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

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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 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. 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.
Response to Reviewers:	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.

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

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Cover letter

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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,

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Hybrid [^{18}F]-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 $\geq$ 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

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

Abbreviations:

TRC: Treatment-Related Changes

TP: Tumour Progression

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

DSC: Dynamic Susceptibility Contrast

ASL: Arterial Spin-Labelling

F-DOPA: ^{18}F-fluoro-L-3,4-dihydroxyphenylalanine

PET: Positron Emission Tomography

ROI: region-of-interest

FET: ^{18}F-fluoroethyl-tyrosine

SWI: susceptibility-weighted imaging MRI sequence

IDH: Isocitrate Dehydrogenase

rCBF: regional cerebral blood flow

FLAIR: Fluid-attenuated inversion recovery (FLAIR) T2 sequence

TBR: tumour-to-background ratio

SUVmax: maximum standard uptake value

T/S: tumour-to-striatum ratio

ROC: receiver operating characteristic

OS: overall survival

Introduction:

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

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

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

Based on these hypotheses, the purpose of this exploratory work was to create hybrid parameters and scores combining MRI and PET features to use for clinical routine interpretation of F-DOPA PET scans in glioma 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 ($IDH_{m\text{-}non\text{-}codel}$), IDH mutated and 1p-19q co-deleted ($IDH_{m\text{-}codel}$), 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 $IDH_{m\text{-}non\text{-}codel}$, and within 12 months for $IDH_{m\text{-}codel}$ 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 $IDH_{m\text{-}non\text{-}codel}$ 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 (SUVmax) of the most intense lesion in each patient. Its ratios to the contralateral striatal SUVmax (T/S) and the healthy brain SUVmean (TBR) were then calculated. The latter was measured using a spherical peripheral 3 cm^3 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 cm^2 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

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

Statistical analysis

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

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

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

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

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

Results:

Patients

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

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

Conventional PET analysis and hybrid parameters performances

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

Quantitative parameters results

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 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 rCBF ratio led to accuracies to differentiate TP from TRC of 74%, 76% and 84%, respectively. These were not significantly different from each other (p = 0.134 in between T/S and rCBF). Quantitative parameters are summarized in Table 4.

Scores construction and performances

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

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

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

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

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

PET and ASL features of different glioma subgroups

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

Survival analyses

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

Discussion

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

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

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

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

Having selected among our imaging parameters through logistic regression analyses, we created a 3-point score, based on two morpho-metabolic parameters and ASL rCBF. It classified patients more accurately than any individual parameter, with an AUC of 0.93 and an accuracy of 87%. The performance of our 3-point score is similar to that found for the sequential use of DSC and FET-PET in a study by Steidl et al. on 104 patients with accuracies of 87% and 83% (with leave-one-out cross-validation), respectively [30]. However, our score offers a more balanced distribution between sensitivity and specificity than their algorithm, with sensitivities of 91% versus 96 %, and specificities of 78% vs 25%, respectively. We also created a 2-point score that only included T1G-/PET and SWI/PET, to be used when ASL perfusion is not available, whose performances appeared slightly but not significantly lower than the 3-point score. Indeed, extreme values of both scores were very reliable for

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

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

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

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

In conclusion, we propose practical hybrid F-DOPA-PET and MRI interpretation criteria and scores to be used in patients with a suspicion of glioma recurrence. Our 3-point score performed better than the F-DOPA PET conventional method of interpretation in this exploratory study. These results should be confirmed prospectively. How it compares exactly with the sequential use of different MRI perfusion methods and PET quantitative analysis would also be interesting to study but requires a large number of patients.

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TABLES

Table 1 Summary of visual semi-quantitative parameters

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

T1G: T1 weighted sequences after gadolinium contrast agent injection. SWI: susceptibility-weighted imaging MRI sequence.
"+ or –"means that each of those binary criteria can be either positive or negative in a given patient.

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	$IDH_{m\text{-}non\text{-}codel}$	20 (26%)
	$IDH_{m\text{-}codel}$	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. $IDH_{m\text{-}non\text{-}codel}$: IDH mutation without 1p19q co-deletion. $IDH_{m\text{-}codel}$: 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)					
$IDH_{m\text{-}non\text{-}codel}$	11	1.3 ± 0.4	3.7 ± 1.2	2.5 ± 1.8	247 ± 205
$IDH_{m\text{-}codel}$	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 SUVmax to striatum SUVmax. TBR: ratio of lesion SUVmax 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. $IDH_{m\text{-}non\text{-}codel}$: IDH mutation without 1p19q co-deletion. $IDH_{m\text{-}codel}$: 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)	Not applicable
	$IDH_{m\text{-}non\text{-}codel}$	0.004	0.3	0.1 – 0.7
	$IDH_{m\text{-}codel}$	0.004	0.2	0.1 – 0.6
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

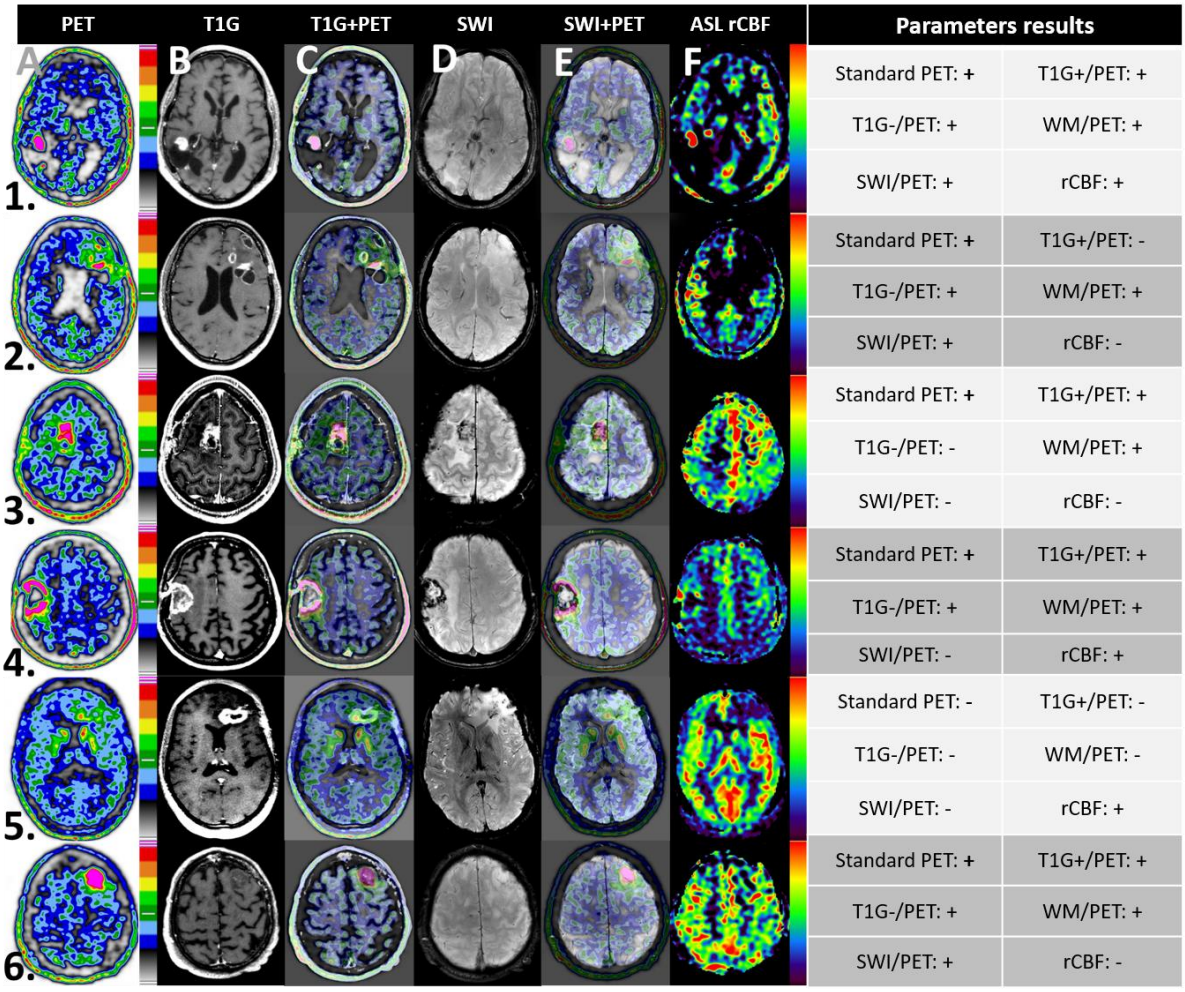
Variable		p-value	HR	95% IC
Tumour type	**IDH_{WT}**	0.02	Not applicable (reference)	Not applicable
	$IDH_{m\text{-}non\text{-}codel}$	0.03	0.4	0.2 – 0.9
	$IDH_{m\text{-}codel}$	0.02	0.3	0.1 – 0.8
WM/PET (+)		0.14	1.8	0.8 – 4.0
rCBF ratio ≥ 2.7		0.03	2.3	1.1 – 4.8
Enhancement size ≥ 135 mm^2		0.50	1.4	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 $IDH_{m\text{-}non\text{-}codel}$ and $IDH_{m\text{-}codel}$ 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



Parameters results	
Standard PET: +	T1G+/PET: +
T1G-/PET: +	WM/PET: +
SWI/PET: +	rCBF: +
Standard PET: +	T1G+/PET: -
T1G-/PET: +	WM/PET: +
SWI/PET: +	rCBF: -
Standard PET: +	T1G+/PET: +
T1G-/PET: -	WM/PET: +
SWI/PET: -	rCBF: -
Standard PET: +	T1G+/PET: +
T1G-/PET: +	WM/PET: +
SWI/PET: -	rCBF: +
Standard PET: -	T1G+/PET: -
T1G-/PET: -	WM/PET: -
SWI/PET: -	rCBF: +
Standard PET: +	T1G+/PET: +
T1G-/PET: +	WM/PET: +
SWI/PET: +	rCBF: -

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 $IDH_{m\text{-}non\text{-}codel}$ 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*

the SWI hypointense areas (SWI/PET (+)). No hyperperfused area is found with ASL (F2). Monthly temozolomide was continued for another 4 months. Subsequent MRI showed a decrease in T1G enhancements. The final diagnosis was TRC.

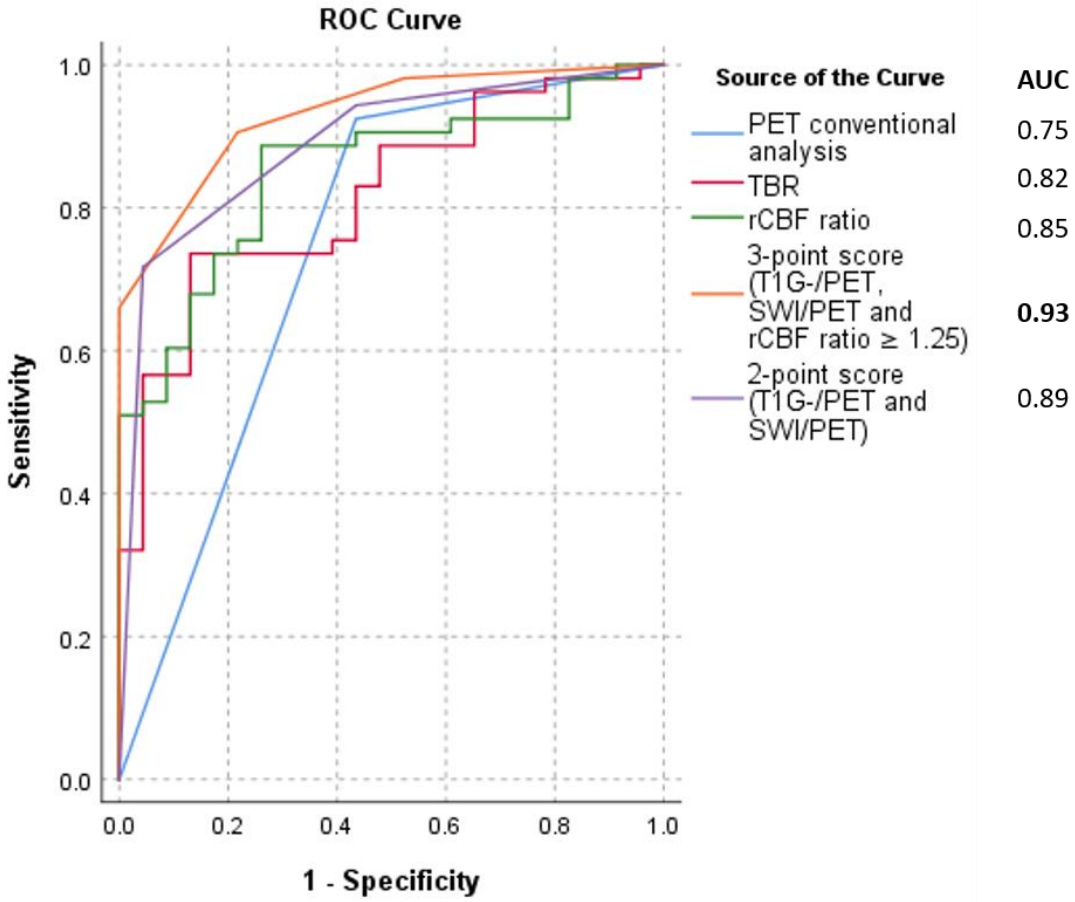
Patient 3: *Suspicion of IDH_{WT} type glioblastoma recurrence 4 months after the end of radio-chemotherapy. An "intense" PET uptake is seen (conventional analysis +), which covers most of the T1G enhanced lesion (T1G+/PET (+)) seen in the right frontal lobe. PET uptake is seen in the white matter (WM/PET (+)), but not outside the T1G enhanced areas (T1G-/PET (-)). PET uptake is only in the vicinity of SWI hypointense areas (SWI/PET (-)). No hyperperfused area is found with ASL. Monthly temozolomide chemotherapy was continued for another 5 months until TP occurred in a different localization than the present lesion. The final diagnosis was TRC.*

Patient 4: *Suspicion of IDH_{WT} glioblastoma progression 8 months after the end of radio-chemotherapy. An "intense" F-DOPA PET uptake is seen all around the right frontal ring-enhanced lesion (conventional analysis (+), T1G+/PET (+), T1G-/PET (+), WM/PET (+)) but metabolic abnormalities are confined in the vicinity of haemorrhagic changes as shown with SWI sequence (SWI/PET (-)). ASL shows some moderately hyperperfused areas within PET uptake. The final diagnosis was TP.*

Patient 5: *Suspicion of IDH_{WT} glioblastoma progression 2 months after the end of radio-chemotherapy. No "valid" F-DOPA uptake is seen (conventional analysis (-), T1G-/PET (-), SWI/PET (-), WM/PET (-)), with most of the ring-enhanced lesion showing only faint uptake (T1G+/PET (-)). ASL shows a tiny hyperperfused area in the most medial and posterior part of the ring-enhanced lesion, which is easily recognized because it corresponds to the F-DOPA hottest spot. The patient was finally classified as TP and died one year later despite multiple treatment changes.*

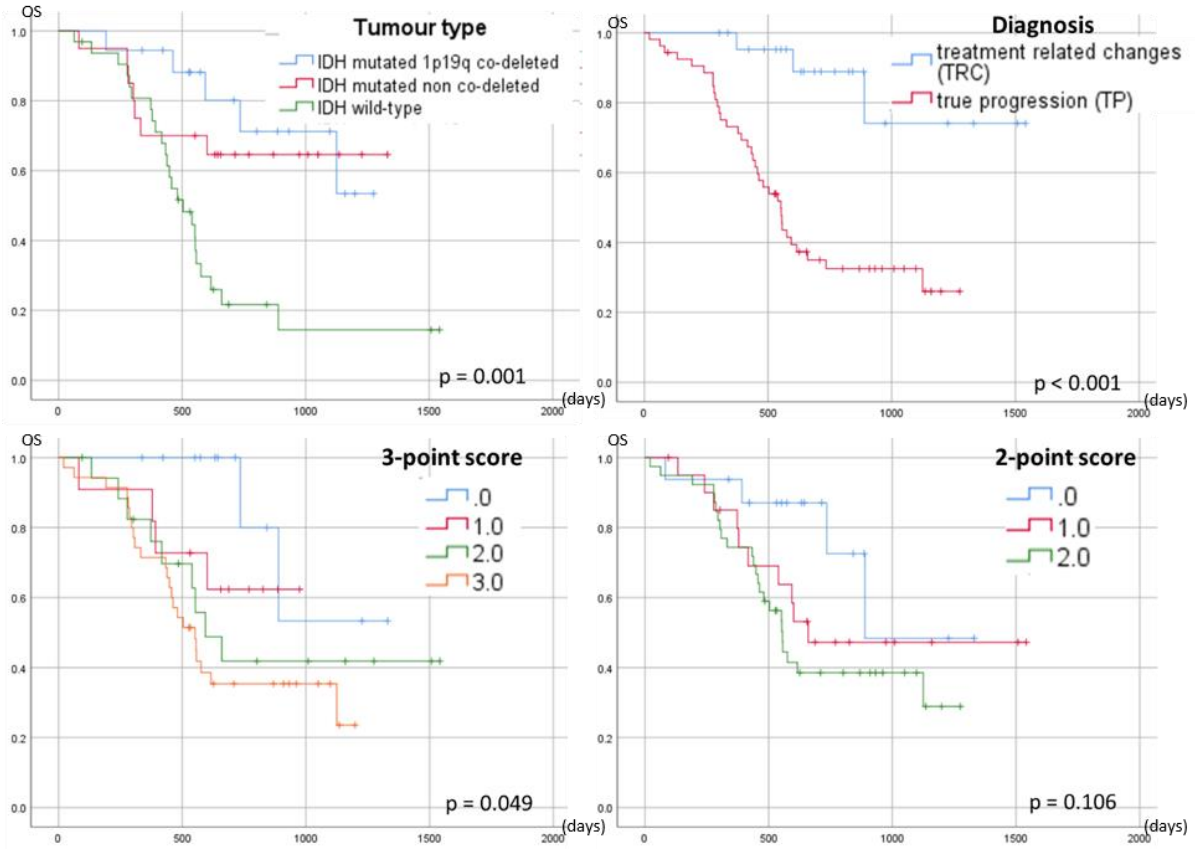
Patient 6: *Suspicion of oligodendroglioma recurrence more than 10 years after surgery and radiation therapy. An "intense" PET uptake entirely covers the focally slightly enhanced left frontal lobe lesion without corresponding SWI hypointense area (conventional analysis (+), T1G-/PET (+), T1G+/PET (+), SWI/PET (+)). No ASL hyperperfusion is found. The final diagnosis was TP, as histological analysis after surgical resection showed grade II oligodendroglioma IDH m-codel tumour recurrence.*

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.

SUPPLEMENTARY MATERIALS

Table S.1 Variance inflation factor (VIF) values

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 ≥ 1.25	1.44

Figure S.1 Flow chart of patients

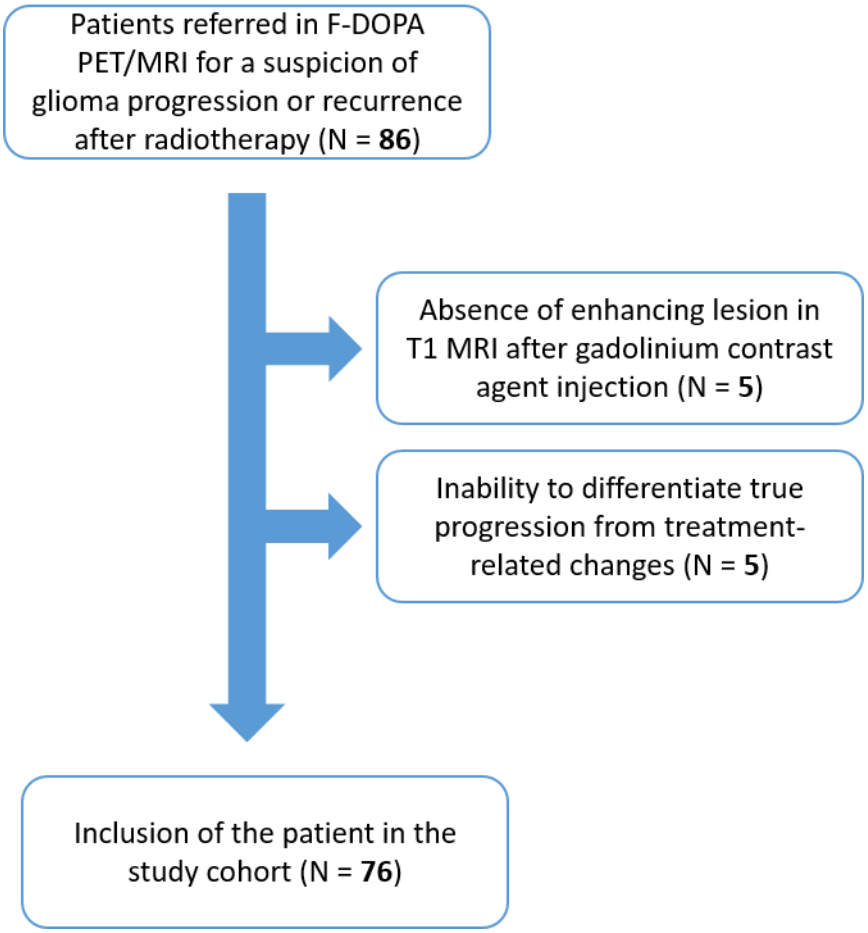


Figure S.2 Logistic regression predicted probability of TP and TRC using T1G+/PET, SWI/PET, and rCBF (3-point score)

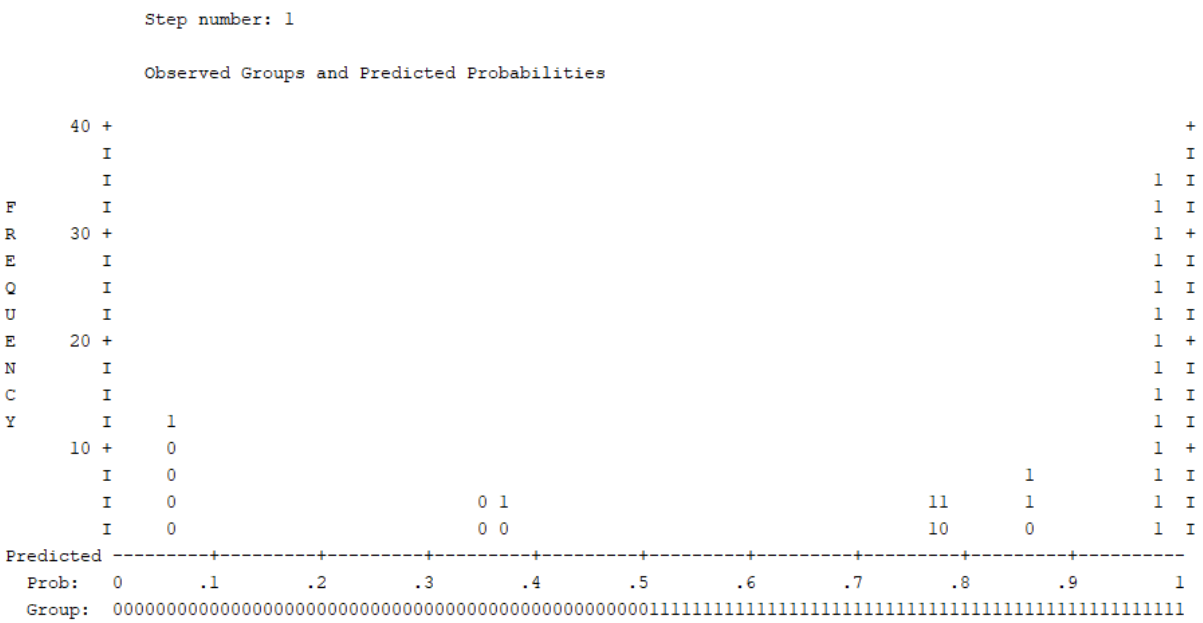


Figure S.3 Logistic regression predicted probability of TP and TRC using T1G+/PET and SWI/PET (2-point score)