Prognostic Value of O-(2-[^{18}F]Fluoroethyl) -L-Tyrosine PET/CT in Newly Diagnosed WHO 2016 Grade II and III Glioma

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Abstract

Purpose: The use of [^{18}F]fluoroethyl)-L-tyrosine ([^{18}F]FET) positron emission tomography/computed tomography (PET/CT) has proven valuable in brain tumor management. This study aimed to investigate the prognostic value of radiotracer uptake in newly diagnosed grade II or III gliomas according to the current 2016 World Health Organization (WHO) classification.

Procedures: A total of 35 treatment-naive patients (mean age, 48 ± 17 years) with histologically proven WHO grade II or III gliomas as defined by the current 2016 WHO classification were included. Static PET/CT imaging was performed 20 min after intravenous [^{18}F]FET injection. Images were assessed visually and semi-quantitatively using regions of interest for both tumor (SUVmax, SUVmean) and background (BKGmean) to calculate tumor-to-background (TBR) ratios. The association among histological results, molecular markers (including isocitrate dehydrogenase enzyme and methylguanine-DNA methyltransferase status), clinical features (age), and PET findings was tested and compared with outcome (progression-free [PFS] and overall survival [OS]).

Results: Fourteen patients presented with grade II (diffuse astrocytoma $n = 10$, oligodendroglioma $n = 4$) and 21 patients with grade III glioma (anaplastic astrocytoma $n = 15$, anaplastic oligodendroglioma $n = 6$). Twenty-seven out of the 35 patients were PET-positive (grade II $n = 8/14$, grade III $n = 19/21$), with grade III tumors exhibiting significantly higher amino acid uptake (TBR_{mean} and TBR_{max}; $p = 0.03$ and $p = 0.02$, respectively). PET-negative lesions demonstrated significantly prolonged PFS ($p = 0.003$) as compared to PET-positive gliomas. PET-positive disease had a complementary value in prognostication in addition to patient age, glioma grade, and molecular markers.

Olivia Kertels and Almuth F. Kessler contributed equally to this work.
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Conclusions: Amino acid uptake as assessed by [^{18}F]FET-PET/CT imaging is useful as non-invasive read-out for tumor biology and prognosis in newly diagnosed, treatment-naive gliomas according to the 2016 WHO classification.

Key Words: Glioma, FET, PET, WHO, Prognosis

Introduction

Positron emission tomography (PET) using O-(2-[^{18}F]fluoroethyl)-L-tyrosine ([^{18}F]FET) as a marker of amino acid uptake has proven its value in brain tumor management including grading [1–3], tumor extent delineation [4], biopsy guidance [5, 6], prognostication [7–9], treatment monitoring [10–12], as well as differentiation of unspecific post-therapeutic changes from tumor recurrence [13–15].

However, despite a growing body of literature [16–18], most studies have included gliomas categorized according to the World Health Organization (WHO) 2007 classification, which did not implement molecular features for glioma (sub-)classification [19]. Given the distinct tumor biology associated with the status of different molecular markers (such as O(6)-methylguanine-DNA methyltransferase (MGMT) promoter methylation and isocitrate dehydrogenase enzyme (IDH) mutation, or a 1p/19q co-deletion) and the subsequent implications for patient outcome [20], the WHO classification for CNS tumors was updated in 2016 to better reflect and integrate these new diagnostic features [21].

Given the well-established role of amino acid PET in brain tumor imaging, some pilot studies have taken into account brain tumor grading, molecular characteristics, or prognostication with respect to the new classification and generally confirmed the clinical value of PET using both [^{18}F]FET as well as 3,4-dihydroxy-6-[^{18}F]fluoro-L-phenylalanine ([^{18}F]DOPA) [17, 18, 22–25].

The aim of this study was to investigate the prognostic value of amino acid uptake as non-invasive read-out of tumor biology in treatment-naive WHO gliomas grade II and III according to and beyond the current 2016 WHO classification.

Material and Methods

Subjects

The present single-center retrospective cohort study included 35 consecutive patients with a newly diagnosed by magnetic resonance imaging (MRI), untreated brain lesion suspicious for WHO grade II or III glioma who were referred for further [^{18}F]FET-PET/CT work-up between October 2010 and September 2017. Subsequent histological proof (surgery, stereotactic biopsy) of the respective brain lesion was acquired in all subjects after a median of 24 days (range, 2–71 days). The study adhered to the standards established in the declaration of Helsinki. Given its retrospective nature, the local ethics committee of the University of Würzburg waived the requirement for additional approval. All subjects gave written informed consent prior to [^{18}F]FET-PET/CT imaging.

Tracer Synthesis and PET

Synthesis of [^{18}F]FET was performed in-house at the University Hospital of Würzburg using a GE TRACERlab FX-FN synthesis module (GE Medical Systems, Uppsala, Sweden) as previously described [26].

All patients fasted for at least 12 h before PET imaging [27]. Twenty minutes after intravenous injection of [^{18}F]FET (217 ± 13 MBq), patients were scanned using a dedicated PET/CT scanner (Siemens Biograph mCT 64, Siemens, Knoxville, USA). PET emission data were collected in three-dimensional mode using a 200 × 200 matrix for 10 min.

Subsequent CT scans for attenuation correction were acquired using a low-dose protocol (80 mAs, 120 kV, a 512 × 512 matrix, 5 mm slice thickness, increment of 30 mm/s, rotation time of 0.5 s, and pitch index of 0.8). Decay and scatter corrections were followed by iterative reconstruction of PET data with attenuation correction using dedicated software (HD, PET, Siemens Esoft).

Image Analysis

Images were analyzed according to methods by Fueger et al. [28]. In brief, image analysis began with a visual inspection of scan slices (M.M., C.L.). Upon identification of the axial image slice presenting the maximum tumor uptake, regions of interest (ROI) were selected. The first region consisted of a 15-mm-diameter circle centered on the area of peak activity and allowed calculation of maximum (SUV_{max}, T_{max}) and mean (SUV_{mean}, T_{mean}; defined as the mean SUV of the 15 mm ROI around the pixel with maximum uptake) standardized uptake values. A second region was selected in an area of normal-appearing brain tissue including white and gray matter on the contralateral hemisphere of the same slice. This normal reference region featured of 50 mm according to German guidelines [27]. SUV_{mean} (B_{mean}) of these regions were derived for calculation of mean and maximum tumor-to-background ratios (TBR_{max}; TBR_{mean}): The SUVs were derived from the radiotracer in the ROIS normalized to the injected dose per kilogram of patient's body weight.

Histopathology, WHO Grading, and Molecular Genetic Markers

All patients underwent either serial ([^{18}F]FET-PET-guided) stereotactic biopsy or surgery for histopathological analysis. Histological classification, molecular genetic analysis, and tumor grading were accomplished by an experienced neuropathologist (CMM).

The biopsy samples/surgical specimens were fixed in formalin and embedded in paraffin. All samples were histologically assessed and graded using 3–4 μm hematoxylin and eosin (H&E) stained sections according to the 2016 WHO criteria [21]. The astrocytic origin of the tumors was confirmed by positive immunoreaction for the glial fibrillary acidic protein (GFAP 1:200, Dako, Glostrup, Denmark). Oligodendroglial features were assured by the distinct pattern of microtubule-associated protein 2 immunoreactivity (MAP 2 1:250, Dako, Glostrup, Denmark). Immunohistochemistry for detection of the IDH1 R132H mutation was performed using the monoclonal antibody anti-IDH1 R132H (clone H09, 1:50, Dianova, Hamburg, Germany).

Co-deletion of 1p/19q was analyzed using fluorescence *in situ* hybridisation (FISH) according to standard protocols [29]. Determination of IDH1 mutation was performed using pyrosequencing of an 88-bp-long fragment of the IDH1 gene including the mutation hotspot at codon 132. For IDH2 mutations, pyrosequencing was performed on an 83-bp-long fragment of the IDH2 gene including the mutation hotspot at codon 172. In addition, determination of MGMT promoter methylation was performed using methylation-specific pyrosequencing [30].

Follow-up

Patient age, resection status (complete/incomplete resection [as assessed by early (<48 h) post-operative MRI], biopsy), histological results, molecular markers, and PET findings were correlated with outcome (progression-free [PFS, available in 33/35 patients] and overall survival [OS], available in all) as determined according to RANO recommendations [31, 32]. Follow-up data for calculation of progression-free (PFS) and overall survival (OS) was available for 31 ± 25 months (median, 8 m; range, 6–89) from the date of PET/CT.

Statistical Analysis

Quantitative data are presented as median, range, and mean ± SD. Pearson correlation was used to assess the association between two continuous variables. The Student's *t* test was used for unpaired comparisons of quantitative parameters. Univariate Cox regression was used for survival analyses.

Statistical analyses were performed in R (version 3.3.1) using package survival (Version 2.38). All statistical tests were two-sided and a p value < 0.05 was considered to indicate statistical significance. No correction of p values was applied to adjust for multiple tests.

Results

Patient Characteristics

Between October 2010 and September 2017, 35 consecutive patients (mean age, 48 ± 17 years) with treatment-naive, histologically proven WHO glioma grade II or III as defined by the WHO 2016 classification for CNS tumors were included in this study. Karnofsky performance status was well preserved, ranging between 80 and 100 % with a median of 100 %.

Fourteen patients were diagnosed with WHO grade II glioma (10 diffuse astrocytomas, 4 oligodendrogliomas) and 21 patients with WHO grade III glioma (15 anaplastic astrocytomas, 6 anaplastic oligodendrogliomas).

MGMT was methylated in 23/35 patients and 21/35 subjects were IDH mutated. Individual patient data as well as molecular features including IDH, MGMT, and 1p/19q were determined for each patient as shown in Table 1 and Supplemental Table 1 (see Electronic Supplementary Material (ESM)).

In total, 21/35 patients underwent surgery (4 complete resections) while stereotactic biopsy was performed in the remainder ($n = 14/35$). Subsequently, treatment was initiated in 26/35 subjects with administration of radiotherapy in 9/26 patients, chemotherapy with temozolomide in 4/26 and combined radiochemotherapy in 13/26 subjects. Eight out of 35 (7 grade II, 1 grade III) were followed up without treatment initiation. In the remaining patient, information on treatment regimens was not available.

During follow-up, 14 patients remained clinically stable (with PFS not available in 2 additional patients). Nineteen patients experienced disease progression; of these, 10 subjects died of their disease. No non-glioma-related deaths were observed.

PET Imaging Results and Semi-quantitative Image Analysis

In visual analysis, 27 out of 35 patients were PET-positive (grade II, $n = 8/14$, 4 diffuse astrocytomas, 4 oligodendrogliomas; grade III, $n = 19/21$, 13 anaplastic astrocytomas, 6 anaplastic oligodendrogliomas) with no different tumor uptake pattern noticed between the two different glioma grades. Notably, all oligodendrogliomas presented with increased [^{18}F]FET uptake, whereas 17 out of 25 astrocytomas (grade II, $n = 4/10$ and grade III, $n = 13/15$) were PET-positive.

Semi-quantitative image analysis demonstrated significantly higher amino acid uptake for WHO grade III gliomas as compared to WHO grade II (TBR_{mean}, 2.8 ± 0.5 *versus* 3.7 ± 1.4, $p = 0.03$; TBR_{max}, 3.7 ± 0.8 *versus* 4.8 ± 1.7; $p = 0.02$, respectively; Fig. 1). Histologic subtype could not be predicted from [^{18}F]FET uptake. Regarding molecular features, mutant IDH was present in six out of eight PET-negative patients. All MGMT non-methylated patients presented with metabolically active disease. Uptake values and calculated TBR values for individual patients are listed in Supplemental Table 2 (see ESM).

Table 1. Patient characteristics

	Number (%)
Sex	
Female	15 (43)
Male	20 (57)
Age	48 ± 17
KPS	
100 %	23 (66)
90 %	11 (31)
80 %	1 (3)
Diagnosis	
Diffuse astrocytoma, grade II	10 (29)
Oligodrendroglioma, grade II	4 (11)
Anaplastic astrocytoma, grade III	15 (43)
Anaplastic oligodrendroglioma, grade III	6 (17)
WHO	
Grade II	14 (40)
Grade III	21 (60)
Contrast enhancement in MRI	
Yes	11 (31)
No	24 (69)
IDH status	
Mutant	21 (60)
Wild type	11 (31)
Not known	3 (9)
1p/19q	
Positive	9 (26)
Negative	22 (63)
Not known	4 (11)
MGMT methylation	
Methylated	23 (66)
Non-methylated	6 (17)
Not known	6 (17)
Extent of resection	
Biopsy	14 (40)
IR	17 (49)
CR	4 (11)
Subsequent therapy	
RCTx	13 (37)
RTx	9 (26)
CTx	4 (11)
None	8 (23)
Not known	1 (3)

Age is given in years as mean ± standard deviation
CR complete resection, *CTx* chemotherapy with temozolomide, *IR* incomplete resection, *KPS* Karnofsky performance status, *RCTx* radio-chemotherapy, *RTx* radiotherapy

Prognostic Value of Histopathologic Diagnosis (Including Molecular Markers) and Individual Features

In the total cohort, there was no significant difference in PFS and OS between WHO glioma grades II and III ($p > 0.30$, respectively). With regard to histopathologic categorization, patients with oligodendroglioma had significantly longer PFS as compared to patients with astrocytoma (PFS, 27.2 ± 14.0 m *versus* 14.6 ± 13.9 m, $p = 0.04$; OS, $p = 0.16$).

Considering molecular features, both IDH mutation and MGMT methylation status proved to be significant prognostic factors. Patients with IDH mutant type showed a significantly longer PFS and OS with a mean of 23.9 ± 15.6 m and 35.6 ± 25.2 m (wild type, 7.0 ± 5.2 m and 15.5 ± 14.0 m; $p = 0.001$ and $p = 0.004$, respectively).

MGMT methylation status also conferred significantly longer PFS and OS (PFS, 21.2 ± 15.6 m *versus* 4.5 ± 2.6 m, $p = 0.001$; OS, 36.5 ± 25.8 m *versus* 7.8 ± 1.9 m, $p = 0.001$).

On the individual level, age correlated with outcome with older patients experiencing significantly shorter PFS ($r = -0.471$, $p = 0.006$) and a trend towards shorter OS ($r = -0.286$, $p = 0.095$).

No significant influence of the extent of tumor resection could be observed (PFS and OS for complete *versus* incomplete resection *versus* biopsy; all $p > 0.11$, respectively). Hazard ratios for the individual prognostic factors are derived from Fig. 4.

Prognostic Value of [^{18}F]FET-PET

PET negative lesions demonstrated a significantly prolonged PFS as compared to PET positive patients (23.1 ± 16.7 m *versus* 16.4 ± 14.2 m; $p = 0.003$, Fig. 2). Overall survival did not differ significantly between both groups ($p = 0.30$). Prognostic capability of [^{18}F]FET-PET/CT trended towards statistical significance in MGMT methylated (PFS, 27.6 ± 20.5 m *versus* 19.4 ± 14.0 m, $p = 0.05$) as well as IDH mutated tumors (PFS, 27.6 ± 20.5 m *versus* 19.4 ± 14.0 m, $p = 0.07$) and was significant in IDH wild-type tumors (PFS, 15.0 ± 2.8 m *versus* 5.2 ± 3.7 m, $p = 0.004$; trend for OS, 15.0 ± 2.8 m *versus* 15.6 ± 15.6 m, $p = 0.05$).

PET-negative patients demonstrated equally favorable outcomes irrespective of IDH mutation status (PFS, 23.1 ± 16.7 m (PET-/IDH mut and wt) *versus* 23.1 ± 14.8 m (PET+/IDH mut) *versus* 5.2 ± 3.7 m (PET+/IDH wt; $p = 0.052$ and $p < 0.001$, respectively; Fig. 3).

Additionally, the presence of all three beneficial features (IDH mutation, MGMT methylation, PET negativity) identified the subgroup with the best PFS as compared to all other patients (PFS, 27.6 ± 20.5 m *versus* 16.3 ± 13.4 m, $p = 0.02$, OS, 27.8 ± 20.7 m *versus* 30.8 ± 26.0; $p = 0.67$).

Hazard ratios regarding PFS and OS for all prognostic factors (both clinical and imaging-based) are given in Fig. 4.

Discussion

This study confirms [^{18}F]FET-PET/CT as non-invasive readout for prognostication in patients with newly diagnosed and treatment-naïve grade II and III glioma as categorized according to the current 2016 WHO classification for CNS tumors. Irrespective of patient age, resection status, underlying histopathologic glioma biology or molecular markers, [^{18}F]FET-PET negativity inferred significantly better outcome in terms of longer PFS and trended towards longer OS. Whereas patient age as well as both MGMT methylation and IDH mutation status were also prognostic factors for PFS and OS, conventional histopathologic finding was correlated neither with progression-free nor with overall survival. Notably, only one PET-negative patient experienced tumor progression during follow-up (potentially due to tumor de-

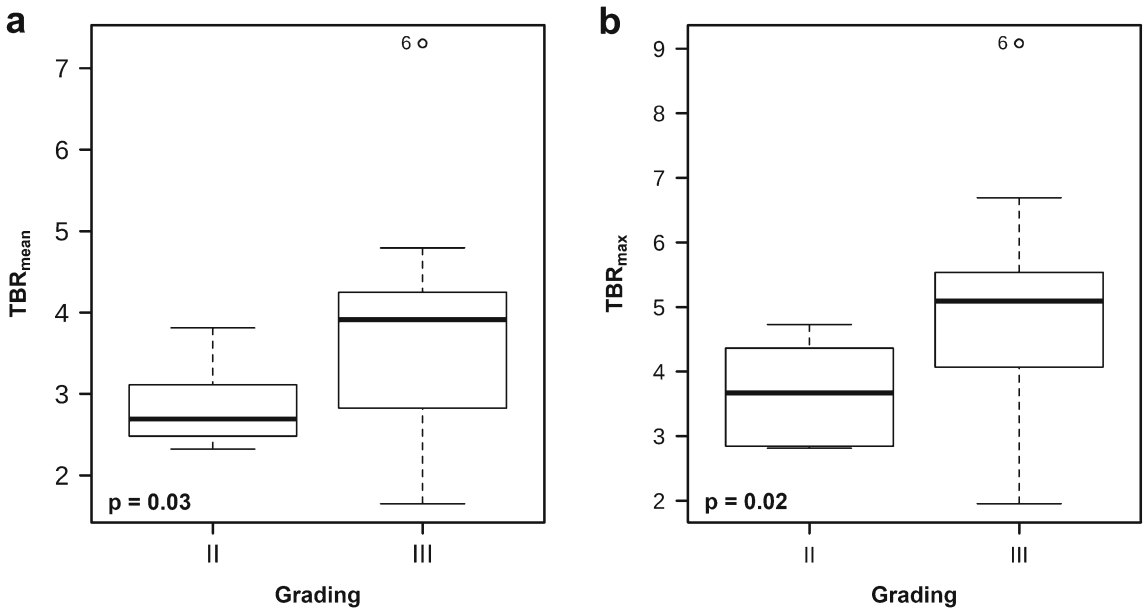


Fig. 1 **a** [^{18}F]FET-PET-derived mean (TBR_{mean}) and **b** maximum (TBR_{max}) tumor-to-background ratios (TBR) in newly diagnosed WHO grade II and III glioma. WHO grade III gliomas demonstrate significantly higher TBR_{mean} as well as TBR_{max} as compared to grade II tumors (TBR_{mean}, 2.8 ± 0.5 *versus* 3.7 ± 1.4, $p = 0.03$; TBR_{max}, 3.7 ± 0.8 *versus* 4.8 ± 1.7; $p = 0.02$, respectively).

differentiation as described in [9]), which is in line with previous reports on the prognostic value of [^{18}F]FET-PET/CT with beneficial outcomes in amino acid PET-negative disease [22, 33, 34].

The combination of [^{18}F]FET-PET/CT results and molecular markers yielded complementary prognostic information. In detail, PET negativity predicted significantly longer PFS and a favorable OS trend in IDH wild-type patients. In IDH mutated patients, PET trended towards PFS prediction (with 6 out of 8 PET-negative cases presenting with mutant

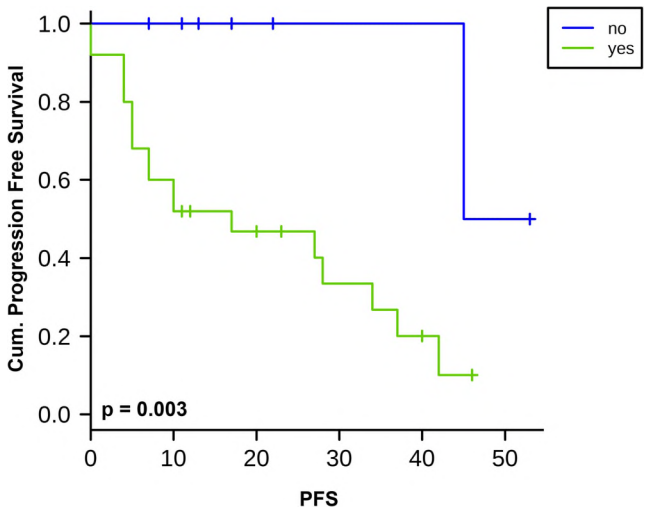
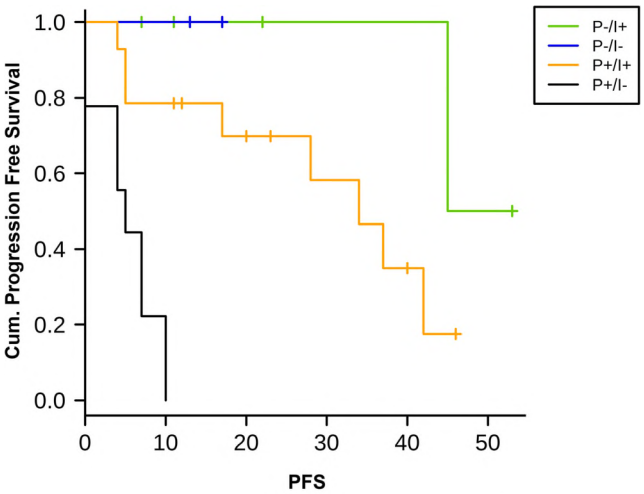


Fig. 2 Cumulative (cum.) progression-free survival (PFS) in newly diagnosed WHO grade II and III glioma according to [^{18}F]FET-PET positivity (yes) or negativity (no). PET negative patients presented with significantly longer PFS than PET-positive subjects (23.1 ± 16.7 m *versus* 16.4 ± 14.2 m; $p = 0.003$). PFS is given in months.



PFS	IDH+ & PET-	IDH- & PET-	IDH- & PET+
IDH- & PET-	1		
IDH- & PET+	**0.001**	**0.005**	
IDH+ & PET+	0.072	0.300	**0.001**

Fig. 3 Cumulative progression-free survival (PFS) in newly diagnosed WHO grade II and III glioma according to [^{18}F]FET-PET positivity (P+) or negativity (P–) and IDH mutational status (I+ = IDH mutation, I– = IDH wild type). PET-negative patients present with equally favorable PFS irrespective of IDH mutation status. In [^{18}F]FET-positive disease, IDH wild type signifies significantly shorter PFS. Separate *p* values are given in the table.

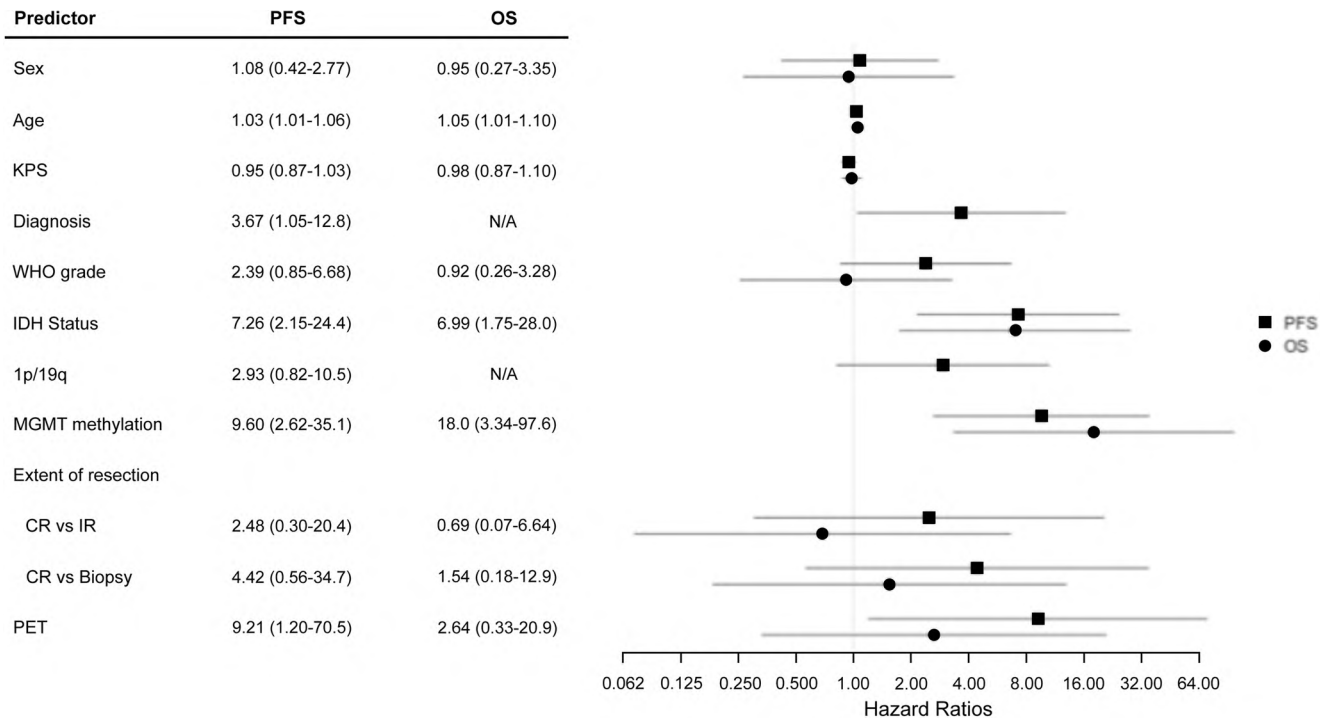


Fig. 4. Hazard ratios (and 95 % confidence intervals) for progression-free (PFS) and overall survival (OS) for various clinical, molecular, and imaging-based factors. The category "Diagnosis" compares astrocytoma *versus* oligodendroglioma.

IDH status). Furthermore, PET negativity proved a favorable prognostic factor irrespective of IDH mutation status.

In MGMT methylated glioma, PET negativity also trended to demonstrate beneficial PFS. In contrast, all MGMT non-methylated patients presented with [^{18}F]FET-PET-positive disease.

Although no final conclusions can be drawn from this rather small retrospective study, amino acid PET/CT can be considered a robust tool for visualization of glioma biology, even when using the current 2016 WHO classification for brain tumors. Thus, these results add to the growing body of evidence that amino acid PET retains its prognostic value in newly diagnosed glioma [22, 23] and may assist in non-invasive determination of molecular characteristics such as IDH mutation status with dynamic PET imaging demonstrating particularly promising results for non-invasive glioma characterization [17, 18, 22]. Further prospective trials are needed to fully elucidate the potential of this technique in brain tumor diagnostics and management.

In line with previous literature, all gliomas with oligodendroglial differentiation exhibited intense tracer accumulation [35, 36]. Also concordant to previous studies demonstrating the correlation of higher levels of L-type amino acid transporter 1 (LAT1) expression with high-grade gliomas [37], WHO grade III gliomas exhibited significantly higher TBR_{mean} and TBR_{max} than grade II gliomas in our cohort. Still, given the substantial overlap between the two groups, a significant correlation between semi-quantitative SUV uptake and grading pattern solely by [^{18}F]FET-PET/CT is lacking [36, 38]. Additionally, tumor grading might not be the most relevant indication for [^{18}F]FET-PET/CT with the broad implementation of molecular glioma features.

The current study has several limitations. It is retrospective and comprises only a limited number of patients, all featuring different tumor histologies, differentiation grades, and varying follow-up, thus limiting statistical power. Multivariate Cox regression analyses were limited by the total number of patients and events, respectively. Dynamic PET acquisitions for further analysis were not available. However, the present setting including static imaging only reflects the situation for centers with a heavy daily workflow. Heterogeneity of subsequent treatment protocols has to be acknowledged and might have confounded outcome results.

Our approach to both tumor delineation and tracer uptake analysis varied slightly from methods previously described, with a different approach for derivation of tumor SUV [2, 4, 13]. Despite ongoing research, standardization of image analysis in [^{18}F]FET-PET remains to be accomplished. Selection of a single approach could facilitate comparisons between study centers as well as potentially establish an optimal technique for future research. In fact, standardization is strongly emphasized in the current RANO/EANO recommendations for the clinical use of PET imaging in gliomas [39]. This might, however, be achieved in the near future. A first step has already been taken through the recent release of new technical guidelines for glioma PET imaging protocols by the Response Assessment in Neuro-Oncology, European

Association of Neuro-Oncology, and European Association of Nuclear Medicine which advocate the use of crescent-shaped volumes of interest for background delineation [40].

Despite the limitations outlined, our data confirm [^{18}F]FET-PET/CT as a robust means of tumor biology visualization. In PET-positive disease, it was able to stratify patient risk groups in addition to the more established molecular markers MGMT and IDH. Future larger multi-center trials to further validate our findings are highly warranted.

Conclusion

Amino acid uptake as assessed by [^{18}F]FET PET/CT is useful as a non-invasive read-out for tumor biology and prognosis in newly diagnosed, treatment-naive gliomas as categorized according to the 2016 WHO classification. Further larger, prospective and multi-center studies are warranted.

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Conception and design: OK, MIM, TL, AFK, CL
Development of methodology: AS, SSa, SB, CMM, ML, CL
Acquisition of data: OK, MIM, TL, AKB, ML, AFK, CL
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Writing, review and/or revision of the manuscript: all authors
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Supervision: RIE, AKB, ML, AFK, CL.

Compliance with Ethical Standards. The study adhered to the standards established in the declaration of Helsinki. Given its retrospective nature, the local ethics committee of the University of Würzburg waived the requirement for additional approval. All subjects gave written informed consent prior to [^{18}F]FET-PET/CT imaging.

Conflict of Interest

The authors declare that they have no conflict of interest.

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