Late Pseudoprogression in glioblastoma: diagnostic value of dynamic O-(2-[18F]fluoroethyl)-L-tyrosine PET

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Running title: Pseudoprogression/Radionecrosis and kinetic FET-PET

Keywords: Pseudoprogression, Radionecrosis, FET-PET, O-(2-[18F]fluoroethyl)-L-tyrosine PET, glioblastoma, Dynamic FET-PET

Financial support: none

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Conflict of Interest: none

Total manuscript word count: 2676 words (max 5000)

Number of figures: 3

Number of tables: 2
Statement of 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 pseudopropagation. Late pseudopropagation is diagnosed when the initially increasing contrast-enhancement does not increase in size further on a follow-up MRI performed about 4-8 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-[18F]fluoroethyl)-L-tyrosine (18F-FET-PET) has the potential for detecting late pseudopropagation with a higher accuracy than conventional MRI alone. 18F-FET-PET usage in this setting has direct clinical relevance in that it assists in making the decision whether or not to change treatment.

Abstract

**Background:** Pseudopropagation (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 (RCX), 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-[18F]fluoroethyl)-L-tyrosine (18F-FET-PET) to approach the diagnostic dilemma.

**Methods:** Twenty-six patients with glioblastoma that presented with increasing contrast-enhancing lesions later than 3 months after completion of RCX underwent 18F-FET-PET. Maximum and mean tumor/brain ratios (TBR$_{\text{max}}$, TBR$_{\text{mean}}$) of 18F-FET uptake as well as time-to peak (TTP) and patterns of the time-activity curves were determined. The final diagnosis of true progression vs. latePsP was based on follow-up MRI using RANO criteria.

**Results:** LatePsP occurred in seven patients with a median time from RCX completion of 24 weeks while the remaining patients showed true tumor progression. TBR$_{\text{max}}$ and TBR$_{\text{mean}}$ were significantly higher in patients with true progression than in patients with latePsP (TBR$_{\text{max}}$ 2.4±0.1 vs. 1.5±0.2, p=0.003; TBR$_{\text{mean}}$ 2.1±0.1 vs. 1.5±0.2, p=0.012) while TTP was significantly shorter (mean TTP 25±2 vs. 40±2 min, p<0.001). ROC analysis yielded an optimal cut-off of 1.9 for TBR$_{\text{max}}$ to differentiate between true progression and latePsP (sensitivity 84%, specificity 86%, accuracy 85%, p=0.015).

**Conclusion:** O-(2-[18F]fluoroethyl)-L-tyrosine PET provides valuable information in assessing the elusive phenomenon of late pseudoproggression.
Introduction

Despite surgery, radiation therapy 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 may mimic true recurrent tumor. Pseudoprogression 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). Pseudoprogression after previous radiochemotherapy with temozolomide is more frequently observed in patients with a methylated MGMT promoter gene (8). Treatment-related changes such as pseudoprogression are thought to be secondary to radiosensitizing effects of temozolomide, thus predominantly occurring in patients with methylated MGMT promoter (7). Pseudoprogression 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 pseudoprogression is supposed to occur relative to radiotherapy. As defined by the Response Assessment in Neuro-Oncology (RANO) working group, pseudoprogression occurs within 12 weeks after completion of radiation therapy (7). In a recent report, however, we pointed out that pseudoprogression may well occur beyond 12 weeks and was designated late pseudoprogression (5). Early and late pseudoprogression may lie at the opposite sites of a temporal continuum. It is possible that pseudoprogression may be more
influenced by chemotherapy than early pseudoprogression. Also, late pseudoprogression may be particularly frequent under the influence of temozolomide/lomustine combination therapy (5).

If an increasing contrast-enhancing lesion on MRI indicates (late) pseudoprogression, the current gold standard is to perform follow-up MRIs to evaluate changes in lesion size. Consequently, a diagnosis of (late) pseudoprogression can only be made retrospectively based on follow-up MRI. It would be, however, advantageous for patient management if pseudoprogression 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 4-8 weeks for a follow-up MRI to have decided whether secondary surgery or any other therapeutic adjustments are needed.

Position-Emission-Tomography (PET) using radiolabeled amino acids such as O-(2-[18F]fluoroethyl)-L-tyrosine (18F-FET) allows imaging of amino acid transport in brain tumors and has shown promise in distinguishing pseudoprogression from truly progressive tumor (9). Comparing with the most known tracer 18F-FDG 18F-FET is considered particularly suitable for glioma research because of its low background activity (10). Also, 18F-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 pseudoprogression and it may be particularly helpful in making the difficult diagnosis of latePsP. We have already demonstrated the applicability of $^{18}$F-FET PET for diagnosing early pseudoprogression in a recent case series (16). To furthermore assess whether $^{18}$F-FET PET is capable of drawing a distinction between true progression and late pseudoprogression/radionecrosis - which is even more infrequent and thus difficult to diagnose - we retrospectively examined the predictive value of $^{18}$F-FET PET for detecting latePsP 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: (1) patients experiencing increasing contrast-enhancing lesions on MRI (+25% in 2 perpendicular diameters and/or any new lesion according to RANO (17), 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; (2) patients having a \(^{18}\text{F-FET-PET}\) following detection of increasing contrast-enhancing lesions, (3) after initial MRI and \(^{18}\text{F-FET-PET}\), 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 \(^{18}\text{F-FET}\)

The amino acid \(^{18}\text{F-FET}\) was produced as described previously (18, 19). According to the German guidelines for brain tumor imaging using labelled amino acid analogues, all patients remained fasted for at least 12 h before PET scanning (20). Dynamic PET studies were acquired up to 50 min after intravenous injection of approximately 200 MBq \(^{18}\text{F-FET}\) on an ECAT EXACT HR+ scanner (Siemens Medical Systems, Inc.) in 3-dimensional mode (32 rings; axial field of view, 15.5 cm). The emission recording consisted of 16 time frames (time frames 1-5: 1 min, 6-10: 3 min, and 11-16: 5 min) covering the period up to 50 min post injection. For attenuation correction, transmission was measured with 3 \(^{68}\text{Ge}/^{68}\text{Ga}\) 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, Kerpen, Germany). The fusion results were inspected
and, if necessary, adapted based on anatomical landmarks. The Region-of-Interest
(ROI) analysis was based on the summed PET data from 20-40 min post 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 (20). Mean amino acid uptake
in the tumor was determined by a 2-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 tumor-brain-ratios ($\text{TBR}_{\text{max}}, \text{TBR}_{\text{mean}}$) 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 data set. 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 described
(12, 21), 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 (≤ 20 min)
followed by a constant descent (pattern III). The assignment of TACs to the various
curve patterns was performed by 3 experienced raters (NG; KJL; GS).

**Diagnosis of True Progression**

The diagnosis of tumor progression was made when progressive contrast-enhancing
lesions according to RANO criteria (17) 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 pseudoprogression was applied when the follow-
up MRI showed stabilization or regression of the contrast-enhancing lesions.

**Statistics**

Descriptive statistics are reported as mean and standard error of mean (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 latePsP from true progression
was assessed by receiver-operating-characteristic (ROC) curve analyses using the
results of follow-up MRI as reference. The optimal cut-off was the value where the square of the difference between sensitivity and specificity was minimized; i.e., where both sensitivity and specificity were highest. Moreover, the area under the ROC curve (AUC), its standard error (SE) and its level of significance were determined as an estimation of diagnostic quality. The diagnostic performance of curve patterns alone to assess for latePsP was determined by a Fisher exact test for 2 x 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 of 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 patients. A methylated MGMT promoter was found in 17 and a non-methylated MGMT promoter in 8 patients. 22/26 patients included in the study underwent PET investigation during first-line treatment and 4/26 during second-line treatment. Of the 22 patients analyzed at first-line treatment, 17 received temozolomide (TMZ)-based radiochemotherapy (standard radiotherapy applying a total dose of 54-60 Gy combined with standard TMZ 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 TMZ-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 TMZ); two of them additionally had re-irradiation (Table 1).

Diagnosis of tumor progression versus latePsP

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 latePsP 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 ≥ 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 out of 7 patients with latePsP (86%). In one patient, the MGMT promoter was not methylated. In patients with true progression, the MGMT promoter gene was found methylated in 11/19 patients (58%).

**18F-FET uptake and tracer kinetics**

TBR\(_{\text{max}}\) and TBR\(_{\text{mean}}\) of 18F-FET uptake were significantly increased in patients with true progression compared to patients with latePsP (TBR\(_{\text{max}}\) 2.4±0.1 vs. 1.5±0.2, p=0.003; TBR\(_{\text{mean}}\) 2.1±0.1 vs. 1.5±0.2, p=0.012). 18F-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 latePsP (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 latePsP (Fisher’s exact test; p<0.001). TTP showed significant difference in patients with true progression and with latePsP (mean TTP 25±2 vs. 40±2 min, p<0.001). Representative examples of 18F-FET PET finding in a patient with tumor progression and a patient with latePsP are shown in figures 1 and 2, respectively.
**ROC analysis**

ROC analysis yielded an optimal cut-off of 1.9 for $TBR_{\text{max}}$ to differentiate between true progression and latePsP (sensitivity 84 %, specificity 86 %, accuracy 85 %, AUC $0.88\pm0.07$; 95%CI 0.73 - 1.0, p=0.015) (Figure 3). The same cut-off (1.9) was obtained for $TBR_{\text{mean}}$ which achieved a slightly poorer yet significant diagnostic performance (sensitivity 74 %, specificity 86 %, accuracy 77 %, AUC $0.86\pm0.07$; 95%CI 0.72 – 1.0, p=0.023). TTP significantly predicted true progression vs. latePsP (AUC $0.86\pm0.07$; 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 non-invasive tool to distinguish latePsP from progressive disease in patients with glioblastoma. Using this method, latePsP may be identified earlier than with conventional MRI.

Regarding clinical decision making, it seems logical to assume true late progression when TBRmax is higher than 2.4 since no patient with late pseudoprogresasion had TBRmax values in excess of that. Conversely, it seems advisable to assume late pseudoprogresasion when TBRmax is below 1.0, since no patient with late progression had TBRmax 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 pseudoprogresasion as it reflects an ongoing benefit from previous/current treatment. Hence, in the event of a TBRmax value in between 1.0 and 2.4 it might be safest (when trying to avoid missing pseudoprogresasion) to defer the iniatiion of a salvage treatment until a follow-up MRI has been performed or to obtain a tumor specimen via biopsy to confirm diagnosis. The latter decision has to be tailored to the patient’s condition and clinical status.

Patients with O6-methylguanine methyltransferase (MGMT)–methylated glioma are more likely to develop pseudoprogresasion, amounting to an incidence of up to 31% as compared with 5% in patients with non-methylated tumors (8, 17, 22). Accordingly, our study found that almost all patients with latePsP had a methylated MGMT promoter. Nevertheless, one patient with a non-methylated MGMT promoter
was diagnosed with latePsP. Therefore, patients with non-methylated MGMT promotor also should be considered for latePsP.

\( TBR_{\text{max}} \) and \( TBR_{\text{mean}} \) were both useful in predicting progression with \( TBR_{\text{max}} \) 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 \( TBR_{\text{mean}} \) and \( TBR_{\text{max}} \). This cut-off value is close to the previously reported cut-off for \( TBR_{\text{max}} \) (2.3) for distinguishing glioblastoma patients with early pseudoprogression from true early progressive disease (9).

Similarly, the presence of curve patterns type II and III were predictive for true progression. TTP of \( ^{18}\text{F-FET} \) 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 (23). In our series of patients TTP confirmed these finding by showing significant differences between true tumor progression and latePsP.

Our study supports further larger scale prospective studies that include histopathologic confirmation to confirm the high diagnostic accuracy of \( ^{18}\text{F-FET PET} \) for differentiating recurrent glioma and non-specific post-therapeutic changes as reported in previous studies (24) but the high diagnostic accuracy of TBR of \( ^{18}\text{F-FET} \) uptake of more than 90 % could not be confirmed here.

There are a number of non-invasive imaging tools (diffusion-weighted MRI, DWI; Diffusion-tensor imaging, DTI; Perfusion MRI (DSC, DCE); susceptibility-weighted imaging, SWI; MR spectroscopy, MRS; single photon emission computed
tomography, SPECT) currently being investigated in the differentiation between pseudoprogression and true progression (25). 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 pseudoprogression. 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. Additionally, 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 latePsP, 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.
Funding

None.

Acknowledgments

The authors thank Suzanne Schaden, Elisabeth Theelen, Kornelia Frey and Silke Frensch for assistance in the patient studies as well as Dr. Johannes Ermert, Silke Grafmüller, Erika Wabbals, and Sascha Rehbein for radiosynthesis of $^{18}$F-FET.
Reference List

Figures

Figure 1. Patient with true tumor progression (patient No. 1). There is increased $^{18}$F-FET uptake in the tumor ($TBR_{\text{max}}$ 2.9, $TBR_{\text{mean}}$ 2.2, D) and a short TTP (17 min, E). PET was obtained 18 weeks (wks) after radiochemotherapy (RCx) (B). On follow-up MRI, obtained 26 wks after RCx, further increasing contrast-enhancing lesions document true tumor progression (C).

Figure 2. Patient with latePsP (patient No. 3). At 23 weeks (wks) after completion of radiochemotherapy (RCx) a newly occurring contrast enhancing area in MRI indicates tumor progression (B) but $^{18}$F-FET uptake in that area is very low (D). Slightly increased $^{18}$F-FET uptake is noted in the vicinity of the lesion ($TBR_{\text{max}}$ 1.8, D) which exhibits a slowly increasing time activity curve (TTP 35 min, E) compatible with non-specific post-therapeutic changes. On follow-up MRI, obtained 31 wks after RCx, a distinct regression of the contrast-enhancing lesion indicates latePsP (C).

Figure 3. Receiver operating characteristic (ROC) curve of $TBR_{\text{max}}$ for detecting true progression. Area under the curve (AUC) was 0.88 and predicted true progression significantly ($p=0.015$).

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

Table 2. [$^{18}$F]-FET PET characteristics
Figure 1

A. Baseline
B. 18 wks after RCx
C. 26 wks after RCx

D.

E.

SUV

Time (min)

0 10 20 30 40 50

1 1.5 2 2.5 3 3.5

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Reference-ROI
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**Abbreviations:** AA, anaplastic astrocytoma; Clin., clinical follow-up.; cR, complete resection; Cx, chemotherapy; Dx, diagnosis; GBM*, secondary glioblastoma; GBM, glioblastoma; CCNU, lomustine; MGMT, O-6-methylguanine-DNA methyltransferase; n.app., not applicable; NA, not available; n/a, not applicable; no prog., no progression; nyr, not yet reached; PET, positon 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; *Line of therapy while under PET investigation
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TBR$_{\text{max}}$ = maximum tumor-to-brain ratio; TBR$_{\text{mean}}$ = mean tumor-to-brain ratio; TTP = time to peak; Clin. = Clinical follow-up; prog. = progression; Curve Pattern 1 = constantly increasing 18F-FET-uptake without identifiable
peak uptake (pattern I); Curve Pattern 2 = 18F-FET-uptake peaking at a midway point (> 20-40 min) followed by a plateau or a small descent; Curve Pattern 3 = 18F-FET-uptake peaking early (≤ 20 min) followed by a constant descent.

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Sied Kebir, Rolf Fimmers, Norbert Galldiks, et al.

Clin Cancer Res  Published OnlineFirst December 16, 2015.

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