Clinical Cancer Research

Late Pseudoprogression in Glioblastoma: Diagnostic Value of Dynamic O-(2-[^{18}F]fluoroethyl)-L-Tyrosine PET

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Abstract

Purpose: Pseudoprogression (PsP) is characterized by therapy-associated but not tumor growth–associated increases of contrast-enhancing glioblastoma lesions on MRI. Although typically occurring during the first 3 months after radiochemotherapy, PsP may occur later in the course of the disease and may then be particularly difficult to distinguish from true tumor progression. We explored PET using O-(2-[^{18}F]fluoroethyl)-L-tyrosine (^{18}F-FET-PET) to approach the diagnostic dilemma.

Experimental Design: Twenty-six patients with glioblastoma that presented with increasing contrast-enhancing lesions later than 3 months after completion of radiochemotherapy underwent ^{18}F-FET–PET. Maximum and mean tumor/brain ratios (TBR_{max} and TBR_{mean}) of ^{18}F-FET uptake as well as time-to-peak (TTP) and patterns of the time-activity curves were determined. The final diagnosis of true progression versus late PsP was based on follow-up MRI using RANO criteria.

Results: Late PsP occurred in 7 patients with a median time from radiochemotherapy completion of 24 weeks while the remaining patients showed true tumor progression. TBR_{max} and TBR_{mean} were significantly higher in patients with true progression than in patients with late PsP (TBR_{max} 2.4 $\pm$ 0.1 vs. 1.5 $\pm$ 0.2, $P =$ 0.003; TBR_{mean} 2.1 $\pm$ 0.1 vs. 1.5 $\pm$ 0.2, $P = 0.012$) whereas TTP was significantly shorter (mean TTP 25 $\pm$ 2 vs. 40 $\pm$ 2 min, $P <$ 0.001). ROC analysis yielded an optimal cutoff value of 1.9 for TBR_{max} to differentiate between true progression and late PsP (sensitivity 84%, specificity 86%, accuracy 85%, $P = 0.015$).

Conclusions: O-(2-[^{18}F]fluoroethyl)-L-tyrosine PET provides valuable information in assessing the elusive phenomenon of late PsP. *Clin Cancer Res; 22(9); 2190–6. ©2015 AACR.*

Introduction

Despite surgery, radiotherapy and chemotherapy, the overall survival of patients with glioblastoma (GBM) is short with a median of about 17 months (1). Considering the very restricted therapeutic options for salvage therapy, it is important that temozolomide (TMZ) chemotherapy is provided for an adequately long time and not terminated prematurely based on misinterpretation of post-radiation treatment effects. Among the latter, pseudoprogression (PsP) may mimic true recurrent tumor. PsP is a retrospective diagnosis built on increasing contrast enhancement on MRI consistent with true tumor progression that eventually remains stable or is even regressive during further follow-up without changing the treatment (2–7). PsP after previous radiochemotherapy with temozolomide is more frequently observed in patients with a methylated MGMT promoter gene (8). Treatment-related changes such as PsP are thought to be secondary to radiosensitizing effects of temozolomide, thus predominantly occurring in patients with the methylated MGMT promoter (7). PsP may be a sign for tumor necrosis rather than for tumor progression, and therefore may reflect therapeutic efficacy.

There are no absolutely strict criteria as to when PsP is supposed to occur relative to radiotherapy. As defined by the Response Assessment in Neuro-Oncology (RANO) working group, PsP occurs within 12 weeks after completion of radiotherapy (7). In a recent report, however, we pointed out that PsP may well occur beyond 12 weeks and was designated late PsP (5). Early and late PsP may lie at the opposite sites of a temporal continuum. It is possible that late PsP may be more influenced by chemotherapy than early pseudoprogression. Also, late PsP may be particularly frequent under the influence of temozolomide/lomustine combination therapy (5).

If an increasing contrast-enhancing lesion on MRI indicates (late) PsP, the current gold standard is to perform follow-up MRIs to evaluate changes in lesion size. Consequently, a diagnosis of

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Translational Relevance

Tumor progression in patients with glioblastoma inevitably occurs despite treatment according to state of the science. A significantly increasing contrast enhancement on MRI appearing later than 12 weeks following completion of last radiotherapy is usually considered a sign of tumor progression. Nevertheless, increasing contrast enhancement on MRI may also reflect late pseudoprogression (PsP). Late PsP is diagnosed when the initially increasing contrast enhancement does not increase in size further on a follow-up MRI performed about 4 to 8 weeks later. For many patients with concomitant clinical deterioration, however, waiting for a follow-up MRI may be not applicable. With the presented data, we show that O-(2-[^{18}F]fluoroethyl)-L-tyrosine (^{18}F-FET-PET) has the potential for detecting late PsP with a higher accuracy than conventional MRI alone. ^{18}F-FET–PET usage in this setting has direct clinical relevance in that it assists in making the decision whether or not to change treatment.

(late) PsP can only be made retrospectively based on follow-up MRI. It would be, however, advantageous for patient management if PsP could be identified at the earliest possible time point when the increasing contrast-enhancing lesions are detected for the first time. This is particularly important for patients with greatly increasing contrast-enhancing lesions and deteriorating clinical status. These patients might not be able to wait 4 to 8 weeks for a follow-up MRI to have decided whether secondary surgery or any other therapeutic adjustments are needed.

PET using radiolabeled amino acids such as O-(2-[^{18}F]fluoroethyl)-L-tyrosine (^{18}F-FET) allows imaging of amino acid transport in brain tumors and has shown promise in distinguishing early PsP from truly progressive tumor (9). Comparing with the most known tracer, ^{18}F-FDG 18F-FET is considered particularly suitable for glioma research because of its low background activity (10). Also, ^{18}F-FET PET has been shown to be useful in treatment planning (11), detecting malignant progression in low grade glioma (12), identifying glioma in newly diagnosed cerebral lesions (13) and the diagnosis of recurrent malignant glioma (13, 14). A disrupted blood–brain barrier (BBB), as indicated by contrast enhancement on MRI, per se does not lead to significant FET uptake (15). Therefore, ^{18}F-FET PET appears to be a promising diagnostic tool to investigate for PsP and it may be particularly helpful in making the difficult diagnosis of late PsP. We have already demonstrated the applicability of ^{18}F-FET PET for diagnosing early PsP in a recent case series (9). To furthermore assess whether ^{18}F-FET PET is capable of drawing a distinction between true progression and late PsP/radionecrosis—which is even more infrequent, and thus difficult to diagnose—we retrospectively examined the predictive value of ^{18}F-FET PET for detecting late PsP in 26 patients with glioblastoma.

Materials and Methods

Study design

For this retrospective analysis, our data bank was searched for histologically confirmed glioblastoma patients meeting the following characteristics: (i) patients experiencing increasing contrast-enhancing lesions on MRI [+25% in 2 perpendicular diameters and/or any new lesion according to RANO (ref. 16), lesion size >10 mm] more than 12 weeks after the end of radiotherapy, or, in case of treatment with alkylating chemotherapy only, beginning of chemotherapy; (ii) patients having a ^{18}F-FET-PET following detection of increasing contrast-enhancing lesions, (iii) after initial MRI and ^{18}F-FET-PET, a further contrast-enhanced MRI ensued at least 4 weeks later without change of therapy. Patients during first-line or second-line alkylating chemotherapy were included. MGMT promotor methylation status was determined by pyrosequencing.

PET imaging with ^{18}F-FET

The amino acid ^{18}F-FET was produced as described previously (17, 18). According to the German guidelines for brain tumor imaging using labeled amino acid analogues, all patients remained fasted for at least 12 hours before PET scanning (19). Dynamic PET studies were acquired up to 50 minutes after i.v. injection of approximately 200 MBq ^{18}F-FET on an ECAT EXACT HR+ scanner (Siemens Medical Systems, Inc.) in three-dimensional mode (32 rings; axial field of view, 15.5 cm). The emission recording consisted of 16 time frames (time frames 1–5: 1 minutes, 6–10: 3 minutes, and 11–16: 5 minutes) covering the period up to 50 minutes after injection. For attenuation correction, transmission was measured with 3 ^{68}Ge/^{68}Ga rotating line sources. After correction for random and scattered coincidences as well as dead time, 63 image planes were iteratively reconstructed (OSEM, 6 iterations, 16 subsets) using the ECAT 7.2 software. The reconstructed image resolution was approximately 5.5 mm.

PET data analysis

^{18}F-FET uptake in the tissue was expressed as standardized uptake value (SUV) by dividing the radioactivity (kBq/mL) in the tissue by the radioactivity injected per gram of body weight. PET and MR images were co-registered using dedicated software (MPI tool version 6.48; ATV). The fusion results were inspected and, if necessary, adapted on the basis of anatomical landmarks. The Region-of-Interest (ROI) analysis was based on the summed PET data from 20 to 40 minutes after injection. The transaxial slices showing the highest tracer accumulation in the tumors were chosen for ROI analyses. The uptake in the unaffected brain tissue was determined by a larger ROI placed on the contralateral hemisphere in an area of normal appearing brain tissue including white and gray matter (19). Mean amino acid uptake in the tumor was determined by a two-dimensional autocontouring process using a tumor-to-brain ratio (TBR) of 1.6 as described previously (13), for maximal amino acid uptake a circular ROI with a diameter of 1.6 cm was centered on maximal tumor uptake. Maximum and mean TBRs (TBR_{max} and TBR_{mean}) were calculated by dividing the mean SUV of these tumor ROIs by the mean SUV of normal brain in the PET scan.

Furthermore, time-activity curves (TAC) of mean SUV of ^{18}F-FET uptake in the tumor and in the brain were generated by application of a spherical volume-of-interest with a volume of 2 mL centered on maximal tumor uptake and of a reference ROI in the unaffected brain tissue (as described above) to the entire dynamic dataset. Time-to-peak (TTP; time in minutes from the beginning of the dynamic acquisition up to the maximum SUV of the lesion) was determined. Furthermore, as previously descibed (12, 20), the TACs of each lesion were assigned to one of the following curve patterns: Constantly increasing ^{18}F-FET uptake without identifiable peak uptake (pattern I); ^{18}F-FET uptake

peaking at a midway point (>20–40 min) followed by a plateau or a small descent (pattern II); and ^{18}F-FET uptake peaking early ($\leq$20 min) followed by a constant descent (pattern III). The assignment of TACs to the various curve patterns was performed by three experienced raters (N. Galldiks, K.-J. Langen, and G. Stoffels).

Diagnosis of true progression

The diagnosis of tumor progression was made when progressive contrast-enhancing lesions according to RANO criteria (16) were noted in initial MRI and when further progression of contrast enhancement was noted in a follow-up MRI at least 4 weeks later. By contrast, the diagnosis of PsP was applied when the follow-up MRI showed stabilization or regression of the contrast-enhancing lesions.

Statistical analysis

Descriptive statistics are reported as mean and SEM. For the purpose of comparing two means, a two-sided Student *t* test for independent samples was used. A *P* value of less than 0.05 was regarded as significant. The diagnostic performance of TBR values to distinguish late PsP from true progression was assessed by ROC curve analyses using the results of follow-up MRI as reference. The optimal cutoff was the value where the square of the difference between sensitivity and specificity was minimized; that is, where both sensitivity and specificity were highest. Moreover, the area under the ROC curve (AUC), its SE and its level of significance were determined as an estimation of diagnostic quality. The diagnostic performance of curve patterns alone to assess for late PsP was determined by a Fisher exact test for 2 $\times$ 2 contingency tables. Statistical analysis was done using Stata (release 13.0; StataCorp. LP) and SPSS (release 22.0; IBM Corp.).

Results

Patient characteristics

The study population comprised 26 adult patients (Table 1) with histologically proven glioblastoma (median age, 58 years; range, 23–76 years; 5 female, 21 male). O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status was tested using pyrosequencing in all but one patient. A methylated MGMT promoter was found in 17 and a non-methylated MGMT promoter in 8 patients. Twenty two of 26 patients included in the study underwent PET investigation during first-line treatment and 4 of 26 during second-line treatment. Of the 22 patients analyzed at first-line treatment, 17 received temozolomide-based radiochemotherapy (standard radiotherapy applying a total dose of 54–60 Gy combined with standard temozolomide chemotherapy) and 5 patients were treated with radiotherapy combined with lomustine/temozolomide (lomustine = CCNU; temozolomide = TMZ) chemotherapy. Four patients were analyzed while being in second-line therapy (after temozolomide-based radiochemotherapy as primary therapy) with alkylating chemotherapy (one patient with CCNU/TMZ, one patient with procarbazine and CCNU, one patient with CCNU only, and one patient with temozolomide); two of them additionally had re-irradiation (Table 1).

Diagnosis of tumor progression versus late PsP

In all patients, MRI scan analysis was carried out by two independent investigators (one of whom being a board-certified neuroradiologist). Seven of 26 patients showed signs of late PsP as their contrast-enhanced lesions on follow-up MRI did not enlarge within a period of at least 4 weeks from the detection of either a new or a $\geq$25% increase in size of an existing contrast-enhanced lesion. Fifteen patients were regarded as having unequivocal progression (Table 1). MGMT promoter methylation status was tested methylated in 6 of 7 patients with late PsP (86%). In one patient, the MGMT promoter was not methylated. In patients with true progression, the MGMT promoter gene was found methylated in 11 of 19 patients (58%).

^{18}F-FET uptake and tracer kinetics

TBR_{max} and TBR_{mean} of ^{18}F-FET uptake were significantly increased in patients with true progression compared with patients with late PsP (TBR_{max} 2.4 $\pm$ 0.1 vs. 1.5 $\pm$ 0.2, P = 0.003; TBRmean 2.1 $\pm$ 0.1 vs. 1.5 $\pm$ 0.2, P = 0.012). ^{18}F-FET uptake values for each patient are presented in Table 2. Curve pattern I was observed in 10 patients, curve pattern II in 10 and curve pattern III in 6 patients. Curve pattern type II or III, which is considered typical of malignant tumor tissue, was more frequently observed in patients with true tumor progression (16/19) than in patients with late PsP (0/7). Presence of curve pattern type II or III achieved a sensitivity of 84%, specificity of 100%, and an accuracy of 89% to differentiate between true progression and late PsP (Fisher exact test; $P < 0.001$). TTP showed significant difference in patients with true progression and with late PsP (mean TTP 25 $\pm$ 2 vs. 40 $\pm$ 2 min, $P < 0.001$). Representative examples of ^{18}F-FET PET finding in a patient with tumor progression and a patient with late PsP are shown in Figs. 1 and 2, respectively.

ROC analysis

ROC analysis yielded an optimal cutoff value of 1.9 for TBR_{max} to differentiate between true progression and late PsP [sensitivity 84%, specificity 86%, accuracy 85%, AUC 0.88 $\pm$ 0.07; 95% confidence interval (CI), 0.73–1.0, P = 0.015; Fig. 3]. The same cutoff value (1.9) was obtained for TBR_{mean}, which achieved a slightly poorer yet significant diagnostic performance (sensitivity 74%, specificity 86%, accuracy 77%, AUC 0.86 $\pm$ 0.07; 95% CI, 0.72–1.0, P = 0.023). TTP significantly predicted true progression versus late PsP (AUC 0.86 $\pm$ 0.07; 95% CI, 0.72–1.0, P = 0.042).

Discussion

The results of this study suggest that ^{18}F-FET–PET, in particular using dynamic and static ^{18}F-FET uptake parameters, may be an indicative noninvasive tool to distinguish late PsP from progressive disease in patients with glioblastoma. Using this method, late PsP may be identified earlier than with conventional MRI.

Regarding clinical decision making, it seems logical to assume true late progression when TBR_{max} is higher than 2.4 because no patient with late PsP had TBR_{max} values in excess of that. Conversely, it seems advisable to assume late PsP when TBR_{max} is below 1.0, because no patient with late progression had TBR_{max} values below 1.0. Values between 1.0 and 2.4 should be interpreted with caution as there is an overlap of final diagnoses. We believe it is more important not to overlook the diagnosis of late PsP as it reflects an ongoing benefit from previous/current treatment. Hence, in the event of a TBR_{max} value in between 1.0 and 2.4 it might be safest (when trying to avoid missing PsP) to defer the initiation of a salvage treatment until a follow-up MRI has been performed or to obtain a tumor specimen via biopsy to confirm

Table 1. Patient characteristics of 26 patients undergoing FET–PET analysis

No	Sex	Age at Dx (y)	Histologic Dx	MGMT methylated?	Line of therapy[a]	Treatment regimen while under PET investigation	Concomitant dexamethasone treatment?	Change in dexamethasone dose between index and follow-up MRI	Course of last Cx before PET	Wks from last Rx	Follow-up MRI + Clin.	Histologic confirmation of follow-up	Follow-up time (m)	Time to progression (m)	Patient dead	Overall survival (m)
1	m	46	GBM	Yes	1st	cR,RT+TMZ/CCNU, TMZ/CCNU	No		4. course TMZ/CCNU	18	Prog.	No	42	n/a	No	41
2	m	41	GBM*	Yes	1st	pR,RT+TMZ/CCNU, TMZ/CCNU	No		5. course TMZ/CCNU	24	No prog.	No	42	24	No	41
3	m	63	GBM	Yes	1st	pR,RT,TMZ/CCNU	Yes	+24 mg/d	1. course TMZ/CCNU	23	No prog.	No	53	16	Yes	26
4	f	39	GBM	Yes	1st	B,RT+TMZ,TMZ	No		6. course TMZ	92	Prog.	No	57	n/a	Yes	44
5	m	56	GBM	Yes	1st	cR,RT+TMZ/CCNU, TMZ/CCNU	No		5. course TMZ/CCNU	18	No prog.	No	35	27	No	34
6	m	59	GBM	Yes	1st	pR,RT+TMZ/CCNU, TMZ/CCNU	No		4. course TMZ/CCNU	22	Prog.	No	34	n/a	Yes	16
7	m	66	GBM	Yes	1st	cR,RT+TMZ,TMZ	No		6. course TMZ	72	No prog.	No	45	13	Yes	40
8	m	49	GBM	Yes	2nd	pR,RT+TMZ/CCNU, TMZ/CCNU	No		3. course TMZ/CCNU	18	Prog.	No	59	n/a	Yes	49
9	f	50	GBM	Yes	1st	cR,RT+TMZ/CCNU, TMZ/CCNU	Yes	No change	4. course TMZ/CCNU	58	Prog.	No	42	n/a	Yes	33
10	m	23	GBM*	No	1st	pR,RT+TMZ,TMZ	No		2. course TMZ	44	Prog.	No	35	n/a	Yes	41
11	f	62	GBM	Yes	2nd	RT,CCNU	No		2. course CCNU	13	Prog.	No	50	n/a	No	41
12	m	65	GBM	Yes	2nd	TMZ	No		1. course TMZ	58	No prog.	No	41	>20 (nyr)	Yes	26
13	m	74	GBM	No	1st	pR+RT/TMZ+TMZ	Yes	+8 mg/d	6. course TMZ	40	Prog.	No	13	11	Yes	13
14	m	39	GBM	No	1st	B+RT/TMZ+TMZ	No	No	12. course TMZ	67	No prog.	No	34	nyr	No	nyr
15	m	76	GBM	No	1st	B+RT+TMZ	Yes	No change	6. course TMZ	44	Prog.	No	16	10	Yes	16
16	m	75	GBM	Yes	1st	?R+RT/TMZ	Yes	+8 mg/d	6. course TMZ	67	prog.	Yes	40	19	Yes	40
17	f	56	GBM	NA	1st	?R+RT/TMZ+TMZ	Yes	No change	6. course TMZ	37	Prog.	Yes	17	10	Yes	17
18	m	58	GBM	Yes	1st	?R+RT/TMZ+TMZ	Yes	+8 mg/d	6. course TMZ	57	Prog.	Yes	16	14	n/a	n/a
19	m	42	GBM	No	1st	cR+RT/TMZ+TMZ	No	No	12. course TMZ	206	Prog.	Yes	68	37	No	nyr
20	m	62	GBM	Yes	1st	B+RT/TMZ+TMZ	No		4. course TMZ	17	Prog.	No	18	n/a	Yes	16
21	f	66	GBM	Yes	2nd	PC	No		2. course PC	103	Prog.	Yes	37	n/a	Yes	31
22	m	59	GBM	No	1st	pR+RT/TMZ+TMZ	Yes	+4 mg/d	3. course TMZ	20	Prog.	No	18	n/a	Yes	11
23	m	65	GBM	No	1st	pR+RT/TMZ+TMZ	Yes	+24 mg/d	3. course TMZ	17	Prog.	No	12	n/a	No	11
24	m	60	GBM	No	1st	cR+RT/TMZ+TMZ	Yes	+8 mg/d	3. course TMZ	29	Prog.	Yes	13	n/a	No	12
25	m	39	GBM	Yes	1st	cR+RT/TMZ+TMZ	Yes	+12 mg/d	12. course TMZ	54	Prog.	No	21	n/a	Yes	20
26	m	50	GBM	Yes	1st	B+RT/TMZ+TMZ	No	No	6. course TMZ	13	No prog.	No	14	nyr	No	nyr

Abbreviations: AA, anaplastic astrocytoma; Clin., clinical follow-up.; cR, complete resection; Cx, chemotherapy; Dx, diagnosis; GBM*, secondary glioblastoma; GBM, glioblastoma; CCNU, lomustine; n.app., not applicable; NA, not available; n/a, not applicable; no prog., no progression; nyr, not yet reached; PET, positron emission tomography; pR, partial resection; prog., progression; R, resection; ?R, resection extent unavailable; RT, radiotherapy; RT+CCNU/TMZ, combined radiotherapy and chemotherapy with temozolomide and lomustine; RT+TMZ, combined radiotherapy and chemotherapy with temozolomide; TMZ, temozolomide; wk, weeks; y, years; B, biopsy; PC, procarbazine and lomustine; m, months.

[a]Line of therapy while under PET investigation.

Table 2. [18F]-FET PET characteristics

Patient No.	TBR_{max}	TBR_{mean}	TTP	Curve pattern	Follow-Up MRI + Clin.
1	2.9	2.2	17	2	Prog.
2	2.4	2.1	40	1	No prog.
3	1.8	1.8	35	1	No prog.
4	1.9	1.9	35	2	Prog.
5	1.9	1.9	30	1	No prog.
6	2.3	2.0	25	2	Prog.
7	0.7	0.7	45	1	No prog.
8	1.0	1.0	45	1	Prog.
9	2.2	2.1	20	2	Prog.
10	2.7	2.1	35	2	Prog.
111	2.0	1.9	45	1	Prog.
12	0.8	0.8	45	1	No prog.
13	2.6	2.2	20	3	Prog.
14	1.1	1.1	45	1	No prog.
15	2.9	2.4	10	3	Prog.
16	2.6	2.2	35	2	Prog.
17	2.7	2.3	30	2	Prog.
18	2.7	2.5	13	3	Prog.
19	2.4	2.4	20	3	Prog.
20	2.3	2.1	17	3	Prog.
21	2.3	2.0	20	2	Prog.
22	2.9	2.5	30	2	Prog.
23	2.3	2.2	35	1	Prog.
24	1.9	1.9	8	3	Prog.
25	2.8	1.8	25	2	Prog.
26	1.9	1.9	40	1	No prog.

Abbreviations: Clin., clinical follow-up; prog., progression; TBR_{max}, maximum tumor-to-brain ratio; TBR_{mean}, mean tumor-to-brain ratio; TTP, time to peak; curve pattern I, constantly increasing 18F-FET-uptake without identifiable; peak uptake (pattern I); curve pattern II, 18F-FET-uptake peaking at a midway; point (>20–40 min) followed by a plateau or a small descent; curve pattern III, 18F-FET-uptake peaking early (≤20 min) followed by a constant descent.

diagnosis. The latter decision has to be tailored to the patient's condition and clinical status.

Patients with MGMT–methylated glioma are more likely to develop PsP, amounting to an incidence of up to 31% as compared with 5% in patients with non-methylated tumors (8, 16, 21). Accordingly, our study found that almost all patients with late PsP had a methylated MGMT promoter. Nevertheless, one patient with a non-methylated MGMT promotor was

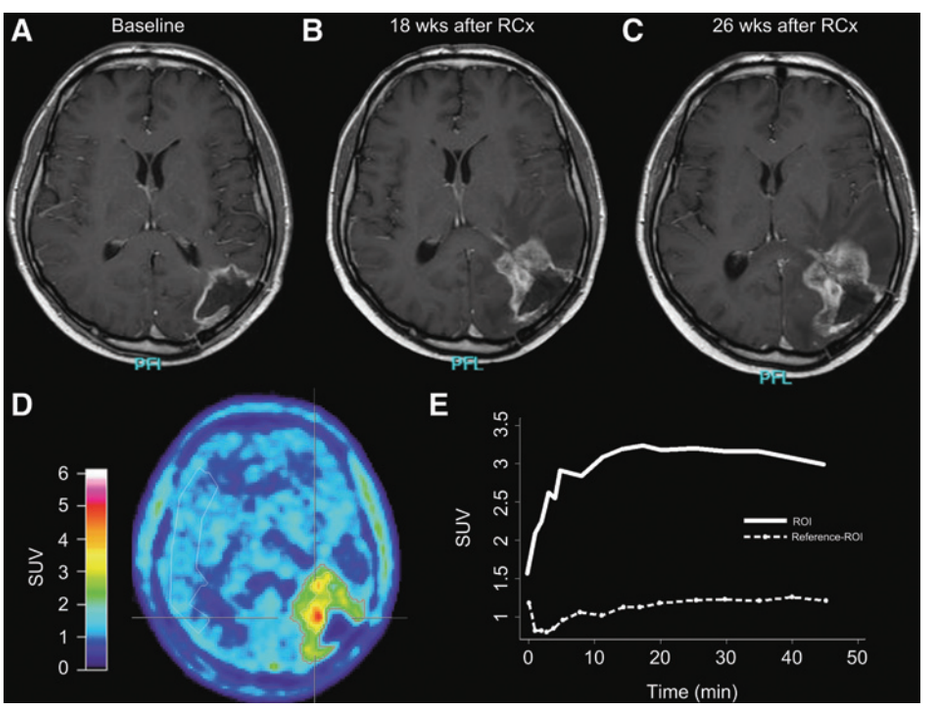

Figure 1.
Patient with true tumor progression (patient No. 1). At baseline (A), there is a slight contrast enhancement at the tumor resection margins. PET was obtained 18 weeks after radiochemotherapy (RCx), when a significant increase in contrast enhancement was observed (B). As demonstrated by PET, there is increased ^{18}F-FET uptake in the tumor (TBR max, 2.9; TBR mean, 2.2, D) and a short TTP (17 min, E). On follow-up MRI obtained 26 weeks after RCx, further increasing contrast-enhancing lesions document true tumor progression (C).

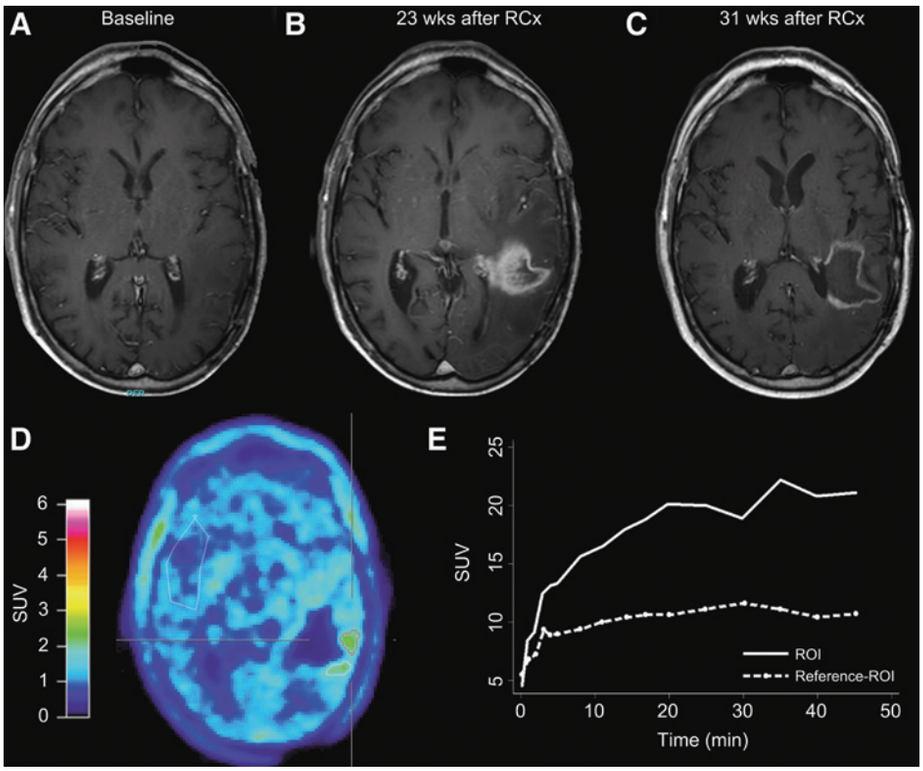

Figure 2.
Patient with late PsP (patient No. 3). At 23 weeks after completion of radiochemotherapy (RCx), a newly occuring contrast-enhancing area in MRI indicates tumor progression (B) as compared with baseline (A). ^{18}F-FET uptake in that area is very low (D). Slightly increased ^{18}F-FET uptake is noted in the vicinity of the lesion (TBR max 1.8, D), which exhibits a slowly increasing time activity curve (TTP 35 min, E) compatible with nonspecific posttherapeutic changes. On follow-up MRI, obtained 31 weeks after RCx, a distinct regression of the contrast-enhancing lesion indicates late PSP (C).

diagnosed with late PsP. Therefore, patients with non-methylated MGMT promotor also should be considered for late PsP.

TBR_{max} and TBR_{mean} were both useful in predicting progression with TBR_{max} providing a slightly higher diagnostic accuracy in this series of patients. In our cohort of patients with glioblastoma, diagnostic accuracy for identifying true progression was highest at a threshold of 1.9 for TBR_{mean} and TBR_{max}. This cutoff value is close to the previously reported cutoff for TBR_{max} (2.3) for distinguishing glioblastoma patients with early PsP from true early progressive disease (9). Similarly, the presence of curve patterns type II and III were predictive for true progression. TTP of ^{18}F-FET uptake has already been described as a helpful parameter for determining malignant progression in patients with low-grade glioma (9) and as a prognostic marker in high-grade glioma (22). In our series of patients TTP confirmed these finding by showing significant differences between true tumor progression and late PsP.

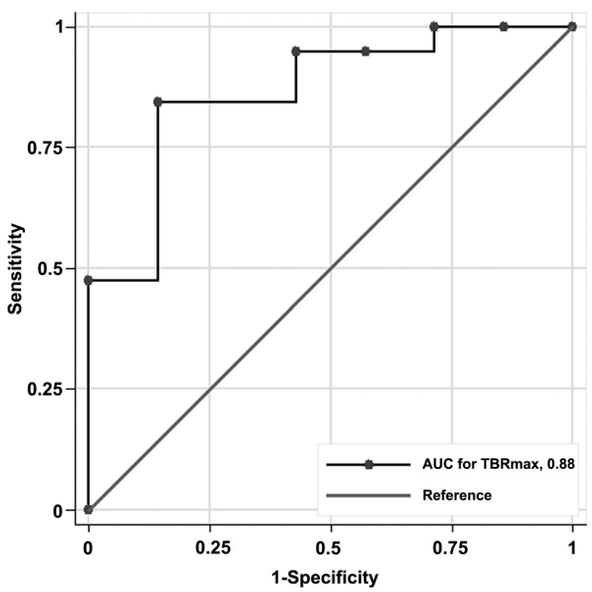

Figure 3.
The ROC curve of TBR_{max} for detecting true progression. AUC was 0.88 and predicted true progression significantly ($P = 0.015$).

Our study supports further larger scale prospective studies that include histopathologic confirmation to confirm the high diagnostic accuracy of ^{18}F-FET–PET for differentiating recurrent glioma and non-specific post-therapeutic changes as reported in previous studies (23), but the high diagnostic accuracy of TBR of ^{18}F-FET uptake of more than 90% could not be confirmed here.

There are a number of noninvasive imaging tools (diffusion-weighted MRI; diffusion-tensor imaging; perfusion MRI (dynamic susceptibility contrast [DSC] and dynamic contrast-enhanced [DCE]); susceptibility-weighted imaging, SWI; MR spectroscopy, MRS; single photon emission computed tomography, SPECT) currently being investigated in the differentiation between PsP and true progression (24). No single technique is able to provide a reliable differentiation. However, it has to be noted that none of them addresses the topic of late PsP. It may be instructive to test whether a combination of different tools, including ^{18}F-FET–PET could provide more accurate data.

This study has several limitations with the predominant one being its small sample size. The small sample size accounts for fragile statistical results. In addition, the retrospective nature of this study inadvertently leads to selection bias, limiting the power

of our conclusions. Therefore, the results here should be interpreted with caution. However, our study documents for the first time that ^{18}F-FET–PET may be a valuable tool in determining late PsP, a condition, whose underdiagnosis might have a serious negative impact on survival for the affected patient because an effective treatment could be erroneously terminated. Thus, this method should be further evaluated in rigorously controlled and prospective trials.

Disclosure of Potential Conflicts of Interest

N. Schaefer reports receiving speakers bureau honoraria from Roche. U. Herrlinger reports receiving commercial research grants from Roche; speakers bureau honoraria from Medac, and Roche; and is a consultant/advisory board member for Bristo-Myers-Squibb, Novocure, and Roche. No potential conflicts of interest were disclosed by the other authors.

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