underpowered to demonstrate such an effect. Nevertheless, the best diagnostic accuracy using standard
7 interpretation criteria or our own was obtained in IDH_{m-codel} gliomas (94%), which had the highest FDOPA
8 uptake. Lastly, our OS analyses confirmed that a diagnosis of TRC was indeed associated with a better prognosis
9 than a diagnosis of TP. In univariate analysis, most PET, MRI, and hybrid parameters were associated with OS,
10 as well as both 2 and 3-point scores. Interestingly, we found that T1G+/PET was not predictive of OS despite its
11 usefulness to differentiate between TP and TRC. This result makes sense as T1G+/PET was meant to look for
12 signs of radionecrosis and not viable tumour tissue and when only the latter is supposed to impact OS.
13 Nevertheless, no F-DOPA-PET parameter was found to be independently associated with OS in multivariate
14 analysis, whereas glioma molecular profile and ASL rCBF were. The fact that IDH_{m-codel} gliomas are usually
15 associated with intense PET uptake and a good prognosis probably contributes to the lower F-DOPA-PET
16 predictive value regarding OS [34, 35]. However, multivariate analyses results were not significantly modified
17 after patients with IDH_{m-codel} tumours were excluded. Our result thus falls between that of Karunanithi et al. [36],
18 who found a strong prognostic value for F-DOPA PET in a cohort of 33 patients with a suspicion of glioma
19 recurrence, and that of Herrmann et al. [8], who found no prognostic value of OS for any of the F-DOPA
20 parameters they studied. It is also consistent with those of Fueger et al. who found a correlation between F-
21 DOPA uptake and tumour grade as well as Ki-67 proliferation index in treatment-naïve glioma but not in
22 recurrent tumours [37].

23 Our study has several limitations. Firstly, we used histological diagnosis as the gold standard for only 20% of
24 our patients, as in many previous investigations. A discussion about the relative value of histological analysis
25 and retrospective diagnosis based on glioma recurrence follow-up is beyond the scope of this article.
26 Nevertheless, our patients were included consecutively, and probably represent quite well the population seen in
27 amino-acid PET in the clinical routine setting. Secondly, we analysed patients irrespectively of the post-
28 radiotherapy delay, mixing pseudoprogression and radionecrosis diagnoses. As we found no significant
29 differences in the parameters' performance between the patients seen within 6 months of their last radiation
30 therapy or chemotherapy and the others, we believe that our results apply in both settings. Because of the limited
31 sample size, we were not able to study the impact of MGMT promoter methylation status of tumours, known to
32 be linked with an increased risk of pseudoprogression [38]. Thirdly, our PET and MRI analyses were blinded to
33 previous MRI and examination request. This is not insignificant as the area where MRI abnormalities worsened
34 or appeared is supposed to be specifically analysed in PET. In this respect, our results do not fully reflect best
35 clinical practice. However, the co-existence of TRC and viable tumour tissue is frequently found in patients
36 treated for glioma. Our parameters and scores, which consider the whole brain, allow reaching a simple
37 conclusion in all cases, with good accuracy, and without analysis of previous MRI. Moreover, many patients
38 referred for amino-acid PET during the follow-up of their glioma are undergoing systemic treatment. For them, it
39 should be kept in mind that even if the question asked by the clinician is usually to differentiate TP from TRC
40 for specific MRI modifications, what he has to decide is whether to continue or change the systemic treatment.
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1 Thus, PET uptakes can be of clinical importance regardless of their localization in the brain. Yet, we
2 acknowledge that in the absence of baseline F-DOPA PET, differentiating an uptake due to residual tumour
3 tissue that is well controlled by treatment from TP can be impossible. Lastly, we used logistic regression results
4 to generate our hybrid scores, using the relative weights of statistically significant predictive factors. In this
5 regard, correlations between studied parameters and multicollinearity could have influenced our results, and this
6 is why we verified they were low enough. These logistic regressions were performed with bootstrap analysis to
7 reduce the risk of overfitting. With scores involving only 2 or 3 parameters of equal weight, we consider this risk
8 as reasonably low.
9

10
11 In conclusion, we propose practical hybrid F-DOPA-PET and MRI interpretation criteria and scores to be used in
12 patients with a suspicion of glioma recurrence. Our 3-point score performed better than the F-DOPA PET
13 conventional method of interpretation in this exploratory study. These results should be confirmed prospectively.
14 How it compares exactly with the sequential use of different MRI perfusion methods and PET quantitative
15 analysis would also be interesting to study but requires a large number of patients.
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Bibliography

1. Patel P, Baradaran H, Delgado D, Askin G, Christos P, John Tsiouris A, et al. MR perfusion-weighted imaging in the evaluation of high-grade gliomas after treatment: a systematic review and meta-analysis. *NEUONC*. 2017 Jan;19(1):118–27.
2. Xu Q, Liu Q, Ge H, Ge X, Wu J, Qu J, et al. Tumor recurrence versus treatment effects in glioma: A comparative study of three dimensional pseudo-continuous arterial spin labelling and dynamic susceptibility contrast imaging. *Medicine*. 2017 Dec;96(50):e9332.
3. Albert NL, Weller M, Suchorska B, Galldiks N, Soffiatti R, Kim MM, et al. Response Assessment in Neuro-Oncology working group and European Association for Neuro-Oncology recommendations for the clinical use of PET imaging in gliomas. *Neuro-Oncology*. 2016 Sep;18(9):1199–208.
4. Chen W. 18F-F-DOPA PET Imaging of Brain Tumors: Comparison Study with 18F-FDG PET and Evaluation of Diagnostic Accuracy. 2006.
5. Treglia G, Muoio B, Trevisi G, Mattoli MV, Albano D, Bertagna F, et al. Diagnostic Performance and Prognostic Value of PET/CT with Different Tracers for Brain Tumors: A Systematic Review of Published Meta-Analyses. *Int J Mol Sci*. 2019 Sep 20;20(19).
6. Yu J, Zheng J, Xu W, Weng J, Gao L, Tao L, et al. Accuracy of 18F-F-DOPA Positron Emission Tomography and 18F-FET Positron Emission Tomography for Differentiating Radiation Necrosis from Brain Tumor Recurrence. *World Neurosurg*. 2018 Jun;114:e1211–24.
7. Xiao J, Jin Y, Nie J, Chen F, Ma X. Diagnostic and grading accuracy of 18F-F-DOPA PET and PET/CT in patients with gliomas: a systematic review and meta-analysis. *BMC Cancer*. 2019 Dec;19(1):767.
8. Herrmann K, Czernin J, Cloughesy T, Lai A, Pomykala KL, Benz MR, et al. Comparison of visual and semiquantitative analysis of 18F-F-DOPA-PET/CT for recurrence detection in glioblastoma patients. *Neuro-Oncology*. 2014 Apr 1;16(4):603–9.
9. Galldiks N, Stoffels G, Filss C, Rapp M, Blau T, Tscherpel C, et al. The use of dynamic O-(2-18F-fluoroethyl)-L-tyrosine PET in the diagnosis of patients with progressive and recurrent glioma. *Neuro-Oncology*. 2015 May 24;nov088.
10. Kebir S, Fimmers R, Galldiks N, Schafer N, Mack F, Schaub C, et al. Late Pseudoprogression in Glioblastoma: Diagnostic Value of Dynamic O-(2-[18F]fluoroethyl)-L-Tyrosine PET. *Clinical Cancer Research [Internet]*. Dec 2015
11. Zaragori T, Ginet M, Marie P-Y, Roch V, Grignon R, Gauchotte G, et al. Use of static and dynamic [18F]-F-DOPA PET parameters for detecting patients with glioma recurrence or progression. *EJNMMI Res*. 2020 Dec;10(1):56.
12. Law I, Albert NL, Arbizu J, Boellaard R, Drzezga A, Galldiks N, et al. Joint EANM/EANO/RANO practice guidelines/SNMMI procedure standards for imaging of gliomas using PET with radiolabelled amino acids and [18F]FDG: version 1.0. *Eur J Nucl Med Mol Imaging*. 2019 Mar;46(3):540–57.
13. Pyka T, Hiob D, Preibisch C, Gempt J, Wiestler B, Schlegel J, et al. Diagnosis of glioma recurrence using multiparametric dynamic 18F-fluoroethyl-tyrosine PET-MRI. *European Journal of Radiology*. 2018 Jun;103:32–7.

14. Fraioli F, Shankar A, Hyare H, Ferrazzoli V, Militano V, Samandouras G, et al. The use of multiparametric 18F-fluoro-L-3,4-dihydroxy-phenylalanine PET/MRI in post-therapy assessment of patients with gliomas: Nuclear Medicine Communications. 2020 Jun;41(6):517–25.
15. Sala Q, Metellus P, Taieb D, Kaphan E, Figarella-Branger D, Guedj E. 18F-DOPA, a Clinically Available PET Tracer to Study Brain Inflammation?: Clinical Nuclear Medicine. 2014 Apr;39(4):e283–5.
16. Dethy S, Manto M, Kentos A, Konopnicki D, Pirotte B, Goldman S, et al. PET findings in a brain abscess associated with a silent atrial septal defect. Clinical Neurology and Neurosurgery. 1995 Nov;97(4):349–53.
17. Morana G, Bottoni G, Mancardi MM, Verrico A, Piccardo A. Seizure-Induced Increased 18F-DOPA Uptake in a Child With Diffuse Astrocytoma and Transient Brain MRI Abnormalities Related to Status Epilepticus: Clinical Nuclear Medicine. 2018 May;43(5):e149–50.
18. Hatazawa J, Inugami A, Shimosegawa E, Noguchi K, Okudera T, Kanno I, et al. Carbon-11-Methionine PET Evaluation of Intracerebral Hematoma: Distinguishing Neoplastic from Non-Neoplastic Hematoma. 1995;5.
19. 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. JCO. 2010 Apr 10;28(11):1963–72.
20. Weller M, van den Bent M, Tonn JC, Stupp R, Preusser M, Cohen-Jonathan-Moyal E, et al. European Association for Neuro-Oncology (EANO) guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas. The Lancet Oncology. 2017 Jun;18(6):e315–29.
21. Wollenweber SD, Ambwani S, Delso G, Lonn AHR, Mullick R, Wiesinger F, et al. Evaluation of an Atlas-Based PET Head Attenuation Correction Using PET/CT & MR Patient Data. IEEE Trans Nucl Sci. 2013 Oct;60(5):3383–90.
22. Youden WJ. Index for rating diagnostic tests. National bureau of standards. 1949.
23. Salber D, Stoffels G, Pauleit D, Oros-Peusquens A-M, Shah NJ, Klauth P, et al. Differential Uptake of O-(2-18F-Fluoroethyl)-L-Tyrosine, L-3H-Methionine, and 3H-Deoxyglucose in Brain Abscesses. Journal of Nuclear Medicine. 2007 Dec 1;48(12):2056–62.
24. Tschoe C, Bushnell CD, Duncan PW, Alexander-Miller MA, Wolfe SQ. Neuroinflammation after Intracerebral Hemorrhage and Potential Therapeutic Targets. J Stroke. 2020 Jan 31;22(1):29–46.
25. Choi YJ, Kim HS, Jahng G-H, Kim SJ, Suh DC. Pseudoprogression in patients with glioblastoma: added value of arterial spin labeling to dynamic susceptibility contrast perfusion MR imaging. Acta Radiol. 2013 May;54(4):448–54.
26. Jovanovic M, Radenkovic S, Stosic-Opincal T, Lavrnic S. Differentiation between progression and pseudoprogression by arterial spin labeling MRI in patients with glioblastoma multiforme. JBUON 2017.
27. Manning P, Daghighi S, Rajaratnam MK, Parthiban S, Bahrami N, Dale AM, et al. Differentiation of progressive disease from pseudoprogression using 3D PCASL and DSC perfusion MRI in patients with glioblastoma. J Neurooncol. 2020 May;147(3):681–90.
28. Ozsunar Y, Mullins ME, Kwong K, Hochberg FH, Ament C, Schaefer PW, et al. Glioma Recurrence Versus Radiation Necrosis? Academic Radiology. 2010 Mar;17(3):282–90.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
29. Pellerin A, Khalifé M, Sanson M, Rozenblum-Beddok L, Kas A, Pyatigorskaya N, et al. Simultaneously acquired PET and ASL imaging biomarkers may be helpful in differentiating progression from pseudo-progression in treated gliomas. *Eur Radiol.* 2021 Mar 31; DOI: 10.1007/s00330-021-07732-0
 30. Steidl E, Langen K-J, Hmeidani SA, Polomac N, Filss CP, Galldiks N, et al. Sequential implementation of DSC-MR perfusion and dynamic [18F]FET PET allows efficient differentiation of glioma progression from treatment-related changes. *Eur J Nucl Med Mol Imaging.* 2021 Jun;48(6):1956–65.
 31. Tatekawa H, Hagiwara A, Yao J, Oughourlian TC, Ueda I, Uetani H, et al. Voxel-Wise and Patient-Wise Correlation of ¹⁸F-F-DOPA PET, rCBV, and ADC in Treatment-Naïve Diffuse Gliomas with Different Molecular Subtypes. *J Nucl Med.* 2020 Jul 9;jnumed.120.247411.
 32. Suchorska B, Giese A, Biczok A, Unterrainer M, Weller M, Drexler M, et al. Identification of time-to-peak on dynamic 18F-FET-PET as a prognostic marker specifically in IDH1/2 mutant diffuse astrocytoma. *Neuro-Oncology* . 2017
 33. Maurer GD, Brucker DP, Stoffels G, Filipski K, Filss CP, Mottaghy FM, et al. ¹⁸F-FET PET Imaging in Differentiating Glioma Progression from Treatment-Related Changes: A Single-Center Experience. *J Nucl Med.* 2020 Apr;61(4):505–11.
 34. Jansen NL, Schwartz C, Graute V, Eigenbrod S, Lutz J, Egensperger R, et al. Prediction of oligodendroglial histology and LOH 1p/19q using dynamic [18F]FET-PET imaging in intracranial WHO grade II and III gliomas. *Neuro-Oncology.* 2012 Dec 1;14(12):1473–80.
 35. For POLA Network, Tabouret E, Nguyen AT, Dehais C, Carpentier C, Ducray F, et al. Prognostic impact of the 2016 WHO classification of diffuse gliomas in the French POLA cohort. *Acta Neuropathol.* 2016 Oct;132(4):625–34.
 36. Karunanithi S, Sharma P, Kumar A, Gupta DK, Khangembam BC, Ballal S, et al. Can 18F-F-DOPA PET/CT predict survival in patients with suspected recurrent glioma? A prospective study. *European Journal of Radiology.* 2014 Jan;83(1):219–25.
 37. 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. *Journal of Nuclear Medicine.* 2010 Oct 1;51(10):1532–8.
 38. Brandes AA, Franceschi E, Tosoni A, Blatt V, Pession A, Tallini G, et al. *MGMT* Promoter Methylation Status Can Predict the Incidence and Outcome of Pseudoprogression After Concomitant Radiochemotherapy in Newly Diagnosed Glioblastoma Patients. *JCO.* 2008 May 1;26(13):2192–7.

1
2 **TABLES**
3
4

5 *Table 1 Summary of visual semi-quantitative parameters*
6

Definitions	‘intense’ F-DOPA uptake: more than twice the healthy brain uptake		‘Valid’ F-DOPA uptake: ‘intense’ in T1G-enhancing or cortical areas, any visible uptake in the non-enhancing white matter		
Parameter	conventional PET analysis (+ or -)	T1G+/PET (+ or -)	T1G-/PET (+ or -)	WM/PET (+ or -)	SWI/PET (+ or -)
Set(s) of data used	PET	T1G and PET	T1G and PET	T1G and PET	SWI and PET
Criteria for positivity	any ‘intense’ uptake	every T1G enhancing lesion > 2 cm is matched with intense uptake in more than 60 % of their volume	any ‘valid’ uptake outside T1G enhancing lesion	any ‘valid’ uptake in the white matter	any ‘valid’ uptake outside blood products deposition induced SWI hypointensities

19 *T1G: T1 weighted sequences after gadolinium contrast agent injection. SWI: susceptibility-weighted imaging MRI sequence.*

20 “+ or -” means that each of those binary criteria can be either positive or negative in a given patient.
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Table 2 Patients' characteristics

Variable	Grouping	N =
Sex	Male	40 (53%)
	Female	36 (47%)
Age	Mean [range] in years	53.5 [24-82]
Tumour grade	II	10 (13%)
	III	26 (34%)
	IV	40 (53%)
Neurosurgical management	Maximum safe resection	53 (70%)
	Biopsy only	23 (30%)
Glioma molecular profile	IDH _{m-non-codel}	20 (26%)
	IDH _{m-codel}	18 (24%)
	IDH _{WT}	36 (42%)
	Unknown	6 (8%)
Delay between end of radiotherapy and PET	Median [range] (months)	19.2 [1-412]
	6 months or less	17 (22%)
	More than 6 months	59 (78%)
Chemotherapy within 6 months before PET	Temozolomide	27 (36%)
	PCV or Lomustine alone	4 (5%)
	None	45 (59%)
Final diagnosis	True progression	53 (70%)
	Treatment-related changes	23 (30%)
Type of proof for final diagnosis	Histology	15 (20%)
	Follow-up	61 (80%)
New line of treatment after PET/MRI	YES	41 (54%)
	NO	35 (46%)

IDH: isocitrate dehydrogenase. IDH_{m-non-codel}: IDH mutation without 1p19q co-deletion. IDH_{m-codel}: IDH mutation and 1p19q co-deletion. IDH_{WT}: IDH wild-type glioma. PCV: Combination of Procarbazine, Lomustine and Vincristine.

Table 1 Summary of qualitative parameters and scores

Variable	Result	N =	Kappa	χ^2	p-value	AUC	Se (%)	Sp (%)	Acc (%)
Conventional analysis	-	17 (23%)	0.81	19.4	<0.001	0.75	92	57	82
	+	59 (77%)							
T1G+/PET	-	23 (30%)	0.87	21.5	<0.001	0.78	87	70	82
	+	53 (70%)							
T1G-/PET	-	36 (47%)	0.66	5.3	0.021	0.66	62	70	64
	+	40 (53%)							
WM/PET	-	31 (41%)	0.77	6.8	0.009	0.67	70	65	68
	+	45 (59%)							
SWI/PET	-	30 (39%)	0.66	23.2	<0.001	0.81	79	83	81
	+	46 (61%)							
3-point score	0	12 (16%)	N/A	42.5	<0.001	0.93	91	78	87
	1	11 (14%)							
	2	18 (24%)							
	3	35 (46%)							
2-point score	0	16 (21%)	N/A	35.5	<0.001	0.89	94	57	83
	1	21 (28%)							
	2	39 (51%)							

Kappa: inter-rater reliability coefficients. AUC: area under the curve in ROC analysis. Se: sensitivity. Sp: specificity. Acc: accuracy. TP: true progression. TRC: treatment-related changes. SWI: susceptibility-weighted imaging MRI sequence. Conventional analysis of F-DOPA PET: positive if there is any "intense" uptake, that is at least twice the intensity of healthy brain uptake. T1G+/PET: negative if any T1G contrast-enhanced lesion has no corresponding "intense" uptake in more than 40% of its volume, as assessed visually. T1G-/PET: positive if there is any "valid" F-DOPA PET uptake(s) outside of T1G contrast-enhanced lesion. WM/PET: positive if there is any "valid" F-DOPA PET uptake(s) in the white matter. When situated in enhancing or cortical areas, an F-DOPA uptake has to be "intense" to be considered "valid"; in the non-enhancing white matter, any visible F-DOPA uptake is considered "valid". SWI/PET: positive if there is any "valid" F-DOPA PET uptake outside haemorrhagic regions as seen with SWI sequence. 3-point score: 1 point each for T1G-/PET, SWI, and rCBF ≥ 1.25). 2-point score: 1 point each for T1G-/PET and SWI.

Table 4 Summary of quantitative parameters

	N =	T/S	TBR	rCBF	enhancement size (mm ²)
Study population	76	1.4 ± 0.6	4.1 ± 1.5	2.1 ± 1.4	561 ± 752
TP	53	1.6 ± 0.3	4.5 ± 1.4	2.6 ± 1.5	507 ± 632
TRC	23	1 ± 0.3	2.9 ± 1.0	1.2 ± 0.4	684 ± 982
Best cut-off		1.35	3.7	1.25	N/A
AUC		0.81	0.82	0.85	N/A
Accuracy		0.74	0.76	0.84	N/A
For patients with TP and known molecular status (N = 49)					
IDH_{m-non-codel}	11	1.3 ± 0.4	3.7 ± 1.2	2.5 ± 1.8	247 ± 205
IDH_{m-codel}	14	1.8 ± 0.6*	5.1 ± 1.4*	2.1 ± 1.2	323 ± 371
IDH_{WT}	24	1.6 ± 0.5*	4.5 ± 1.3	2.8 ± 1.6	751 ± 784*

TP: tumour progression. TRC: treatment-related changes. AUC: area under the curve in ROC analysis. T/S: ratio of lesion SUV_{max} to striatum SUV_{max}. TBR: ratio of lesion SUV_{max} to the normal parietal cortex. rCBF: regional cerebral blood flow ratio (measured with ASL perfusion). Enhancement size: product of axial perpendicular diameters of the greatest lesion on T1G sequence. IDH_{m-non-codel}: IDH mutation without 1p19q co-deletion. IDH_{m-codel}: IDH mutation and 1p19q co-deletion. IDH_{WT}: IDH wild-type glioma; * statistical significance at the p = 0.05 threshold with at least one subgroup. All the quantitative parameters, except the enhancement size, were significantly higher in TP than in TRC and able to discriminate between TP and TRC with similar accuracies.

Table 5 Overall survival analyses

Univariate analyses

Variable	p-value	HR	95% IC
Tumour type	IDH _{WT}	0.001	Not applicable (reference)
	IDH _{m-non-codel}	0.004	0.3
	IDH _{m-codel}	0.004	0.2
T1G+/PET (+)	0.15	1.8	0.8 – 3.9
T1G-/PET (+)	0.55	1.2	0.6 – 2.3
WM/PET (+)	0.01	2.6	1.3 – 5.4
SWI/PET (+)	0.04	2.1	1.0 – 4.4
TBR ≥ 3.7	0.02	2.4	1.2 – 4.7
rCBF ratio ≥ 1.25	0.001	4.1	1.6 – 10.5
rCBF ratio ≥ 2.7	< 0.001	4.1	2.1 – 8.0
Enhancement size ≥ 135 mm ²	0.02	2.7	1.1 – 6.4
3-point score	0.007	1.6*	1.1 – 2.3*
2-point score	0.039	1.6*	1.0 – 2.5*
diagnosis = TP	< 0.001	6.9	2.1 – 22.6

Multivariate analysis

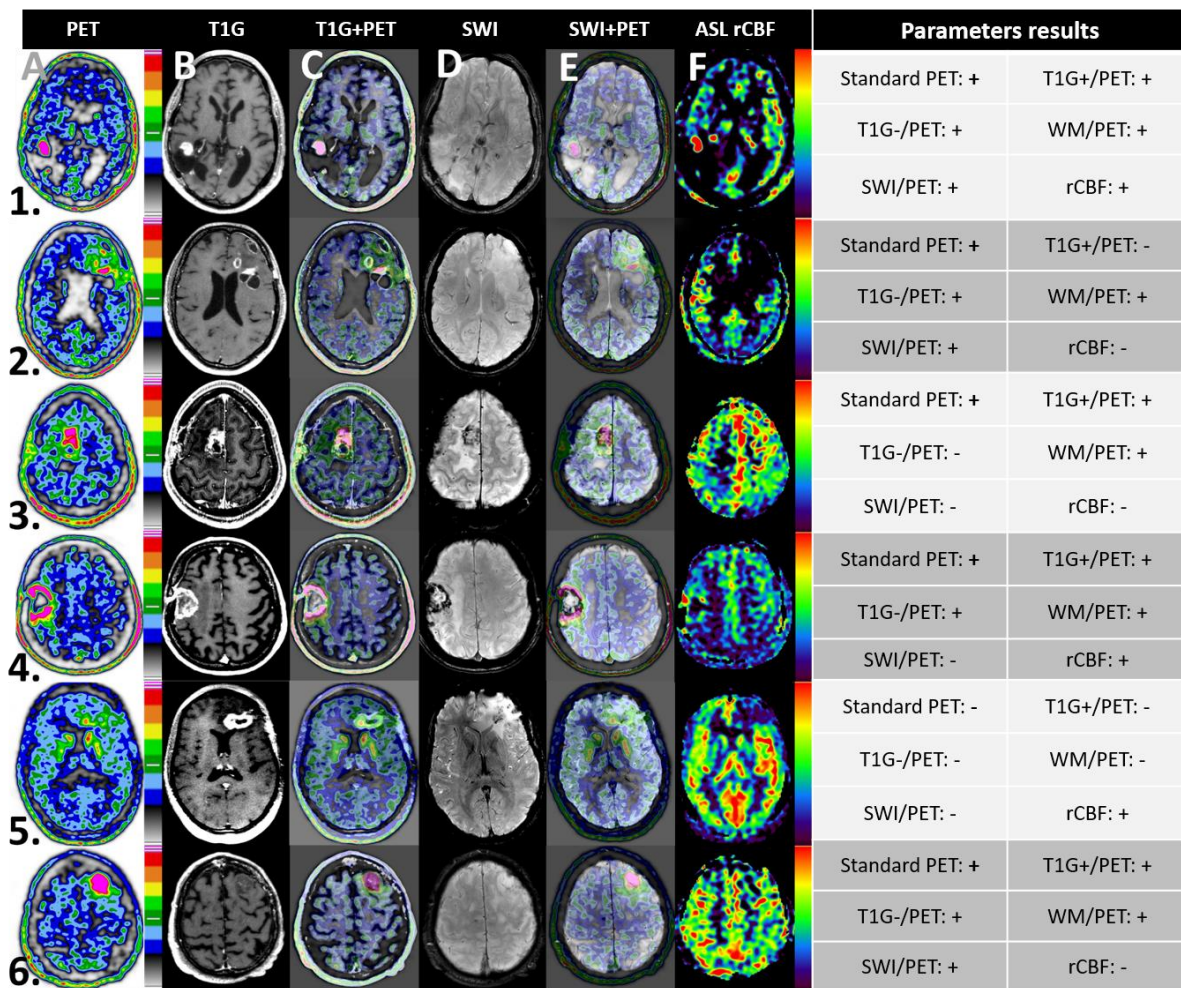
Variable	p-value	HR	95% IC
Tumour type	IDH _{WT}	0.02	Not applicable (reference)
	IDH _{m-non-codel}	0.03	0.4
	IDH _{m-codel}	0.02	0.3
WM/PET (+)	0.14	1.8	0.8 – 4.0
rCBF ratio ≥ 2.7	0.03	2.3	1.1 – 4.8
Enhancement size ≥ 135 mm ²	0.50	1.4	0.5 – 3.6

HR: hazard ratio for overall survival (OS). 95% IC: confidence interval for HR. TP: true progression, as assessed retrospectively. *: HR for 1-unit increase.

Most PET, MRI and hybrid parameters are predictors of OS in univariate analysis. The type of tumour as assessed by the molecular profile is also a strong prognostic factor. Compared to IDH_{WT} gliomas, taken as a reference, prognostic was better in IDH_{m-non-codel} and IDH_{m-codel} gliomas. In multivariate analysis, only tumour type and rCBF ≥ 2.7 appear as independent prognostic factors.

Figures

Figure 1 Examples of PET and MRI hybrid analysis in 6 patients



T1G: MRI T1 weighted sequence after gadolinium contrast agent injection. SWI: susceptibility-weighted imaging MRI sequence. CBF: Cerebral blood flow. ASL: arterial spin labelling.

A: Conventional visual F-DOPA PET analysis with SUV100 colour scale. It is set so that the normal cortex maximum uptake is in the middle of the scale (dark green). The areas with “intense” F-DOPA uptake (at least twice the normal cortex uptake) are thus represented by the highest intensity colour (pink). Conventional analysis is considered positive if any “intense” uptake is visible. **B:** T1G. **C:** Fusion between A and B. T1G+/PET is classified as negative if any contrast-enhanced lesion has more than 40% of its volume without F-DOPA “intense” uptake. T1G-/PET and WM/PET are classified as positive if any “valid” F-DOPA uptake is seen outside contrast-enhanced lesion(s) or in the white matter, respectively. When localized in T1G-enhanced areas or the grey matter, an F-DOPA uptake is considered “valid” only when “intense”. In the non-enhancing white matter, it is considered “valid” whenever visible. **D:** SWI sequence. Areas where haemorrhagic changes occurred appear hypointense. **E:** Fusion between C and D. SWI/PET is classified as positive if any “valid” F-DOPA uptake is seen outside the vicinity of SWI hypointense areas. **F:** CBF as calculated with ASL sequence (ASIST colour scale). Quantitative analysis of rCBF ratio is used instead of visual analysis. F-DOPA images are used to help position regions of interest.

Patient 1: Suspicion of IDH^{wt} glioblastoma recurrence 3 years after radio-chemotherapy. Focal “intense” PET uptake (A1; conventional analysis (+)) and ASL hyperperfusion are matching the whole T1G enhanced lesion (C1; T1G+/PET (+), T1G-/PET (-), WM/PET (+)). SWI sequence shows no hyposignal on D1 (E1; SWI/PET (+)). Histological analysis after surgical resection showed glioblastoma recurrence.

Patient 2: Suspicion of IDH_{m-non-codel} glioblastoma recurrence 4 months after the end of radio-chemotherapy. Focal “intense” PET uptake is seen, corresponding to the peri-cystic enhancement (conventional analysis +) but the ring-like T1G enhancement seen in the most medial part of the left frontal lobe has only faint F-DOPA uptake (T1G+/PET (-)). PET uptake is seen in the white matter of the left frontal lobe (WM/PET (+)) as well as outside the T1G enhanced (T1G-/PET (+)) and

1 the SWI hypointense areas (SWI/PET (+)). No hyperperfused area is found with ASL (F2). Monthly temozolomide was
2 continued for another 4 months. Subsequent MRI showed a decrease in TIG enhancements. The final diagnosis was TRC.

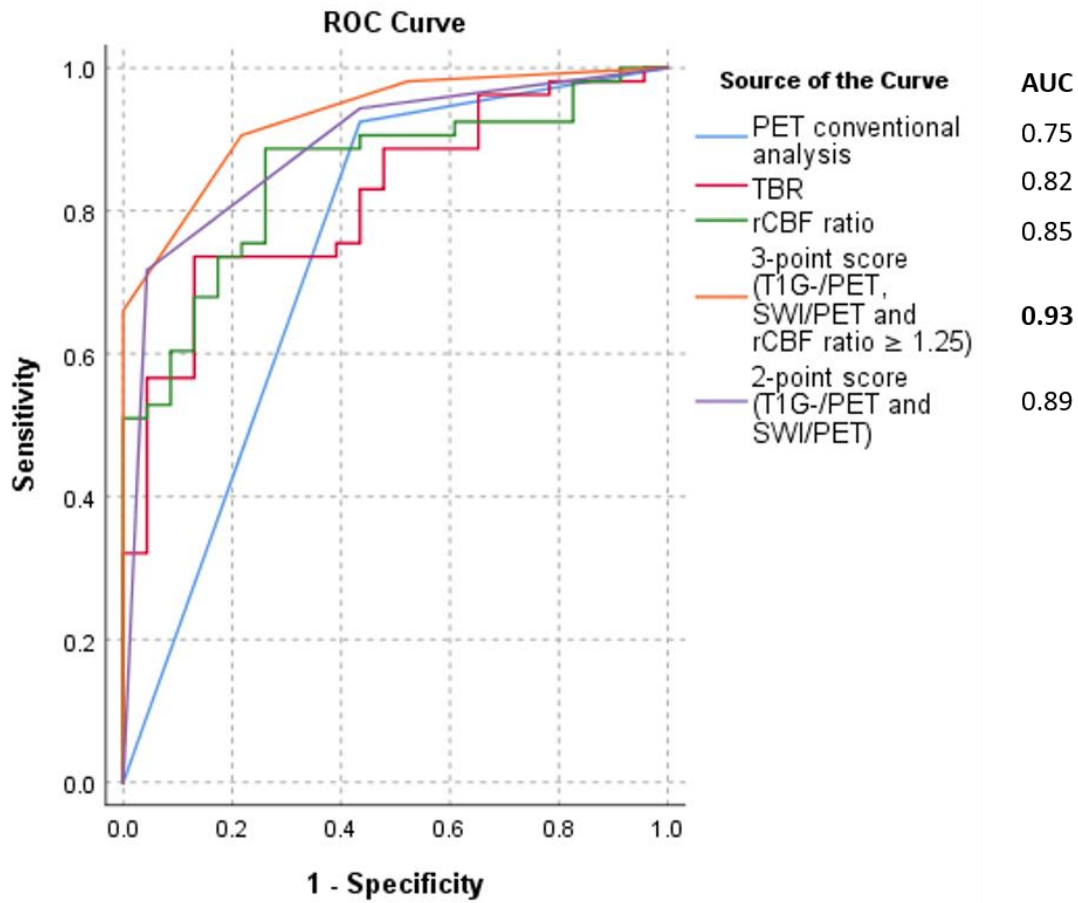
3 **Patient 3:** Suspicion of IDHwt type glioblastoma recurrence 4 months after the end of radio-chemotherapy. An “intense”
4 PET uptake is seen (conventional analysis +), which covers most of the TIG enhanced lesion (TIG+/PET (+)) seen in the
5 right frontal lobe. PET uptake is seen in the white matter (WM/PET (+)), but not outside the TIG enhanced areas (TIG-/PET
6 (-)). PET uptake is only in the vicinity of SWI hypointense areas (SWI/PET (-)). No hyperperfused area is found with ASL.
7 Monthly temozolomide chemotherapy was continued for another 5 months until TP occurred in a different localization than
8 the present lesion. The final diagnosis was TRC.

9 **Patient 4:** Suspicion of IDHwt glioblastoma progression 8 months after the end of radio-chemotherapy. An “intense” F-
10 DOPA PET uptake is seen all around the right frontal ring-enhanced lesion (conventional analysis (+), TIG+/PET (+),
11 TIG-/PET (+), WM/PET (+)) but metabolic abnormalities are confined in the vicinity of haemorrhagic changes as shown
12 with SWI sequence (SWI/PET (-)). ASL shows some moderately hyperperfused areas within PET uptake. The final diagnosis
13 was TP.

14 **Patient 5:** Suspicion of IDHwt glioblastoma progression 2 months after the end of radio-chemotherapy. No “valid” F-DOPA
15 uptake is seen (conventional analysis (-), TIG-/PET (-), SWI/PET (-), WM/PET (-)), with most of the ring-enhanced lesion
16 showing only faint uptake (TIG+/PET (-)). ASL shows a tiny hyperperfused area in the most medial and posterior part of the
17 ring-enhanced lesion, which is easily recognized because it corresponds to the F-DOPA hottest spot. The patient was finally
18 classified as TP and died one year later despite multiple treatment changes.

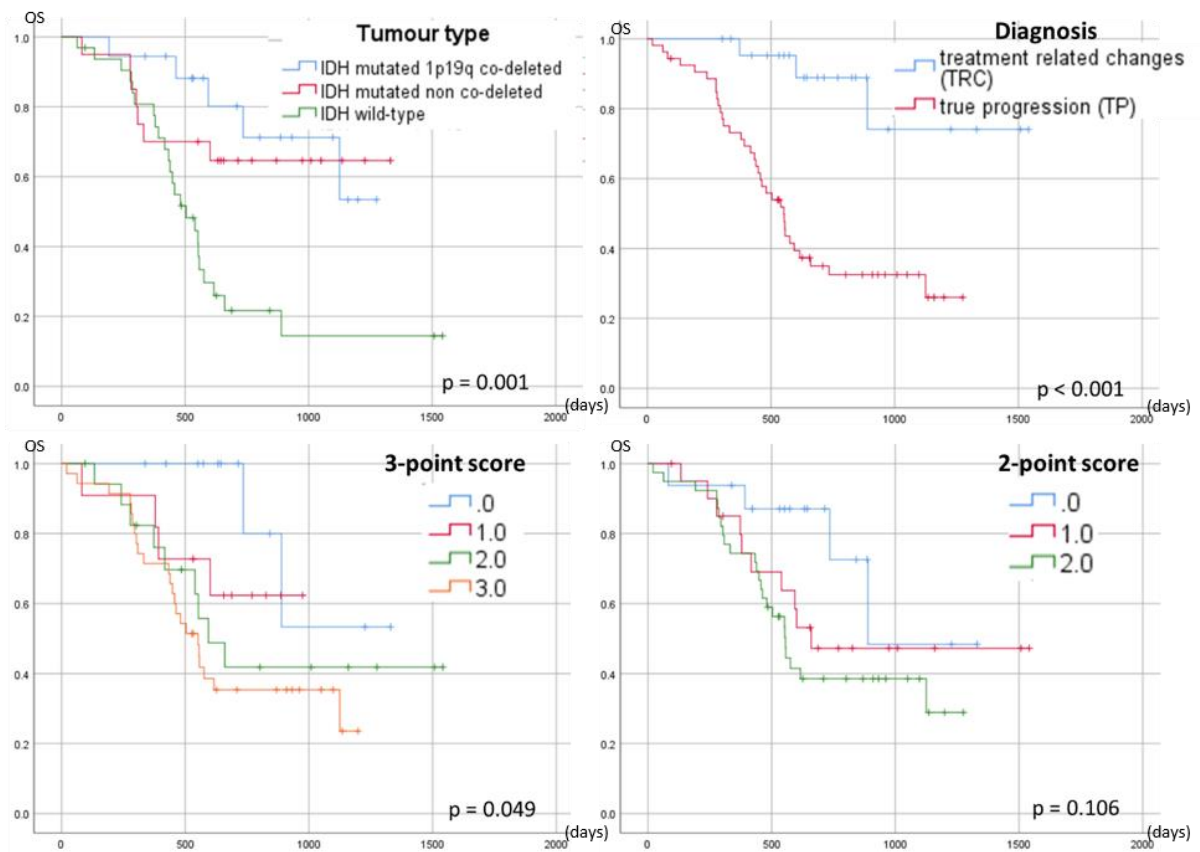
19 **Patient 6:** Suspicion of oligodendroglioma recurrence more than 10 years after surgery and radiation therapy. An “intense”
20 PET uptake entirely covers the focally slightly enhanced left frontal lobe lesion without corresponding SWI hypointense area
21 (conventional analysis (+), TIG-/PET (+), TIG+/PET (+), SWI/PET (+)). No ASL hyperperfusion is found. The final
22 diagnosis was TP, as histological analysis after surgical resection showed grade II oligodendroglioma IDH m-codel tumour
23 recurrence.
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Figure 2 ROC curves comparison



Receiver operating characteristics curves. TBR: ratio of lesion SUVmax to the normal parietal background in F-DOPA PET. PET conventional analysis: intensity as based on visual analysis of PET without MRI data. rCBF ratio: regional cerebral blood flow ratio (measured with ASL perfusion). The 3-point score is based on logistic regression results using hybrid PET and MRI parameters T1G-/PET, SWI/PET and rCBF ratio with a cut-off at 1.25 (1 point for each). The 2-point score is based on logistic regression performed without ASL rCBF, using T1G-/PET and SWI/PET (1 point for each). The area under the curve (AUC) of the 3-point score (0.931) is significantly higher than for the other parameters, with AUC differences of 0.11 for TBR ($p = 0.03$), 0.19 for conventional analysis ($p < 0.001$) and 0.08 for ASL ($p = 0.02$), with the exception of the 2-point score (AUC difference 0.04 and $p = 0.08$).

Figure 3 Kaplan-Meier survival curves



Overall survival curves according to tumour type, final diagnosis for lesions evolution at the time of F-DOPA PET/MRI, 3-point score, and 2-point score. Both tumour type, final diagnosis and 3-point score are significantly associated with overall survival.

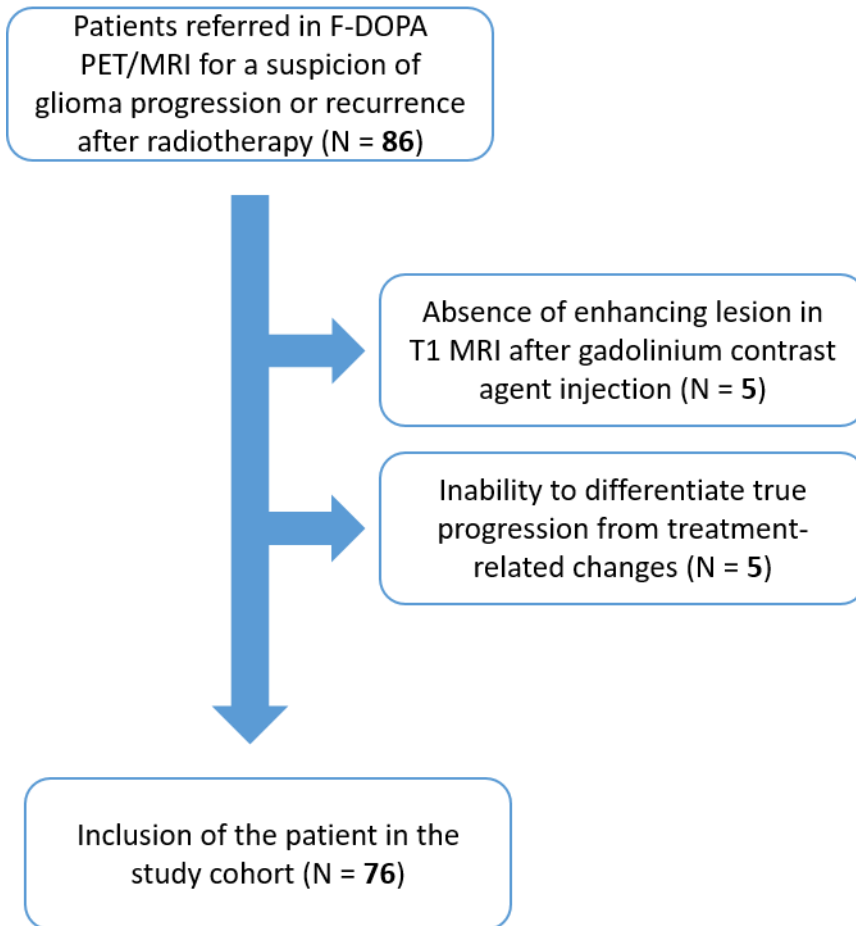
1
2 **SUPPLEMENTARY MATERIALS**
3
4

5
6 *Table S.1 Variance inflation factor (VIF) values*
7

Variable	VIF value
First logistic regression analysis	
T1G+/PET	1.87
T1G-/PET	1.44
WM/PET	1.62
SWI/PET	1.96
rCBF	1.79
TBR	2.98
Second logistic regression analysis	
T1G+/PET	1.25
SWI/PET	1.48
rCBF \geq 1.25	1.44

8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Figure S.1 Flow chart of patients





Click here to access/download
Supplementary Material
Review_answers_corrections.docx

