The diagnostic accuracy of detecting malignant transformation of low-grade glioma using O-(2-[¹⁸F]fluoroethyl)-L-tyrosine positron emission tomography: a retrospective study

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OBJECTIVE The diagnostic accuracy of O-(2-[¹⁸F]fluoroethyl)-L-tyrosine (FET) PET scanning in detecting the malignant transformation of low-grade gliomas (LGGs) is controversial. In this study, the authors retrospectively assessed the diagnostic potential of FET PET in patients with MRI-suspected malignant progression of LGGs that had previously been treated and the relationship between FET uptake and MRI and molecular biomarkers.

METHODS Forty-two patients who had previously undergone surgical or multimodal treatment for a histologically verified LGG were referred for FET PET assessment because of clinical signs and/or MRI findings suggestive of tumor progression. Maximal and mean tumor-to-brain ratios (TBR_{max} and TBR_{mean}, respectively) on FET PET as well as kinetic FET PET parameters (time to peak [TTP] and time-activity curve [TAC]) were determined. Final diagnoses were confirmed histologically. The diagnostic accuracy of FET parameters, separately and combined, for the detection of malignant progression was evaluated using receiver operating characteristic (ROC) curve analysis. Possible predictors that might influence the diagnostic accuracy of FET PET were assessed using multiple linear regression analysis. Spearman's rank correlation *r* method was applied to determine the correlation between TBR_{max} and TAC, and molecular biomarkers from tumor tissues.

RESULTS A total of 47 FET PET scans were obtained and showed no significant association between FET parameters and contrast enhancement on MRI. ROC curve analyses overall were unable to demonstrate any significant differentiation between nontransformed LGGs and LGGs that had transformed to high-grade gliomas when evaluating FET parameters separately or combined. After excluding the oligodendroglial subgroup, a significant difference was observed between nontransformed and transformed LGGs when combining FET parameters (i.e., TBR_{max} > 1.6, TAC describing a plateau or decreasing pattern, and TTP < 25 minutes), with the best result yielded by a combined analysis of TBR_{max} > 1.6 and TAC with a plateau or decreasing pattern (sensitivity 75% and specificity 83%, *p* = 0.003). The difference was even greater when patients who had previously undergone oncological treatment were also excluded (sensitivity 93% and specificity 100%, *p* = 0.001). Multiple linear regression analysis revealed that the presence of an oligodendroglial component (*p* = 0.029), previous oncological treatment (*p* = 0.039), and the combined FET parameters (*p* = 0.027) were significant confounding factors in the detection of malignant progression. TBR_{max} was positively correlated with increasing cell density (*p* = 0.040) and inversely correlated with IDH1 mutation (*p* = 0.006).

CONCLUSIONS A single FET PET scan obtained at the time of radiological and/or clinical progression seems to be of limited value in distinguishing transformed from nontransformed LGGs, especially if knowledge of the primary tumor histopathology is not known. Therefore, FET PET imaging alone is not adequate to replace histological confirmation, but it may provide valuable information on the location and delineation of active tumor tissue, as well as an assessment of tumor biology in a subgroup of LGGs.

<https://thejns.org/doi/abs/10.3171/2017.8.JNS171577>

KEYWORDS low-grade glioma; ¹⁸F-FET PET; malignant transformation; oncology

ABBREVIATIONS AUC = area under the curve; FDOPA = 3,4-dihydroxy-6-¹⁸F-fluoro-L-phenylalanine; FET = O-(2-[¹⁸F]fluoroethyl)-L-tyrosine; FET₁₀₋₃₀ = 10- to 30-minute FET; FET₂₀₋₄₀ = 20- to 40-minute FET; HGG = high-grade glioma; IQR = interquartile range; LGG = low-grade glioma; MET = ¹¹C-methionine; PFS = progression-free survival; RANO = Response Assessment in Neuro-Oncology; ROC = receiver operating characteristic; ROI = region of interest; SUV = standardized uptake value; TAC = time-activity curve; TBR_{max} = maximal tumor-to-brain ratio; TBR_{mean} = mean tumor-to-brain ratio; TTM = time to malignant transformation; TTP = time to peak.

SUBMITTED June 30, 2017. **ACCEPTED** August 2, 2017.

INCLUDE WHEN CITING Published online April 6, 2018; DOI: 10.3171/2017.8.JNS171577.

LOW-GRADE gliomas (LGGs; WHO grade II) are known to comprise a heterogeneous group of diffusely infiltrating primary brain tumors with distinct clinical, histological, and molecular characteristics.^{22,23,39} The natural history of primary LGGs may be characterized by a slow growth rate and an indolent disease course for several years with or without treatment; however, at an unpredictable time, almost all patients experience malignant transformation to high-grade glioma (HGG; WHO grade III or IV), with an ultimately fatal outcome.^{5,22,23} The prognosis is related to age, performance status, lesion size, midline involvement, and histopathology (e.g., astrocytic and oligodendroglial, and the recently demoted category of oligoastrocytic tumors according to “The 2016 World Health Organization Classification of Tumors of the Central Nervous System”).^{22,23,31} The median patient survival has been reported to be 5–8 years for low-grade astrocytomas and 2–3 years for anaplastic astrocytomas, while low-grade oligodendrogliomas confer a somewhat better prognosis with 12–15 years, and more than 7 years for anaplastic oligodendrogliomas.^{22,23} Differentiation between recurrent nontransformed and malignantly transformed LGGs is usually based on conventional MRI findings as defined by the presence of focal contrast enhancement.²⁶ However, MRI lacks diagnostic accuracy in regard to the noninvasive assessment of biological tumor activity and metabolism. Up to 40% of HGGs do not enhance after administration of contrast, while approximately 16% of LGGs show contrast enhancement on MRI at the time of histological diagnosis, a trait typically associated with HGGs. Furthermore, both tumor recurrence without malignant transformation and postradiation effects, including pseudoprogression, occur in up to 20% of previously radiation-treated LGGs and often present as new enhancing lesions on MRI; thus, differentiation of gliomas on conventional MRI is challenging.^{14,26,31,35,37} Reliable neuroimaging modalities therefore are needed as an early guide in the management of patients with suspected tumor progression.

PET is an advanced molecular neuroimaging modality that is increasingly used in the diagnostic workup of patients with brain tumors, including differential diagnosis, evaluation of tumor extension, treatment planning, and follow-up. In the last decade, several studies have evaluated PET by using the radiolabeled glucose analog FDG and various amino acid analogs, such as ¹¹C-methionine (MET), 3,4-dihydroxy-6-¹⁸F-fluoro-L-phenylalanine (FDOPA), and O-(2-[¹⁸F]fluoroethyl)-L-tyrosine (FET), as an aid in the differential diagnoses of suspected glioma recurrence or progression. FDG was the first diagnostic tracer used for the detection and delineation of brain tumors as well as for tumor grading, previously reported with both high sensitivity and specificity.^{9,20} However, recent studies have questioned its efficacy and usefulness due to a high uptake in normal brain and unspecific uptake in inflammatory benign lesions, thus limiting the use of FDG for defining the extent of cerebral tumor. In addition, FDG does not allow further differentiation of these tumors.^{21,28} In contrast, MET has proven useful in determining the extent of cerebral tumors and evaluating treatment response.⁷ However, MET is used in only a few medical cen-

ters with an on-site cyclotron due to the short half-life of ¹¹C (20-minute half-life vs 109 minutes for ¹⁸F). FDOPA is a reasonable alternative to MET, and several studies have shown that FDOPA has a higher sensitivity and specificity for identifying gliomas than other tracers, mainly in evaluating the recurrence of LGG or HGG.^{3,38} FET is another PET tracer that is similar to FDOPA, which has a proven utility for determining the extent of brain tumors in treatment planning and guiding stereotactic biopsy and for differentiating between benign therapy-induced changes and tumor recurrences, and furthermore, it is deemed to be useful for noninvasive grading of tumors.^{11,14} Its use for tumor grading, however, remains controversial, although some studies have shown that dynamic FET PET analysis is superior to static analysis.^{6,12,14,18,29,30} At our institution, FET PET has been used since 2012 as the modality of choice for glioma evaluation in cases in which the MRI findings have been ambiguous.

The purpose of this study was 1) to investigate the diagnostic potential of static and dynamic FET PET parameters as a noninvasive indicator of malignant transformation, performed in response to a suspicion raised on MRI, in previously histologically proven and surgical or multimodal-treated LGGs; and 2) to assess the relationship between FET uptake and the corresponding MRI and various molecular biomarkers of tumor tissue.

Methods

Patient Characteristics

In this retrospective single-center study, a total of 77 consecutive patients referred for FET PET assessment during the years 2012–2015 were identified. Study inclusion criteria consisted of patients with histologically verified LGGs that had previously been treated (resection or stereotactic biopsy with or without adjuvant chemo- and/or radiotherapy) who presented with clinical signs and/or new MRI findings that were suggestive of tumor progression and underwent neurosurgical intervention following FET PET assessment at the National University Hospital, Rigshospitalet, Copenhagen, Denmark. Patients with presumed LGG based only on MRI results with no histological verification were excluded from the study. Data on included patients were extracted from a computerized database and reviewed retrospectively, including demographic data, presence or absence of epilepsy, primary tumor management (monitoring, stereotactic biopsy, resection, adjuvant chemo- and/or radiotherapy) and histopathology, progression-free survival (PFS, calculated from the primary tumor management [i.e., primary neurosurgical intervention and histological diagnosis] to the first event of clinical deterioration, including new neurological symptoms and/or tumor growth on conventional MRI according to the Response Assessment in Neuro-Oncology [RANO] criteria),³⁶ time to malignant transformation (TTM, calculated from the time of primary histological diagnosis to the confirmation of the secondary histological diagnosis), clinical deterioration or radiological findings suggestive of tumor progression, and secondary tumor management and histopathology.

Ethics

The study was approved by the health cooperative board and the data inspectorate. All patients provided written informed consent before each FET PET assessment as part of the clinical routine.

Definition of Tumor Progression

Clinical and radiological follow-up with MRI was performed in all patients on a regular basis at an interval of 6–12 months. Criteria for undergoing FET PET were suspicion of tumor progression based on the RANO criteria:³⁶ 1) clinical deterioration, such as the development of new symptoms of increased intracranial pressure with or without new or exacerbation of preexisting focal neurological deficits, but not worsening of seizure control alone, although worsening of seizure control accompanied by radiological progression was considered to indicate FET PET; and 2) radiological deterioration, such as the development of one or more new areas of contrast enhancement within the tumor, significant enlargement of tumor of more than 25% of the initial noncontrast tumor volume, and/or an increasing mass shift.

MRI Examination

Routine MRI was performed in each patient using a 1.5- or 3-T MRI scanner. The enlargement of tumor on FLAIR and T2- and T1-weighted sequences, as well as the presence of contrast enhancement on T1-weighted sequences with a standard head coil, was assessed before and after administration of a gadolinium-based contrast agent (Gadovist 604.72 mg/ml, Bayer).

FET PET Examination

FET PET scanning was performed using an integrated Biograph TruePoint 40- or 64-slice PET/CT system (Siemens). Prior to PET scanning, patients fasted for at least 6 hours. After intravenous injection of 200 MBq FET, a 22-frame dynamic sequence (6 × 10 seconds, 4 × 15 seconds, 2 × 30 seconds, 2 × 60 seconds, 2 × 150 seconds, and 6 × 300 seconds) was performed, followed by the reconstruction of 2 static FET PET frames of the entire brain at 10–30 minutes (FET_{10–30}) and 20–40 minutes (FET_{20–40}). For all images, default random, scatter, and dead time correction and low-dose CT-based attenuation correction were applied. Image reconstruction was performed using a 3D ordered-subsets expectation maximization (OSEM) algorithm with 4 iterations, 12 subsets with a matrix size of 400 × 400 × 74 (0.8 × 0.8 × 3.0-mm voxel size). Images were filtered with a 5-mm full-width at half-maximum gaussian filter.

The FET_{20–40} PET images were analyzed semiquantitatively after coregistration to postcontrast T1-weighted and T2-weighted/FLAIR MRI. The reader (I.L.) was blinded to clinical data, including histological confirmation. A 3D banana-shaped background (B) region of interest (ROI) encompassing the activity > 70% of maximum was delineated in healthy-appearing gray and white matter above the insula in the contralateral hemisphere. The biological tumor volume was defined by 3D isocontouring activity at

a threshold at or above 1.6 of mean activity in the background ROI (Syngo-TrueD, Siemens).²⁷ The maximal and mean tumor-to-brain ratios (TBR_{max} and TBR_{mean}, respectively) were calculated by dividing the maximal and mean standardized uptake value (SUV) of the tumor ROI by the mean SUV of normal brain on FET PET scanning. For inactive tumors, we used the average activity in a circular 1.0-cm² ROI placed in the center of tumor-associated signal change on T2-weighted/FLAIR sequences. To extract time-activity curves (TACs) from metabolically active tumors, a 3D activity volume of the most active 90% was isocontoured on the FET_{10–30}.

PET analysis comprised 1) a qualitative visual classification of LGGs; 2) quantitative assessment of the static parameters, including TBR_{max} and TBR_{mean}; and 3) FET uptake kinetics (i.e., time to peak [TTP]) and the TAC pattern. The TAC pattern was defined as 1) constantly increasing TAC throughout the uptake period without a detectable peak of FET uptake; 2) increasing TAC with a detectable peak of FET uptake followed by plateau (> 20–40 minutes); and 3) early peak of FET uptake (< 20 minutes) followed by a decreasing TAC. The FET_{10–30} was used to detect early peaks of activity as found in most HGGs.²

Histology and Immunohistochemistry

Two of the study authors (A.B. and H.B.) reviewed all histological results separately and were blinded to the FET PET results. The histological diagnosis of glioma was established in all patients using tissue samples obtained during stereotactic biopsy or resection as a basis for subsequent tumor management. The analyses were carried out after formalin fixation and paraffin embedding of the tissue samples. All tumors were graded according to the 2007 WHO classification of gliomas; for the most recent samples (i.e., those obtained in 2015), the 2016 WHO classification criteria were gradually incorporated.^{22,23} These included conventional staining (H & E, van Gieson), as well as immunohistochemical staining for GFAP, EGFR, MAP2, IDH1 mutation, transcriptional regulator (ATRX), Olig2, p53, number of mitoses, cell density, microvessel proliferation and necrosis, and Ki-67 labeling index. Furthermore, molecular investigation of MGMT promoter methylation and 1p19q codeletion was performed using polymer chain reaction analysis when necessary.

Statistical Analysis

Data analysis was performed using the statistical software package IBM SPSS (version 20.0, IBM Corp.). Descriptive data are presented as median values with interquartile ranges (IQRs). As combinations of static and dynamic FET PET parameters have previously proved to have the highest diagnostic accuracy with various cut-offs,¹² the most optimal combination was identified by setting up a 5-level hierarchy as follows: 0, FET-negative (TBR_{max} < 1.6); 1, FET-positive (TBR_{max} > 1.6), increasing TAC, and TTP > 25 minutes; 2, FET-positive (TBR_{max} > 1.6), plateau, and TTP > 25 minutes; 3, FET-positive (TBR_{max} > 1.6), plateau, and TTP < 25 minutes; and 4, FET-positive (TBR_{max} > 1.6), decreasing TAC, and TTP < 25 minutes. Receiver operating characteristic (ROC)

curve analyses were performed with histological verification of glioma as a reference to determine the diagnostic accuracy of MRI alone (i.e., the presence of new contrast enhancement on T1-weighted MRI) and FET PET parameters alone (i.e., TBR_{max} , TAC, and TTP), investigated separately and in different optimal combinations as mentioned above, and finally in conjunction with contrast enhancement on MRI. The analyses were performed for all patients as well as for the different subgroups dependent on tumor histology and previous tumor management. A possible decision cutoff value was considered optimal when both values for sensitivity and specificity reached their maximum. Furthermore, to identify confounding factors influencing the diagnostic accuracy of the FET PET results,¹² a multiple linear regression analysis was performed with recurrent nontransformed and transformed LGGs as the dependent variable, and the presence of an oligodendroglial tissue component,¹⁴ initial tumor surgical intervention (biopsy vs resection), previous adjuvant oncological treatment,²⁰ and the combination of the aforementioned FET PET parameters¹¹ as independent variables. A nonparametric Mann-Whitney U-test was used to assess the association of FET PET parameters and WHO grading. The prognostic influence of FET PET parameters (e.g., TBR_{max} and TAC) on PFS and TTM was calculated with the Kaplan-Meier method using the log-rank test. For correlation analysis for TBR_{max} and TAC, and immunohistochemical analysis, Spearman's rank correlation coefficient was applied. A p value < 0.05 was considered statistically significant.

Results

Records of 77 patients were reviewed for inclusion in this study. Thirty-five patients were excluded for the following reasons: normal findings on FET PET scanning and thus no subsequent surgical intervention ($n = 26$), no primary histopathology of LGG ($n = 5$), diagnosis other than LGG ($n = 3$), and nonspecific subsequent histopathology ($n = 1$). Therefore, 42 patients were eligible for the study (24 females and 18 males; Fig. 1). The median age at the time of FET PET scanning was 41 years (IQR 34–57 years). Thirty-three (79%) patients had secondary epilepsy and received anticonvulsant medication. Thirty-seven (88%) patients had undergone tumor resection, and 5 (12%) had undergone stereotactic biopsy. Five (12%) patients underwent 2 additional investigations with MRI and FET PET followed by neurosurgical intervention, resulting in a total of 47 FET PET scanning sessions. In 2 patients (5%; patients 36 and 40), only diagnostic biopsies had been performed, and since then the patients have been followed by a watch-and-wait approach. Two other patients (5%; patients 1 and 39) had histopathological findings that were nonspecific or inconclusive primary histopathology. However, these patients were included because their radiological findings resembled typical LGG at the time of diagnosis, and because histopathology after suspected malignant progression confirmed glioma. A minority of patients ($n = 8$, 19%) had received adjuvant chemo- and/or radiotherapy. The overall median PFS for the entire group was 35 months (IQR 15–56 months). The

FIG. 1. Patients referred for FET PET scan for malignant transformation in the time period of 2012–2015 and exclusion criteria. †Five patients underwent a total of 6 FET PET scanning sessions.

patient characteristics, initial diagnosis of LGG, the PFS, and median time from MRI to FET PET and FET PET to tumor resection are summarized in Table 1.

MRI Findings

All but 9 (81%) of 47 MR images demonstrated an increased T2-weighted/FLAIR nonenhancing tumor volume, while 15 (32%) had new areas of focal contrast enhancement on MRI (Table 2). Eleven (23%) images demonstrated tumor growth as well as new areas of contrast enhancement, whereas 6 (13%) showed no radiological signs of progression. In the latter, suspicion of progression was based on the lack of seizure control despite optimal anticonvulsant medication and neurological deficits, although the lack of seizure control alone was otherwise not a criterion to refer patients for FET PET scanning.

FET PET Findings

The patients underwent a total of 47 FET PET sessions during the study period, as mentioned above. The median time between MRI and FET PET scanning was 24 days (IQR 13–31 days), and from FET PET scanning to neurosurgical intervention it was 36 days (IQR 25–82 days; Table 1). Quantitative assessment of PET scans revealed 40 FET-positive cases ($TBR_{max} > 1.6$) and 7 FET-negative cases ($TBR_{max} < 1.6$). Of the 40 FET-positive cases, the kinetic analysis was available for 38. Of these, 13 (34%)

exhibited increasing TAC, 14 (37%) showed decreasing TAC, and in the remaining cases (29%) a TAC with plateau was seen (Fig. 2). No kinetic analysis could be derived reliably from the FET PET–negative cases, and these were performed only as static FET_{20–40} scans. The median tumor volume in FET PET–positive cases was 13.8 cm³ (IQR 2.65–34.0 cm³). The median TBR_{max} and TBR_{mean} were 2.51 (IQR 1.82–4.64) and 1.85 (IQR 1.66–2.29), respectively. There was no significant difference between gliomas with and without an oligodendroglial component with regard to TBR_{max} ($p = 0.278$) and TBR_{mean} ($p = 0.229$). In addition, there was no significant difference in TAC and TTP in these 2 groups ($p = 0.864$ and $p = 0.928$, respectively). As only 3 (7%) patients underwent baseline FET PET scanning at the time of confirmation of LGG, the possible changes of FET uptakes at the time of tumor progression were not investigated.

Tumor Management and Histological Analyses

At suspected tumor recurrence after FET PET scanning, stereotactic biopsies were performed in 13 (31%) patients, while 29 (69%) underwent tumor resection (Table 2). Five (12%) patients underwent additional surgical intervention (2 diagnostic biopsies and 3 tumor resections) later in the clinical course. Twenty-one (45%) LGGs had transformed to WHO grade III, including anaplastic astrocytoma ($n = 13$, 28%), anaplastic oligodendroglioma ($n = 6$, 13%), anaplastic oligoastrocytoma ($n = 1$, 2%), and anaplastic ganglioglioma ($n = 1$, 2%), while 2 (4%) had transformed to WHO grade IV (glioblastoma). The overall median TTM was about 35 months (IQR 15–54 months).

Relationship Between MRI and Tumor Histopathology

Significant tumor growth was observed on conventional MRI, equally distributed between nontransformed ($n = 18$) and transformed ($n = 19$) LGGs, while a new occurrence of or change in contrast enhancement was mostly seen in cases of progression (Table 2). However, in 14 (30%) cases with a histologically proven malignant transformation, T1-weighted MRI failed to demonstrate new occurrence or changes in contrast enhancement, while in 6 (13%) cases without malignant transformation MRI showed contrast enhancement, indicating no significant correlation ($p = 0.304$). MRI findings at the time of suspected malignant progression therefore was unable to demonstrate a significant differentiation between nontransformed and transformed LGGs (sensitivity 43%, specificity 77%, and area under the curve [AUC] 0.597; $p = 0.311$; Table 3).

Relationship Between FET Uptake and Tumor Histopathology

Among 40 FET-positive cases, 23 (58%) had a progressive disease course with malignant transformation. Malignant transformation was observed in 7 (18%) cases with plateau and 8 (20%) cases with decreasing TAC, while it was seen in 6 (15%) cases with increasing TAC (3 anaplastic oligodendrogliomas and 3 anaplastic astrocytomas). In 7 FET-negative cases, only 1 (14%) demonstrated tumor progression with malignant transformation to anaplastic astrocytoma. In transformed LGGs, the median TBR_{max}

TABLE 1. Patient characteristics

Variable	Value
Median age in yrs	41 (34–57)
Sex	
Female	24 (57)
Male	18 (43)
Epilepsy	33 (79)
Initial neurosurgical intervention	
Biopsy	5 (12)
Resection	37 (88)
Subsequent chemo-/radiotherapy	8 (19)
Initial histological diagnosis, WHO grade	
Astrocytoma, II	26
Oligodendroglioma, II	12
Oligoastrocytoma, II	5
Ganglioglioma, I	1
Neuroepithelial tumor, I/II	1
Nonspecific or inconclusive	2
Median PFS in mos	35 (15–56)
Median time from MRI to PET in days	24 (13–31)
Median time from PET to surgery in days	36 (25–82)
Malignant transformation	23 (55)
Median time to malignant progression in mos	35 (15–54)
Deceased	3 (7)

Values are presented as the number of patients (%) unless stated otherwise.
Median values are presented as the median (IQR).

was 2.59 (IQR 2.10–4.64) and TBR_{mean} 1.85 (IQR 1.74–2.35), while in recurrent nontransformed LGGs, the median TBR_{max} was 2.36 (IQR 1.49–4.33) and TBR_{mean} 1.83 (IQR 1.42–2.14). No significant difference was found in FET uptake between nontransformed and transformed LGGs (TBR_{max}, $p = 0.307$ and TBR_{mean}, $p = 0.292$). Kinetic parameters did not differ significantly between WHO groups (TAC, $p = 0.585$ and TTP, $p = 0.904$). Results remained nonsignificant after excluding the oligodendroglial subgroup. Finally, 8 (57%) of 14 stereotactic biopsies were performed using PET/MRI-guided navigation, and yet no significant difference was observed between nontransformed and transformed LGGs. In contrast, when evaluating the prognostic value of FET PET parameters, patients with decreasing TAC presented with significantly shorter PFS and TTM ($p = 0.008$ and $p = 0.032$, respectively; Fig. 3).

In all tumors, a panel of immunohistochemical staining was used, including GFAP, p53, EGFR, MAP2, Ki-67, MGMT, and IDH1 mutation, and, when necessary, molecular investigation of 1p19q codeletion and MGMT promoter methylation was performed, as previously mentioned. Later, ATRX and Olig2 were included. A significant positive correlation was found between TBR_{max} and increasing cell density ($r = 0.301$, $p = 0.040$). Results of IDH1 mutation analysis were available for 43 of 47 specimens, and the mutation was found in 72% of gliomas, equally distributed between nontransformed LGGs ($n = 16$) and transformed LGGs ($n = 18$). IDH1 mutation was

TABLE 2. Patient characteristics including age, sex, primary and secondary diagnosis of tumor and grade, MRI and FET PET findings, and primary and secondary tumor management

Patient No.	Age (yrs), Sex	Initial Histology	WHO Grade	Location	Side	Treatment Before PET	MRI Findings			FET PET Findings				Treatment After PET	Subsequent Histology	WHO Grade
							Epilepsy	Enhancement	Enlargement	TBR _{max}	TBR _{mean}	TAC	TTP			
1	65, M	NS		T	Rt	TR	++	No	Yes	1.82	2.59	↓	22	Bx + RT + CTx	A	III
2	64, M	A	II	Fr	Lt	TR		Probable	Yes	0.98	1.08			STR	A	II
3	39, M	A	II	T	Rt	TR	++	No	Yes	1.63	1.72	↑	38	Bx + RT	A	III
4	40, M	A	II	Fr	Lt	TR	+	No	Yes	2.38	6.18	↓	18	Bx + RT	A	III
5	59, M	A*		Pa	Rt	TR	+	Yes	Yes	2.16	3.15	↓	18	Bx	OD	II
6	35, F	A	II	Pa	Rt	Bx	+	No	Yes	2.25	3.80			STR + RT + CTx	OD	III
7	36, F	A	II	Fr	Lt	TR	++	No	Yes	0.65	0.78			TTR + RT	A†	II
8	36, F	A	II	Pa	Rt	TR	+	No	Yes	1.65	1.74	↑	38	TTR	OA	II
9	36, F	A	II	FrT	Lt	TR	++	No	No	1.14	0.16			TTR	A	II
9†	61, M	A	II	FrT	Lt	TR + RT	+	Yes	Yes	1.95	2.76	↑	38	TTR	A	II
10	41, M	A	II	T	Lt	TR	+	No	Yes	1.28	1.72	P	28	STR + RT	A	III
11	45, M	OA	II	Fr	Lt	TR	+	No	Yes	2.42	4.47	↓	12	STR + RT + CTx	OA	III
12	54, M	A	II	Pa	Rt	TR	+	No	Yes	1.75	2.19	↑	38	STR + RT + CTx	A	III
13	40, M	A	II	T	Rt	TR	+	Yes	No	1.89	2.64	P	28	TTR + RT + CTx	A	III
14	38, M	OD	II	Fr	Rt	TR	+	No	Yes	1.66	1.82	P	28	TTR	OD	II
15	42, F	GG	I	Fr	Rt	TR	+	Yes	Yes	3.69	7.41	↓	12	STR + RT	GG	III
16	46, M	OD	II	Fr	Lt	TR	+	No	Yes	2.60	5.81	↓	12	Bx	OD	II
17	37, F	OD	II	FrP	Lt	TR	+	No	Yes	2.07	3.32	↑	38	STR + RT	OD	II
18	56, F	OD	II	T	Rt	TR + RT		Yes	No	2.59	5.10	↓	18	Bx	OD	II
19	29, F	A	II	FrI	Rt	TR	+	No	Yes	0.93	1.14			Bx + RT	A	II
20	38, F	OA	II	Fr	Lt	TR + RT	+	Yes	No	2.45	7.62	↓	22	STR + CTx	OD†	III
21	37, M	A	II	Fr	Lt	TR	+	No	Yes	1.78	2.22	↓	22	STR + RT + CTx	GBM	IV
22	52, F	OD	II	FrI	Lt	TR	++	No	No	1.87	2.68	↑	38	TTR	OD	II
23	61, F	OD	II	FrI	Lt	TR	+	No	Yes	1.82	2.42	↑	38	STR + RT	OD	III
24	25, F	OA	II	Pa	Lt	TR	++	No	No	1.74	2.02	↑	38	STR + RT + CTx	OD	III
25	30, F	A	II	Fr	Rt	TR		No	No	0.77	1.00			TTR	A†	II
26	30, F	A	II	Fr	Lt	TR	+	Yes	Yes	2.29	5.14	↑	38	TTR + RT + CTx	OD	III
27	32, F	A	II	FrP	Lt	Bx + CTx	++	No	No	1.98	3.13	↑	33	STR	A	II
28	22, F	A	II	Fr	Rt	TR + RT + CTx		Yes	No	1.95	2.88	P	22	Bx + CTx	GBM	IV
29	37, M	A	II	T	Lt	TR	++	No	Yes	1.69	2.10	P	32	STR + RT	A	III
30	27, F	OD	II	Fr	Lt	TR	+	No	Yes	1.73	2.04	P	22	STR	OD	II
31	27, F	OD	II	Fr	Lt	TR	+	No	Yes	1.87	2.46	↓	18	Bx + RT	OD	II
32	30, F	A	II	O	Lt	TR + RT	+	No	Yes	2.43	5.69	P	22	Bx + CTx	A	II
33	30, F	A	II	O	Lt	Bx; CTx	+	No	No	2.32	4.66			Bx + CTx	A	II

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TABLE 2. Patient characteristics including age, sex, primary and secondary diagnosis of tumor and grade, MRI and FET PET findings, and primary and secondary tumor management

Patient No.	Age (yrs), Sex	Initial Histology	WHO Grade	Location	Side	Treatment Before PET	MRI Findings			FET PET Findings			Treatment After PET	Subsequent Histology	WHO Grade
							Epilepsy	Enhancement	Enlargement	TBR _{max}	TBR _{mean}	TAC	TTP		
31	31, F	A	II	T	Lt	TR	+	No	Yes	1.01	1.18		TTR + RT	A	II/III
32	58, F	NE	I/II	Fr	Lt	TR	++	No	Yes	1.77	2.12	↑	38 STR + RT	A	III
33	61, F	A	II	T	Lt	Bx + RT	+	No	Yes	2.37	5.58	↓	22 STR	A	II
		A	II	T	Lt	TR	+	Yes	Yes	2.35	4.64	↓	22 STR + CTx	A	III
34	67, F	A	II	Fr	Lt	Bx + RT		Yes	Yes	1.75	2.23	↑	38 Bx	A	II
35	28, F	A	II	Fr	Rt	TR		Yes	Yes	3.18	6.59	P	28 PTR → TTR + RT	A	III
36	53, F	A	II	Fr	Rt	Bx	+	No	Yes	2.06	4.69	↑	38 Bx + RT	OD	II
37	49, M	OA	II	Fr	Rt	TR		No	Yes	1.62	1.66	P	32 STR + RT	OD†	III
38	27, F	OD	II	Fr	Lt	TR	+	No	Yes	1.73	2.25	P	32 STR + RT	OD	II
39‡	61, F	NS		Fr	Rt	TR	++	Yes	Yes	1.34	1.41		STR	A	II
40‡	43, F	OA	II	T	Lt	Bx	+	Yes	Yes	2.23	4.25	P	22 Bx + RT	A†	III
41	59, M	OD	II	T	Lt	TR		N	Yes	1.78	2.17	↓	9 TTR	OD	II
42	48, M	A	II	T	Lt	TR		Yes	Yes	1.85	2.51	↓	28 STR + RT + CTx	A	III

A = astrocytoma; Bx = biopsy; CTx = chemotherapy; Fr = frontal; FrI = frontoinsula; FrP = frontoparietal; FrT = frontotemporal; GBM = glioblastoma; GG = ganglioglioma; NE = neuroepithelial tumor; NS = nonspecific; O = oligoastrocytoma; OD = oligodendroglioma; P = plateau; Pa = parietal; PTR = partial tumor resection; RT = radiotherapy; STR = subtotal tumor resection; T = temporal; TR = tumor resection; TTR = total tumor resection; + = epilepsy present; ++ = worsening of epilepsy; ↓ = decreased; ↑ = increased.

* Diagnosed as a benign astrocytoma, but a slight uncertainty remains that this is the correct diagnosis.

† Reclassified according to the 2016 WHO classification.

‡ Deceased.

FIG. 2. Patient examples showing static FET₂₀₋₄₀ PET images fused to T1-weighted postcontrast (T1+c) and T2-weighted MR images. **A:** Patient 5. Significant growth and new contrast enhancement on T1-weighted MR images with 13 ml of metabolically active tumor tissue, $TBR_{max} = 3.15$, with a TTP of 18 minutes and decreasing TAC indicative of transformation. Biopsy demonstrated WHO grade II oligodendroglioma. **B:** Patient 25. Significant growth and new contrast enhancement on T1-weighted MR images with 29 ml of metabolically active tumor tissue, $TBR_{max} = 5.14$, with a TTP of 38 minutes and increasing TAC indicative of LGG. Resection showed transformation to a WHO grade III anaplastic oligodendroglioma. **C:** Patient 33. Significant growth with stable contrast enhancement on T1-weighted MR images with 17 ml of metabolically active tumor tissue, $TBR_{max} = 5.58$, with a TTP of 22 minutes and decreasing TAC indicative of transformation. Resection showed astrocytoma WHO grade II. **D:** The TACs. Figure is available in color online only.

significantly and inversely associated with TBR_{max} and TAC ($r = -0.415$, $p = 0.006$ and $r = -0.414$, $p = 0.013$, respectively; Fig. 4). No significant correlation was found between 1p19q codeletion and FET parameters (TBR_{max} , $r = 0.137$, $p = 0.504$ and TAC, $r = -0.229$, $p = 0.306$). Furthermore, no significant correlation could be established between the Ki-67 proliferation index and FET parameters (TBR_{max} , $r = 0.027$, $p = 0.858$ and TAC, $r = 0.031$, $p = 0.855$).

Relationship Between MRI and FET Uptake

Increasing $TBR_{max} > 1.6$ and new occurrences of contrast enhancement on MRI were consistent in 38% and inconsistent in 62% of cases. ROC curves were generated for contrast enhancement on MRI and FET PET parameters (Table 3), as described in *Statistical Analysis*. ROC analysis of any of the imaging parameters separately, FET PET or contrast enhancement on MRI, did not significantly differentiate malignant transformation of LGGs. In addition, the interindividual variability in FET uptake in different WHO groups was high, so that a reliable cutoff

value could not be determined for TBR_{max} and TBR_{mean} using ROC analysis. When evaluating the combination of FET PET parameters ($TBR_{max} > 1.6$, TAC pattern 2 or 3, and TTP < 25 minutes) in conjunction with the findings of new contrast enhancement on MRI, the analysis showed a trend toward differentiation between nontransformed and transformed LGGs ($p = 0.093$), whereas the best result was yielded for a combined analysis of $TBR_{max} > 1.6$ and TAC pattern 2 or 3 and contrast enhancement on MRI ($p = 0.067$). After excluding oligoastrocytomas in light of the new 2016 WHO classification,²³ no significant differences or trend between nontransformed and transformed LGGs were seen.

Confounders Influencing FET Parameters

To identify confounding factors influencing FET parameters, a multiple linear regression model (adjusted $R^2 = 0.128$, $p = 0.044$) was performed and revealed that the presence of an oligodendroglial component, previous oncological treatment, and the combination of FET PET parameters (e.g., $TBR_{max} > 1.6$, TAC with pattern 2 or 3, and

TABLE 3. ROC analyses for all cases and cases excluding the oligodendroglial subgroup

Imaging Parameter	Overall Cases (n = 47)*				Excluding OA (n = 45)†				Excluding OA & OD (n = 28)			
	Sensitivity	Specificity	AUC	p Value	Sensitivity	Specificity	AUC	p Value	Sensitivity	Specificity	AUC	p Value
FET PET parameter												
TBR _{max}	57%	41%	0.476	0.803	55%	38%	0.441	0.545	40%	40%	0.347	0.315
TAC	71%	41%	0.549	0.607	70%	38%	0.516	0.874	80%	60%	0.700	0.190
TTP‡	57%	47%	0.511	0.907	60%	50%	0.556	0.567	53%	40%	0.360	0.359
MRI CE	43%	77%	0.597	0.311	45%	75%	0.600	0.308	47%	60%	0.533	0.827
Combination of all FET PET parameters§	65%	58%	0.634	0.115	64%	57%	0.616	0.184	75%	83%	0.818	0.005
Combination of all FET PET & MRI CE	70%	50%	0.643	0.093	68%	48%	0.621	0.166	63%	83%	0.794	0.009
Combination of TBR _{max} & TAC¶	65%	58%	0.639	0.101	64%	57%	0.622	0.163	75%	83%	0.828	0.003
Combination of TBR _{max} , TAC, & MRI CE	52%	75%	0.656	0.067	68%	48%	0.640	0.107	63%	100%	0.810	0.006
Combination of TBR _{max} & TTP**	96%	25%	0.591	0.287	96%	26%	0.576	0.382	44%	83%	0.750	0.026
Combination of TBR _{max} , TTP, & MRI CE	57%	58%	0.620	0.160	96%	17%	0.608	0.216	63%	67%	0.729	0.041

CE = contrast enhancement.

Boldface type indicates statistical significance.

* According to the 2007 WHO classification.

† According to the 2016 WHO classification (i.e., oligoastrocytomas are excluded).

‡ An optimal cutoff for TTP for cases with or without oligodendroglial glioma: 25 minutes.

§ The combinations of PET parameters were set up as follows: 0, FET-negative (TBR_{max} < 1.6); 1, FET-positive (TBR_{max} > 1.6); increasing TAC, and TTP > 25 minutes; 2, FET-positive (TBR_{max} > 1.6), plateau, and TTP > 25 minutes; 3, FET-positive (TBR_{max} > 1.6), plateau, and TTP < 25 minutes; and 4, FET-positive (TBR_{max} > 1.6), decreasing TAC, and TTP < 25 minutes. Combinations of PET parameters at 2, 3, and 4 were suggestive of malignant transformation.

¶ PET parameters are set up in the manner as mentioned above, excluding TTP.

** PET parameters are set up in the manner as mentioned above, excluding TAC.

FIG. 3. Kaplan-Meier estimates for nontransformed and transformed LGGs stratified by qualitative TAC patterns (increasing vs plateau vs decreasing) for PFS (A) and TTM (B). A significant difference is found between TAC patterns. Figure is available in color online only.

TTP < 25 minutes) had a significant influence with regard to the detection of malignant transformation ($p = 0.029$, $p = 0.039$, and $p = 0.027$, respectively). In contrast, surgical intervention for the initial tumor had no significant influence ($p = 0.828$).

Thus, after excluding the oligodendroglial subgroup (i.e., oligoastrocytoma and oligodendroglioma), the new ROC curve analysis using various combinations of FET PET parameters demonstrated significant increased ability to diagnose malignant transformation of LGGs, where the combined analysis of $TBR_{max} > 1.6$ and TAC patterns 2 and 3 yielded the best results (sensitivity 75%, specificity 83%, and AUC of 0.828; $p = 0.003$) without any obvious benefit of contrast enhancement on MRI alone or in combination with FET parameters. When excluding only patients with previous oncological treatment, however, ROC analysis showed only nonsignificant findings (data not shown). Finally, when excluding the oligodendroglial subgroup as well as cases in which the patient had previously undergone oncological treatment ($n = 20$), ROC analysis could not be performed for the FET PET parameters separately. However, a combined analysis of FET parameters ($TBR_{max} > 1.6$, TAC pattern 2 or 3 with or without TTP < 25 minutes) showed a significant differentiation between nontransformed and transformed LGGs with a sensitivity of 93%, a specificity of 100%, and AUC of 0.964 ($p = 0.001$).

Subsequent Tumor Management and Patient Outcome

Thirty (71%) patients received subsequent adjuvant chemo- and/or radiotherapy, after either histological verification of malignant transformation ($n = 23$; 55%) or a significant growth of the LGG ($n = 7$, 17%). Three (7%) patients died during the study period, all with histologically proven malignant transformation. The data are summarized in Table 2.

Discussion

Detection of disease progression in patients with LGG who have previously undergone treatment is of the utmost importance in planning the appropriate individual management, as it has a major impact on the fate of the patient. A common problem is whether a new focus of contrast enhancement on conventional MRI represents an area of treatment-related changes, or pseudoprogression, or tumor growth or malignant transformation.^{26,31} In addition, the subtle changes in findings between MRI examinations are frequently difficult to detect reliably by visual inspection of the images and can be easily misdiagnosed as stable by using only qualitative analyses. The detection might be further challenged by the irregular shape, especially after surgery and the heterogeneous composition of gliomas.³⁵ Hence, quantitative methods, such as diffusion- and perfusion-weighted MRI sequences and MR spectroscopy, could add information in the differentiation between treatment-related changes and tumor recurrence.²⁵ A recent meta-analysis of the ability of dynamic susceptibility contrast MRI to discriminate between grade II and III gliomas indicated acceptable diagnostic accuracy, particularly in patients with astrocytoma, while this was not the case for those with oligodendroglioma. There was, however, substantial methodological heterogeneity in this study.⁸ These methods were not used in the present study, as the aim was to assess the value of FET parameters combined with contrast enhancement on MRI derived using a basic clinical protocol enabling RANO criteria³⁶ for LGG monitoring in the routine management.

To date, the accurate diagnosis of tumor malignancy is determined by pathological examination of the tumor tissue obtained from either open surgery or stereotactic biopsy. In some cases, resection may not be warranted due to tumor location, e.g., in eloquent areas. Stereotactic biopsy is an option in these situations, although tumor heterogeneity

FIG. 4. Scatterplot showing the FET PET TBR_{max} as a function of IDH status. The median and IQR delineated are found to be significantly smaller when IDH status is positive. 0 = negative IDH status; 1 = positive IDH status.

neity carries a major risk of sampling bias and incorrect tumor grading, leading to an underestimation of the clinical severity. Hence, to achieve a better therapeutic outcome in the management of LGG growth, a noninvasive imaging technique that allows early tumor detection and correct assessment of possible malignant transformation is warranted.

In the present study, we evaluated the diagnostic value of FET PET scanning for the differentiation of LGGs with either progressive growth or malignant transformation after previously applied surgical and multimodal treatment. FET PET scans were performed only on indication in a selected subgroup with equivocal MRI findings. The results showed that diagnostic accuracy of FET PET was poor when reviewing ROC curve analyses for a mixed group of patients with and without oligodendroglial pathology. Although the median values of TBR_{max} and TBR_{mean} were higher in transformed LGGs compared with nontransformed ones, there was no significant difference between the standard metrics derived from analysis of the static FET PET_{20–40} scan. Furthermore, the dynamic evaluations of FET uptake, which previously has been shown to be a useful supportive parameter in tumor grading,^{6,12,14,16,18,29,30} did not allow for an accurate separation of transformed LGGs from nontransformed ones at any point. When investigating FET parameters combined, the ROC analysis was only able to show a trend toward a difference ($p = 0.067$) with a combination of TBR_{max} > 1.6 and TAC pat-

tern 2 or 3 in conjunction with contrast enhancement on MRI, with a low sensitivity of 52% and a moderate specificity of 75%. A multiple linear regression analysis was subsequently performed and demonstrated a significant independent modifying effect of an oligodendroglial tissue component in the ability of FET to identify nontransformed and transformed LGGs at the time of suspected malignant transformation. This finding is consistent with those of previous studies that have documented lower performance of FET PET in differentiating between WHO groups including oligodendrogliomas.^{14,27} Interestingly, the presence of an oligodendroglial component is not reported as a significant confounder if the change of FET PET parameters is used as an independent model variable.¹²

A subgroup of ROC curve analyses excluding patients with oligodendroglial tumors demonstrated a significant differentiation between nontransformed and transformed LGGs using different combinations of static and kinetic parameters (Table 3), where the best result was yielded by a combined analysis of TBR_{max} > 1.6 and TAC showing a plateau or decreasing pattern with a sensitivity of 75%, a specificity of 83%, and AUC of 0.828 ($p = 0.003$). After excluding only patients with previous oncological treatment but keeping those with oligodendroglial tumors, no significant difference was found, although previous oncological treatment was suggested as an independent variable by the linear regression model. Finally, when excluding the oligodendroglial tumors as well as tumors that had previously been treated, the combined FET PET parameters showed a significant high sensitivity of 93% and a specificity of 100% for differentiation between nontransformed and transformed LGGs ($p = 0.001$). Based on these results, PET with FET parameters, when assessed combined or in conjunction with conventional MRI, might provide valuable diagnostic information with higher diagnostic accuracy than that of MRI alone when evaluating a possible malignant progression in patients with previously treated LGGs. However, a single FET PET scan obtained at the time of radiological and/or clinical progression seems to be of limited value in distinguishing transformed LGGs from nontransformed ones, particularly if knowledge of the primary tumor histopathology is not known. Due to this concern, along with the high intervariability of FET uptake in gliomas, FET PET imaging alone is not sufficiently adequate to justify a clinical decision at this point, and a histological biopsy-based evaluation remains necessary for selected patients.

Over the last decade, FET PET has been increasingly used in several different clinical settings to optimize diagnosis and therapy in neurooncology (i.e., biopsy guidance, planning of surgery and radiotherapy).^{10,11} In addition, it has shown proven utility for monitoring the efficacy of treatment, differentiation of tumor recurrences from radiation-related damage, and prognosis.^{13,18} However, the results are not consistent throughout the literature. Studies vary widely in sample size, patient selection (i.e., untreated and/or pretreated), tumor characteristics (histological type, WHO grade, primary diagnosis, and/or recurrence), analysis methodologies, and data interpretation.^{2,6,12,14–16,18,27,29,30,33,34} In the present study, the cutoff value of TBR_{max} for differentiating tumor tissue from the healthy surrounding

tissue was set at 1.6 according to current European guidelines.²⁷ However, we were unable to determine a reliable discriminative cutoff value to differentiate transformed from nontransformed LGGs due to a marked overlap of FET uptake, in contrast to previously reported results.^{2,10} In a systematic review and meta-analysis by Dunet et al.,¹⁰ the authors reported significantly lower TBR_{mean} and TBR_{max} in LGGs than in HGGs (1.7 ± 0.7 [LGG] vs 2.6 ± 1.0 [HGG], $p < 0.001$ and 2.2 ± 0.9 [LGG] vs 3.1 ± 1.1 [HGG], $p < 0.001$, respectively). Albert et al.² reported that a standard analysis of the 20- to 40-minute time frame revealing a mean TBR_{max} with a cutoff value of 2.1 could significantly differentiate an unselected group of newly diagnosed LGGs from HGGs with a cutoff value of 3.3 ($p < 0.001$), but only with a moderate diagnostic accuracy (AUC of 0.704). They demonstrated that early TBR_{max} assessment (5–15 minutes postinjection) was more accurate for the differentiation between LGGs and HGGs due to a higher FET uptake of HGGs in the initial phase, with an improved AUC of 0.774. Another study reported similar results, but with an overall diagnostic accuracy no higher than 72%, indicating a limited diagnostic value.⁶ In contrast, Pauleit et al.²⁷ were unable to show any significant differences for the FET ratios among different WHO grades ($p = 0.123$). Jansen et al.¹⁴ reported similar results when investigating MRI-suspected de novo LGGs. The authors observed a high interindividual variability in FET uptake in gliomas, and only after excluding the oligodendroglial subgroup were the authors able to find significance in differentiating WHO groups ($p < 0.05$), which is in line with the present study. Finally, Galldiks et al.¹² investigated possible changes in FET uptake metrics from baseline to the time of suspected malignant transformation in multimodal-treated LGGs and reported that significant increases in FET uptake with TBR_{max} of more than 33% ($p = 0.002$) and TBR_{mean} of more than 13% ($p = 0.014$) as cutoff values, combined with TAC changes to a more malignant type, indicated malignant transformation, with an overall diagnostic accuracy of 81%. In contrast to the present study, the authors did not report the diagnostic accuracy of a single FET PET scan at the time of suspected malignant transformation. When reanalyzing their results at that time point, we were unable to find any significant differentiation between nontransformed and transformed LGGs (TBR_{max} , $p = 0.455$; TBR_{mean} , $p = 0.606$; TAC, $p = 0.059$; and TTP, $p = 0.145$). The results remained nonsignificant after excluding the oligodendroglial subgroup. In addition, when ROC analyses for single and combined FET parameters were generated, they were unable to demonstrate any significant difference between WHO subgroups, even after excluding the oligodendroglial subgroup. Thus, the diagnostic accuracy in this study was contingent on the changes in uptake and kinetic parameters from baseline within the same individual, while a single FET PET scan obtained at the time of suspected malignant transformation was of limited value. Furthermore, in initial FET-negative LGGs on baseline PET scanning, the advent of tumor uptake might indicate transformation. In other words, a baseline FET PET scan routinely obtained at the time of LGG diagnosis could be the most optimal to identify characteristic biological changes at later transformation, particularly for oligodendrogliomas, while a single FET

PET scan at the time of suspected malignant transformation might be primarily of value in the nonoligodendroglial subgroup.

The additional use of kinetic parameters has been reported to provide information about tumor biological behavior that might be useful in detecting HGGs.^{6,19} HGGs are characterized by an early peak of FET uptake at 10–15 minutes after tracer injection, followed by a decreasing TAC, while LGGs typically exhibit a steadily increasing TAC. In the present study, although malignant progression usually was seen in the cases with plateau and decreasing TAC, no significant prediction could be made at any point when investigating kinetic parameters separately. In 10 cases with nontransformed LGGs (21%), decreasing TAC was seen in 6 cases and plateau in 4. The decreasing TAC was found to be highly prognostic of shorter PFS and faster malignant transformation. It has previously been shown that the dynamic FET PET analysis could help in identifying LGGs that have a high risk of malignant progression over time.^{16,34} Unterrainer et al.³⁴ reported similar results in histologically proven LGGs with a short TTP (< 17.5 minutes) in 3 patients, who experienced a subsequent tumor progression shortly after (5–9 months). The authors suggested that an increased FET uptake and TTP < 17.5 minutes might be able to identify the risk of malignant transformation prior to MRI by depicting subcellular changes in the tumor biology.

Previous studies have reported high FET uptake in tumors with an oligodendroglial component and 1p19q codeletion.^{4,15} It has been suggested that a low FET uptake excludes an oligodendroglial differentiation and 1p19q codeletion with a high probability, whereas the high uptake might not be predictive of oligodendroglial tumors. Bette et al.⁴ reported a high FET uptake in LGGs with an oligodendroglial component ($TBR > 1.3$) and higher in LGGs with 1p19q codeletion ($TBR > 2.0$). These TBR values, however, are somewhat lower, compared with $TBR_{mean} > 1.9$ and $TBR_{max} > 2.6$ in the low-grade oligodendroglial tumors, and $TBR_{mean} > 1.9$ and $TBR_{max} > 2.7$ in LGGs with 1p19q codeletion in the present study. We found no significant correlation between FET uptake and gliomas with an oligodendroglial component or 1p19q codeletion. Only when a combination of static and kinetic FET PET parameters were investigated, both the linear regression model and ROC analyses show that the diagnostic value of FET PET was certainly influenced by gliomas with an oligodendroglial component.

The influence on molecular markers on FET uptake and the different static and dynamic uptake characteristics are not yet fully understood. IDH1 mutation status was inversely correlated with TBR_{max} , mostly within the range of $TBR_{max} > 1.6$ and < 3.0 , and TAC patterns. It has been shown that IDH1 mutation carries a better prognosis with longer survival in patients with gliomas and better response to chemotherapy. As only few studies have investigated the correlation between FET uptake and IDH1 mutation to date,^{1,17,24} certainty cannot yet be achieved. However, it has previously been suggested that the low frequency of IDH1 mutations with a decreasing TAC pattern might point toward a pathway typical for primary HGGs.⁴⁰ TBR_{max} correlated positively with increasing cell density, which is in accord with the literature.³² The difference be-

tween the median TBR_{max} in patients with nontransformed LGGs and in those with transformed LGGs was not significant due to overlapping distribution of FET uptake in these distinct tumor classes, thus hindering a discriminative cutoff value of TBR_{max} . However, FET PET still seems to be helpful in pure astrocytic tumors, and it is likely that targeting hot-spot areas on PET when performing biopsies is helpful.

Strength and Limitations

The study has several limitations inherent to its retrospective design and a small number of patients with histologically different LGGs and different treatment modalities. The results should therefore be considered with caution. Both contrast-enhancing and non-contrast-enhancing tumors on MRI were included in the study. The newest WHO classification, from 2016,²³ was gradually employed, and therefore, the histological analysis from the sampling period (2012–2015) did not hold the relevant information for reclassification for all tumors. Hence, few oligoastrocytomas were present as a diagnostic group. A number of surgeries and stereotactic biopsies were done using MRI-guided navigation, and it is plausible that the histopathology might be different from areas of FET PET positivity. In addition, the histopathological assessment of stereotactic tissue samples might not always yield their actual grade and/or extent due to glioma heterogeneity. The study did not focus on patient outcome in general, which might be influenced by different therapies, but was to describe FET PET findings, and to correlate these with concomitant MRI and histopathological findings. Nevertheless, the case group comprised patients who underwent surgery with and without adjuvant oncological treatment, which reflects the typical pattern of referral in clinical practice.

Conclusions

In this retrospective study, we have evaluated the diagnostic reliability of FET PET for assessing recurrent or progressive gliomas after previous surgical or multimodal treatment. The considerable interindividual variability of static FET uptake prohibits reliable individual tumor grading. In addition, the dynamic evaluations of FET uptake do not allow an accurate separation of transformed LGGs to HGGs from nontransformed ones at any point. After excluding the subgroup of oligodendroglial tumors, a combination of static and kinetic FET PET parameters was able to demonstrate a moderate sensitivity of 75% and specificity of 83% in distinguishing transformed from nontransformed LGGs as opposed to FET parameters separately or conventional MRI findings alone. The distinction was even greater after excluding previously oncologically treated tumors as well, with a high sensitivity of 93% and specificity of 100%. Hence, these results suggest that a single FET PET measured at the time of radiological and/or clinical progression has low diagnostic value, particularly if the primary tumor histopathology is not known. At this point, an FET PET scan alone is therefore not adequate to replace histological confirmation, but it may provide other valuable information on the location and delineation of active tumor tissue, as well as an assessment of tumor biology in a subgroup of LGGs.

Acknowledgments

The work was supported by a grant from the Danish Cancer Society (R146-A9508-16-S2).

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: all authors. Acquisition of data: Law, Bashir, Broholm. Analysis and interpretation of data: all authors. Drafting the article: Bashir. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Law. Statistical analysis: Bashir. Administrative/technical/material support: all authors. Study supervision: Law, Broholm.

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