TSPO PET Signal is Associated with Survival in Recurrent Gliomas

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Research Article

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Abstract

Purpose

Glioma patients, especially recurrent glioma, suffer from a poor prognosis. While advances to classify glioma on a molecular level improved prognostication at initial diagnosis, markers to prognosticate survival in the recurrent situation are still needed. As 18 kDa translocator protein (TSPO) was previously reported to be associated with aggressive histopathological glioma features, we correlated the TSPO positron emission tomography (PET) signal in a large cohort of recurrent glioma patients with their clinical outcome.

Methods

In patients with TSPO PET at glioma recurrence, TSPO PET parameters (e.g. SUV_{max}) as well as other imaging features (e.g. MRI volume, [^{18}F]FET PET parameters when available) were evaluated together with patient characteristics (age, sex, Karnofsky-Performance score) and neuropathological features (e.g. WHO grade, *IDH*-mutation status). Uni- and multivariate Cox regression and Kaplan-Meier survival analyses were performed to identify prognostic factors for post-recurrence survival (PRS) and time to treatment failure (TTF).

Results

88 consecutive patients were evaluated. TSPO tracer uptake correlated with tumor grade at recurrence ($p < 0.05$), with no significant differences in *IDH*-wildtype versus *IDH*-mutant tumors. Within the subgroup of *IDH*-mutant glioma (n = 46), patients with low SUV_{max} (median split, ≤ 1.60) had a significantly longer PRS (median 41.6 vs. 25.3 months, $p = 0.031$) and TTF (32.2 vs 8.7 months, $p = 0.001$). Also among *IDH*-wildtype tumors (n = 42), patients with low SUV_{max} (≤ 1.89) had a significantly longer PRS (median not reached vs 8.2 months, $p = 0.002$). SUV_{max} remained an independent prognostic factor for PRS in the multivariate analysis including CNS WHO grade, *IDH* status and age. Tumor volume defined by [^{18}F]FET PET or contrast-enhanced MRI correlated weakly with TSPO tracer uptake. Treatment regimen did not differ among the median split subgroups.

Conclusion

Our data suggest that TSPO PET can help to prognosticate recurrent glioma patients even among homogeneous molecular subgroups and may therefore serve as valuable non-invasive biomarker for individualized patient management.

Key Points

QUESTION: to assess the prognostic value of TSPO PET in recurrent glioma.

PERTINENT FINDINGS: In this prospective observational study, recurrent glioma patients with low TSPO PET signal survived significantly longer, even within molecularly defined subgroups of *IDH*-mutant and *IDH*-wildtype glioma.

IMPLICATIONS FOR PATIENT CARE: TSPO PET may serve as prognostic biomarker and provide additional information to the neuropathological diagnosis, which may help to stratify patients for individualized treatment concepts.

Introduction

Diffuse gliomas are the most frequent adult primary brain tumors [1] and almost all relapse after initial treatment. Efforts to understand the molecular mechanisms and prognostic factors of these heterogeneous tumors have led to the discovery of molecular markers which shape the most recent 2021 World Health Organization (WHO) classification of brain tumors to distinguish different glioma subgroups [2]. This molecular classification is mirrored in the current treatment guidelines [3]. All guidelines emphasize magnetic resonance imaging (MRI) as the gold standard for diagnostic imaging to gain information about the presumable histology and composition of the lesion as well its extent and, as a consequence, its amenability for treatment and its potential prognosis [4]. Beyond MRI, amino acid PET such as [^{18}F]Fluoroethyltyrosine (FET) positron emission tomography (PET) has proven valuable to delineate tumor extent, identify intratumoral heterogeneity and distinguish recurrent disease from pseudoprogression [5–7]. Subsequently, amino acid PET has entered current diagnostic guidelines for primary and recurrent glioma [8, 9]. However, it is becoming increasingly clear that the interplay between tumor cells and the tumor microenvironment plays an important role in disease progression and treatment response or resistance. In this context, tumor associated macrophages and microglia gain considerable attention, also in recurrent glioma [10–12]. Thus, PET imaging of the respective cellular elements is of interest to provide insight into the tumor mircroenvironment and tumor-host interaction. As such, PET imaging of the 18 kDa translocator protein (TSPO) as a marker of activated microglia and neuroinflammation [13] has shown increased uptake in glioma patients, as well [14–17].

TSPO is a mitochondrial membrane protein with a variety of functions in health and disease. Beyond classical mitochondrial functions such as respiration and oxidative stress regulation, more diverse functions such as cell proliferation and apoptosis have recently been implied [18]. TSPO is expressed ubiquitously and upregulated in steroid synthesizing cells, microglial and malignant cells [18].

Preliminary data show an upregulation of TSPO expression in high-grade glioma and hint at a correlation between histologically increased TSPO expression and shorter survival, yet this was before description of molecularly defined glioma subgroups [19, 20]. To visualize TSPO expression and its spatial distribution in vivo, different radiolabeled TSPO ligands such as [^{11}C]-(R)PK11195 were used and shown to correlate with histological TSPO expression [21], but usability was limited by a low binding affinity or a short half-

life of [^{11}C]. In contrast, the third generation TSPO radioligand [^{18}F]GE180 shows a high binding affinity [22] and convenient half-life for the clinical use due to the labelling with [^{18}F]. In glioma patients, tracer uptake volumes were reported to exceed areas of contrast enhancement on MRI [23]. Several clinical case series showed a trend of higher TSPO tracer uptake in histologically or molecular biologically more aggressive tumors, such as isocitrate dehydrogenase (*IDH*) wildtype tumors [24, 25]. We here aim to describe the relationship between TSPO tracer uptake and clinical outcome in molecularly defined groups of recurrent glioma patients.

Methods

Patients

Eligible were patients with a histologically verified glioma and an [^{18}F]GE180 PET at recurrence as suspected by Response Assessment in Neuro-Oncology (RANO) criteria [26] between 2016 and 2020. All patients with histologically or clinically verified progression were included in the analysis. All patients provided written informed consent. The study was approved by the local ethics committee (No. 16–601, 17–769).

Imaging acquisition and analysis

All PET scans were performed on a Biograph 64 PET/CT scanner (Siemens, Erlangen, Germany). Tracer production and image acquisition were performed as described previously [25]. For [^{18}F]GE180 PET, approximately 180 MBq [^{18}F]GE180 were injected as an intravenous bolus and summation images 60–80 minutes post injection (p. i.) were used for image analysis. Maximal tumor uptake was assessed as maximum standardized uptake value (SUV_{max}). For [^{18}F]FET PET, approximately 180 MBq [^{18}F]FET were injected and 0–40 minutes p. i. dynamic scans were analysed using a Hermes workstation (Hermes Medical Solutions, Stockholm, Sweden). As described previously [27], the mean background activity was defined as the mean activity of at least 6 crescent-shaped cortical areas in the healthy contralateral side and SUV_{max} was divided by the mean background activity to obtain maximum tumor-to-background ratio (TBR_{max}). The biological tumor volume was semiautomatically delineated using the standard 1.6 background activity as threshold. Routine MRI included gadolinium-enhanced T1- and T2-weighted images. MRI volumes were calculated using BRAINLAB ELEMENTS™ (Brainlab AG, Munich, Germany).

Neuropathological analysis

All tumors were classified according to WHO 2016 [28] at the Center for Neuropathology and Prion Research of the University of Munich and re-classified according to WHO 2021 [2] retrospectively. *IDH* mutation status was determined by PCR analysis of hotspots R132 of the *IDH1* and R172 of the *IDH2* gene locus. Sanger sequencing was used to detect telomerase reverse transcriptase (*TERT*) promoter mutations, as well as microsatellite analysis for detection of 1p and 19q deletions. O^6-methylguanine-DNA methyltransferase (*MGMT*) promoter methylation was analyzed by methylation-specific polymerase

chain reaction and sequencing analysis. *MGMT* promoter methylation status was classified dichotomously as methylated or unmethylated.

Data analyses

Post-recurrence survival (PRS) was defined as the time between MRI suggestive of recurrence initiating PET imaging and date of death. Time to treatment failure after recurrence (TTF) was defined as the time between MRI showing recurrence and MRI showing further recurrence according to RANO criteria. Categorical variables were compared by $\chi 2$ test, and continuous variables were compared by the Mann–Whitney U test. Pearson's correlation coefficient was used to test for correlation between two continuous variables. Uni- and multivariate Cox regression and Kaplan-Meier survival analyses were performed to identify prognostic factors for post-recurrence survival (PRS) and time to treatment failure (TTF). $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS statistics version 23 (IBM, Armonk, New York, USA).

Results

Patients

[^{18}F]GE180 PET scans of 88 recurrent glioma patients were evaluated. Median age was 49 years (range 23.6–71.9). 56 (63.6%) patients were male, 32 female (36.4%). 42 (47.7%) tumors were diagnosed as *IDH*-wildtype glioblastoma, 46 (52.3%) as *IDH*-mutant glioma. Among all 28 *IDH*-mutant astrocytoma, 10 were classified as WHO grade 4, 17 as WHO grade 3 and one as WHO grade 2, respectively. 18 tumors were classified as oligodendroglioma, *IDH*-mutant, and 1p/19q-codeleted, 11 WHO grade 3 and 7 WHO grade 2.

Median follow-up time was 15.6 months (95% confidence interval (CI): 13.3–18.0 months). In 59 (67.0%) cases, tumor recurrence was verified histologically, in all other cases, further clinical course confirmed tumor recurrence. All cases of low-grade tumors with new contrast enhancement or new [^{18}F]FET enhancement were histologically verified to prove or rule out malignant transformation. Radiotherapy was performed in 60 cases (68.2%), 26 of them (29.5% of all patients) in combination with chemotherapy. Chemotherapy alone was administered in 22 cases (25.0%), 15 (17.0%) patients received an open tumor resection, 3 (3.4%) received other/experimental treatment and 3 received best supportive care due to clinical deterioration or refusing therapy. Binding affinity status was available for 78 patients; of these, 7 (9.0%) were low-affinity binders, 27 (34.6%) were medium-affinity binders, and 44 (56.4%) were high-affinity binders.

PET Specifications According to Patient Groups

SUV_{max} values were correlated with CNS WHO grade (Table 1). No significant difference was found between recurrent *IDH*-mutant and *IDH*-wildtype tumors.

Table 1

[^{18}F]GE180 uptake characteristics in the examined patient population.

All recurrent gliomas	**SUV_{max} (median (range))**	**P-value**
Overall (n = 88)	1.68 (0.59–4.36)	
Male (n = 56)	1.73 (0.59–3.83)	0.370
Female (n = 32)	1.56 (0.59–4.36)	
CNS WHO grade 2 (n = 8)	**0.90 (0.59–3.83)**	**0.031**
CNS WHO grade 3 (n = 28)	**1.45 (0.59–3.82)**	
CNS WHO grade 4 (n = 52)	**1.91 (0.85–3.83)**	
IDH-mutant (n = 46)	1.60 (0.59–4.36)	0.071
IDH-wildtype (n = 42)	1.89 (0.85–3.83)	
IDH mut. -1p/19 codel (n = 28)	1.72 (.59-3.79)	0.714
IDH mut. +1p/19 codel (n = 18)	1.28 (.61-4.36)	
IDH wt, TERT wildtype (n = 5)	1.70 (1.29–3.83)	0.909
IDH wt, TERT mutant (n = 22)	1.89 (1.00-3.12)	
IDH wt, MGMT methylated (n = 19)	2.29 (0.85–3.83)	0.114
IDH wt, MGMT unmethylated (n = 22)	1.81 (1.00-3.03)	
Low-affinity binding status (n = 7)	2.32 (0.80–3.79)	0.231
Medium-affinity binding status (n = 27)	1.76 (0.59–3.08)	
High-affinity binding status (n = 44)	1.58 (0.61–3.83)	

SUV_{max} – maximum standardized uptake value, CNS WHO – World Health Organization Classification of Tumors of the Central Nervous System, IDH – isocitrate dehydrogenase, TERT – telomerase reverse transcriptase

Post-recurrence treatment

Among all 42 patients with *IDH*-wildtype tumors, 3 patients with a lower SUV_{max} and 2 patients with a higher SUV_{max} received an open tumor resection as part of their recurrence treatment (p = 0.892). Among patients with *IDH*-mutant tumors, 7 with a lower SUV_{max} and 3 with a higher SUV_{max} received an open tumor resection (p = 0.355). Systemic post-recurrence therapies did not differ between patients with a lower or higher SUV_{max} (p = 0.215 for *IDH*-wildtype, p = 0.302 for *IDH*-mutant tumors, Table 2).

Table 2
Treatment regimens in patients with lower or higher than median SUV_{max}.

	SUV_{max} ≤ median (n; %)	SUV_{max} > median (n; %)	P-value
IDH-wildtype (n = 42)	21 (100)	21 (100)	0.215
Radio-and chemotherapy	7 (33.3)	5 (23.8)	
Radiotherapy only	7 (33.3)	8 (38.1)	
Chemotherapy only	4 (19.0)	6 (28.6)	
Experimental/others	0 (0.0)	2 (9.5)	
No tumor-specific therapy	3 (14.3)	0 (0.0)	
IDH-mutant (n = 46)	23 (100)	23 (100)	0.302
Radio-and chemotherapy	7 (30.4)	7 (30.4)	
Radiotherapy only	12 (52.2)	7 (30.4)	
Chemotherapy only	4 (17.4)	8 (34.8)	
Experimental/others	0 (0.0)	1 (4.3)	

SUV_{max} – maximum standardized uptake value, IDH – isocitrate dehydrogenase

Post-recurrence survival and time to treatment failure

Overall, uptake intensity on TSPO PET at recurrence was highly associated with patients' outcome: patients with low SUV_{max} (≤ 1.68; median split) survived more than three times longer than those with high SUV_{max} (median 41.6 vs. 12.6 months; $p < 0.001$). Also, the TTF was significantly longer in cases with low SUV_{max} (14.9 vs. 6.2 months; $p < 0.001$). Other significant factors in the univariate analysis were *IDH* and CNS WHO grade for TTF (both $p < 0.001$) and PRS ($p < 0.001$ and $p = 0.001$). In the multivariate analysis, SUV_{max} remained an independent significant factor for PRS ($p = 0.027$) and TTF ($p = 0.032$), whereas CNS WHO grade ($p = 0.016$) was the only other independent factor for TTF. Accordingly, the association between uptake intensity on TSPO PET and outcome was likewise found in the subgroups of molecularly defined tumors: for patients with recurrent *IDH*-wildtype tumor, median PRS after recurrence was 8.2 months for patients with an SUV_{max} higher than the median of 1.89, and not reached for patients with a lower SUV_{max} ($p = 0.002$). TTF after recurrence was 6.1 months (6.8 vs. 5.4 months, $p = 0.142$).

Among patients with *IDH*-mutant tumors, median PRS was 36.9 months and TTF was 18.4 months. PRS was significantly longer in patients with low SUV_{max} (≤ 1.60; median split; 41.6 vs. 25.3 months, $p = 0.031$, see Fig. 1). This difference was also found for TTF (32.2 vs 8.7 months, $p = 0.001$), also in the subgroups of all astrocytoma, *IDH*-mutant, and even within the very homogeneous subgroup of CNS WHO

grade 3 astrocytoma, *IDH*-mutant. The small subgroup of oligodendroglioma, *IDH*-mutant and 1p/19q codeleted, did not have enough events for a separate statistical evaluation (see Table 3).

Table 3
Survival of recurrent glioma patient groups according to tracer uptake.

All recurrent glioma cases	PRS (median; months)	P-value	TTF (median; months)	P-value
All diagnoses (n = 88)	**27.9**	**< 0.001**	**8.7**	**< 0.001**
SUV_{max} ≤ 1.68 (n = 44)	**41.6**		**14.9**	
SUV_{max} > 1.68 (n = 44)	**12.6**		**6.2**	
All IDH-wildtype (n = 42)	**10.6**	**0.002**	6.1	0.142
SUV_{max} ≤ 1.89 (n = 21)	**Not reached**		5.4	
SUV_{max} > 1.89 (n = 21)	**8.2**		6.8	
All IDH-mutant (46)	**36.9**	**0.031**	**18.4**	**0.001**
SUV_{max} ≤ 1.60 (n = 23)	**41.6**		**32.2**	
SUV_{max} > 1.60 (n = 23)	**25.3**		**8.7**	
All astrocytoma, IDH-mutant (28)	**27.9**	**0.009**	**11.7**	**0.007**
SUV_{max} ≤ 1.72 (14)	**36.9**		**22.6**	
SUV_{max} > 1.72 (14)	**13.5**		**6.2**	
Astrocytoma WHO grade 3, IDH mutant (17)	**36.9**	**0.015**	**11.7**	**0.025**
SUV_{max} ≤ 1.55 (9)	**36.9**		**32.2**	
SUV_{max} > 1.55 (8)	**13.1**		**2.7**	
All low-grade (2 or 3) astrocytoma, IDH-mutant (18)	**36.9**	**0.003**	14.5	0.063
SUV_{max} ≤ 1.33 (9)	**36.9**		32.2	
SUV_{max} > 1.33 (9)	**13.1**		6.2	
All oligodendroglioma, IDH-mutant and 1p/19q codeleted (18)	Not reached	0.464	Not reached	0.147
SUV_{max} ≤ 1.28 (9)	Not reached		Not reached	
SUV_{max} > 1.28 (9)	Not reached		18.4	

SUV_{max} – maximum standardized uptake value, IDH – isocitrate dehydrogenase; PRS – post recurrence survival; TTF – time to treatment failure

Subgroup analyses

Among patients with *IDH*-wildtype glioma and a high [^{18}F]GE180 SUV_{max}, slightly more tumors were *MGMT*-methylated than in the subgroup of patients with a lower SUV_{max} (Table 4). *MGMT*-methylated tumors tended to be treated with chemotherapy, either alone or combined with radiotherapy, more often than unmethylated tumors (63.2% vs 45.5%, p = 0.257). In the 35 *IDH*-wildtype tumors for whom additional [^{18}F]FET PET was available, [^{18}F]FET TBR_{max} was higher in the subgroup with high [^{18}F]GE180 uptake, while [^{18}F]FET PET based volume did not differ significantly. Inversely, no significant difference in TTF (p = 0.954) or PRS (p = 0.950) could be seen between patients with a TBR_{max} higher or lower than the median of 3.18 (Supplementary Fig. 1).

Table 4

Characteristics of high and low [^{18}F]GE180 uptake groups.

	SUV_{max} ≤ median (n; % or median; range)	**SUV_{max} > median** (n; % or median; range)	**P-value**
IDH-wildtype (n = 42)	21 (50.0)	21 (50.0)	0.739
Male / female sex	14 / 7 (33.3 / 16.7)	15 / 6 (35.7 / 14.3)	0.427
MGMT methylated / unmeth. (n = 41)	8 / 12 (19.5 / 29.3)	11 / 10 (26.8 / 24.4)	0.223
TERT wildtype / mutant (n = 27)	4 / 11 (14.8 / 40.7)	1 / 11 (3.7 / 40.7)	0.858
Age	55.5 (32.3–70.0)	55.8 (30.8–70.2)	**0.045**
[^{18}F]FET TBR_{max} (n = 35)	3.10 (1.55–4.83)	3.44 (2.47–5.28)	0.109
[^{18}F]FET tumor volume (n = 35)	12.60 (0.0-76.66)	28.71 (4.49-124.75)	0.075
T2 volume	50.80 (0.0-198.10)	80.10 (8.09–337.3)	**0.022**
Contrast volume	3.74 (.27-66.2)	16.50 (0.0-85.6)	
IDH-mutant (n = 46)	23 (50.0)	23 (50.0)	0.369
Male / female sex	12 / 11 (26.1 / 23.9)	15 / 8 (32.6 / 17.4)	**0.004**
CNS WHO grade 2 / 3 / 4	7 / 15 / 1 (15.2 / 32.6 / 2.2)	1 / 13 / 9 (2.2 / 28.3 / 19.6)	0.437
MGMT methylated / unmeth.	20 / 3 (43.5 / 6.5)	18 / 5 (39.1 / 10.9)	0.686
TERT wildtype / mutant (n = 28)	9 / 5 (32.1 / 17.9)	10 / 4 (35.7 / 14.3)	0.456
Age	47.5 (23.6–66.2)	39.8 (29.1–71.9)	**< 0.001**
[^{18}F]FET TBR_{max} (n = 42)	2.51 (1.21–5.29)	4.15 (2.88–7.49)	**0.002**
[^{18}F]FET tumor volume (n = 42)	5.14 (0.0-100.87)	33.08 (1.67-172.04)	0.303
T2 volume	50.7 (13.90-226.50)	59.15 (9.13–253.90)	**0.002**
Contrast volume	0.06 (0.0-12.70)	10.10 (0.0-61.2)	

SUV_{max} – maximum standardized uptake value, IDH – isocitrate dehydrogenase, TERT – telomerase reverse transcriptase, [^{18}F]FET – [^{18}F]Fluoroethyltyrosine, TBR_{max} – maximum tumor-to-brain-ratio, CNS WHO-World Health Organization Classification of Tumors of the Central Nervous System

	SUV_{max} ≤ median (n; % or median; range)	SUV_{max} > median (n; % or median; range)	P-value
Astro, IDH mut., grade 3 (n = 17)	9	8	0.893
Male / female sex	7 / 2 (41.2 / 11.8)	6 / 2 (35.3 / 11.8)	0.490
MGMT methylated / unmeth.	7 / 2 (41.2 / 11.8)	5 / 3 (29.4 / 17.6)	0.198
Age	45.1 (29.9–56.3)	37.4 (30.4–57.6)	**0.001**
[^{18}F]FET TBR_{max}	2.01 (1.56–3.82)	4.91 (3.08–5.86)	**0.016**
[^{18}F]FET tumor volume	3.21 (0.00-71.96)	78.87 (11.44-172.04)	0.842
T2 volume	39.10 (15.70-226.50)	63.50 (12.40-110.10)	**0.013**
Contrast volume	0.00 (0.00-12.20)	16.04 (3.84–61.20)	

SUV_{max} – maximum standardized uptake value, IDH – isocitrate dehydrogenase, TERT – telomerase reverse transcriptase, [^{18}F]FET – [^{18}F]Fluoroethyltyrosine, TBR_{max} – maximum tumor-to-brain-ratio, CNS WHO-World Health Organization Classification of Tumors of the Central Nervous System

In *IDH*-mutant glioma both [^{18}F]FET volume and TBR_{max} (n = 42) as well as contrast-enhancing volume on MRI (n = 47) differed between patients with a high or low [^{18}F]GE180-uptake (Table 4). Similar results were found in the subgroup of patients with grade 3 astrocytoma, *IDH*-mutant. Patients with *IDH*-mutant glioma and a high [^{18}F]FET TBR_{max} had a shorter TTF, but no significantly different PRS compared to patients with a low [^{18}F]FET TBR_{max} (Supplementary Fig. 1).

Among all patients, there was a low to moderate correlation between [^{18}F]GE180 SUV_{max} and both [^{18}F]FET tumor volume ($r = 0.490$, $p < 0.001$), volume in contrast enhanced MRI ($r = 0.474$, $p < 0.001$), and T2 MRI volume ($r = 0.299$, $p = 0.006$).

Discussion

Glioma grading according to molecular features has improved prognostication in recent years, currently resulting in the 2021 revised edition of the WHO classification of CNS tumors [2]. Yet, prognosis for glioma patients remains poor, especially in the almost inevitable case of tumor recurrence. As no standard therapy for recurrent glioma is defined, treatment has to be tailored to the individual patient. For optimally fitting treatments, further markers of tumor aggressiveness are essential.

For individual treatment planning, [^{18}F]FET PET has been established as a valuable imaging method to delineate tumor extent in vivo [8]. As a biomarker for prognostication, dynamic measurements with the evaluation of the time-to-peak (TTP) have proven helpful, especially in case of *IDH*-mutant tumors [29]. In

IDH-wildtype gliomas, however, different results regarding the prognostic value of [^{18}F]FET PET dynamics have been observed [29, 30].

In search of novel diagnostic and therapeutic tools, TSPO has gained interest recently, and earlier works could indeed show an association of tracer uptake on TSPO PET with *IDH* mutation status as a marker of glioma aggressiveness [24, 25]. To our knowledge, this is the first study analyzing the prognostic value of TSPO PET using [^{18}F]GE180 in a larger cohort of recurrent glioma patients.

Here, we could confirm an association of [^{18}F]GE180 uptake with known markers of malignancy such as histological tumor grade. Interestingly, as opposed to the primary situation [25], both recurrent *IDH*-mutant and *IDH*-wildtype tumors show a highly increased maximum uptake value. We found a strong negative correlation with survival time: Survival was more than three times longer in patients with low SUV_{max} compared with those with high SUV_{max} (41.6 vs. 12.7 months). TTF was also significantly longer in cases with low SUV_{max} (14.9 vs. 7.2 months). Notably, this association between TSPO PET signal intensity and poor outcome was also found within the subgroups of *IDH*-wildtype and *IDH*-mutant tumor patients. A significant difference in TTF and PRS could even be seen in the largest homogenous patient subgroup of *IDH*-mutant astrocytoma CNS WHO grade 3. This clear association with survival even within molecularly homogenous subgroups suggests an *added* value of TSPO PET imaging to the clinically established molecular tumor stratification.

Comparing these prognostically different groups of patients with low SUV_{max} versus high SUV_{max}, significant differences were particularly found for the tumor size measured by contrast enhanced MRI, and, among *IDH*-mutant glioma patients, also measured by [^{18}F]FET PET-based tumor volume. Patients with high SUV_{max} had significantly larger contrast-enhancing tumor volumes, and it is tempting to speculate about a causal relationship between these parameters (e.g. high TSPO expression leads to fast tumor growth). However, only a low to moderate association could be found between SUV_{max} values and volume of contrast enhancement or [^{18}F]FET PET-based tumor volume. Another conspicuity was the higher uptake intensity on [^{18}F]FET PET in the group of patients with high SUV_{max}, which can be explained by a moderate degree of correlation between both parameters. However, the strong association with patients' outcome was restricted to the TSPO PET signal and not found for uptake intensity on [^{18}F]FET PET, which is in line with previous data demonstrating that TBR_{max} on [^{18}F]FET does not serve as reliable prognostic biomarker [29, 31].

Despite promising survival data hinting at a role of TSPO in glioma tumorigenesis and progression, the histological and molecular equivalent of a high TSPO tracer uptake remains to be evaluated in detail. Histologically and on mRNA level, tumor cells express high levels of TSPO, especially glioblastoma as opposed to low grade glioma [19, 32]. This difference in TSPO expression even occurs among glioblastoma and other homogeneous molecular groups and correlates with higher tumor aggressiveness [20]. Although the mechanisms leading to this phenomenon are as yet unclear, an association with regulation of proliferation, apoptosis, migration, and/or mitochondrial functions such as respiration and

oxidative stress regulation can be speculated [18]. While tracer uptake on [^{18}F]FET PET is considered as surrogate marker of tumor cells due to overexpression of L-amino acid transporters particularly on tumor cells, upregulated TSPO expression in glioma is not only found in tumor cells but likewise in tumor-associated macrophages, endothelial cells, pericytes and especially microglia [32]. As a microglia activation marker, TSPO PET visualizes neuroinflammation and has been established as a tool for imaging inflammatory CNS processes in neurodegenerative diseases [33, 34] or in multiple sclerosis [13, 35]. In the tumor microenvironment, inflammatory processes are increasingly recognized to play a role in gliomagenesis [36], treatment resistance [37] and tumor recurrence [12, 38]. As effectors of these processes, immunosuppressive myeloid-derived suppressor cells and regulatory T-cells outweigh activating immune effector cells such as T-cells and Natural Killer cells. This mainly immunosuppressive glioma microenvironment is maintained and reinforced by expression and secretion of immune suppressing molecules by glioma cells and tumor-associated astrocytes [10]. Nevertheless, the tumor microenvironment and immune status is highly heterogeneous across tumor entities: For example, immunosuppression more strongly prevails in *IDH*-wildtype glioblastoma, whereas *IDH*-mutant astrocytomas secrete granulocyte colony-stimulating factor which increases the ratio of nonsuppressive neutrophils [11]. Yet, heterogeneity is not only seen between different molecular tumor entities, but also both spatially and temporally within the same tumor [39]. This heterogeneity adds to the difficulty of therapeutically stimulating an anti-glioma immune response [37]. Therefore, illustrating the tumor immune environment in vivo and monitoring changes over time is promising for prognostication and especially in light of recent advances in immunomodulating therapies [40].

Some limitations of this study must be noted. As it contains an unselected population of glioma patients undergoing molecular imaging, statistical power is limited by low numbers in individual subgroups, even though the total number of investigated patients is high. However, evaluating these homogeneous subgroups is extremely important to assess the *added* value of TSPO PET to routine neuropathological and molecular assessment. While further improvements in prognostication might be attained by extraction of radiomic or pharmacokinetic features, this study chose a straightforward method for image analysis, which is easily applicable in the clinical routine. As a purely observational study, the evaluated associations are independent of therapy. As a prognostic value of TSPO PET could be shown in recurrent glioma patients, a longitudinal analysis of individual patients would be of high interest to address changes of TSPO expression and their prognostic value. These aspects will be covered in upcoming studies.

Conclusion

TSPO PET with [^{18}F]GE180 is a promising imaging tool for prognostication in patients with recurrent *IDH*-mutant and *IDH*-wildtype glioma. The biological background and the usefulness of TSPO PET as a personalized read-out needs to be elucidated in mechanistic and prospective studies.

Declarations

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DISCLOSURES

All authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ETHICS STATEMENT

The study was authorized by the local ethics committee (16-601 / 17-457) in accordance with the ICH Guideline for Good Clinical Practice (GCP) and the Declaration of Helsinki. Written informed consent was obtained from all individual patients included in this study.

AUTHOR CONTRIBUTIONS

SQ, JCT, PB, and NLA contributed to conception and design of the study. AH and FD organized the database. SQ and JW performed image analyses and SQ the statistical analysis. LK, VR, MB, LW, LB, JH, MR, SK, AH, FD and MU helped with the data analyses. SQ, LvB, MN and NT evaluated the clinical course of the disease. CW and RR carried out polymorphism genotyping. SL was responsible for radiopharmaceutical production. SQ, JCT and NLA wrote the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Figures

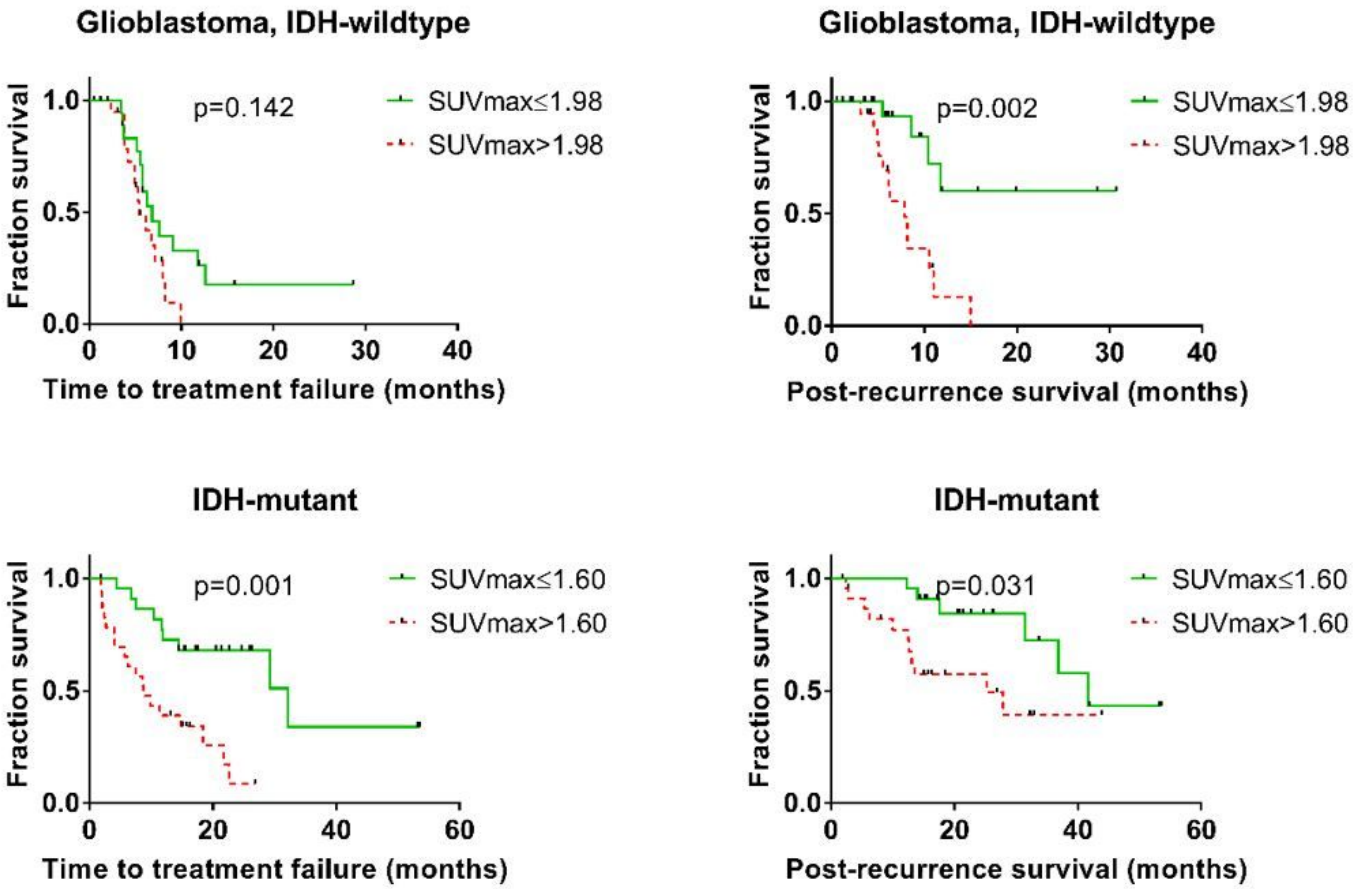

Figure 1

Time to treatment failure and post recurrence survival in IDH-wildtype and IDH-mutant glioma patients according to maximum [^{18}F]GE180 uptake.

SUV_{max} – maximum standardized uptake value, IDH – isocitrate dehydrogenase

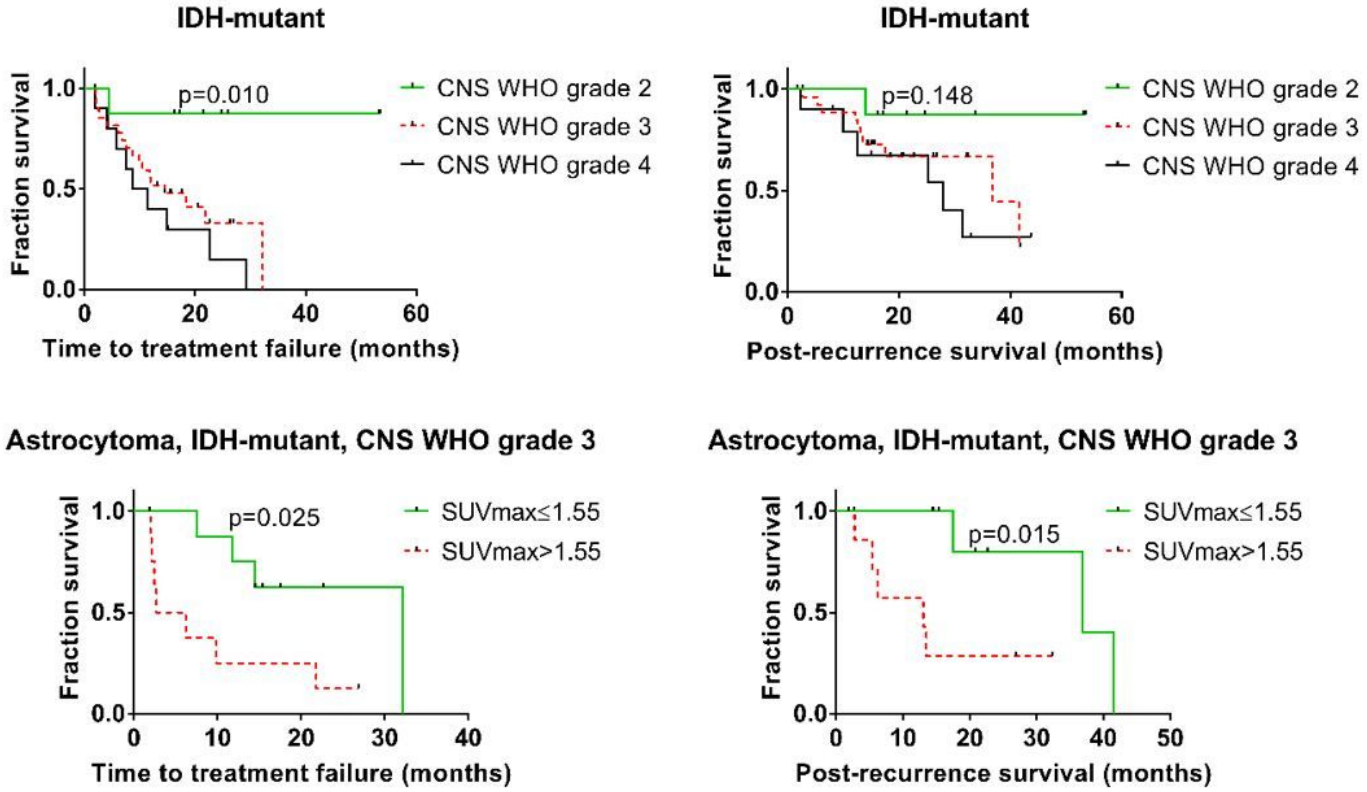

Figure 2

Survival of *IDH*-mutant astrocytoma.

SUV_{max} – maximum standardized uptake value, IDH – isocitrate dehydrogenase

Figure 3

Exemplary case of a 39.5 year-old patient with recurrent astrocytoma, IDH-mutant, CNS WHO grade 3 (SUV_{max} 2.85). The patient progressed soon after re-radiochemotherapy and died 6 months after recurrence.

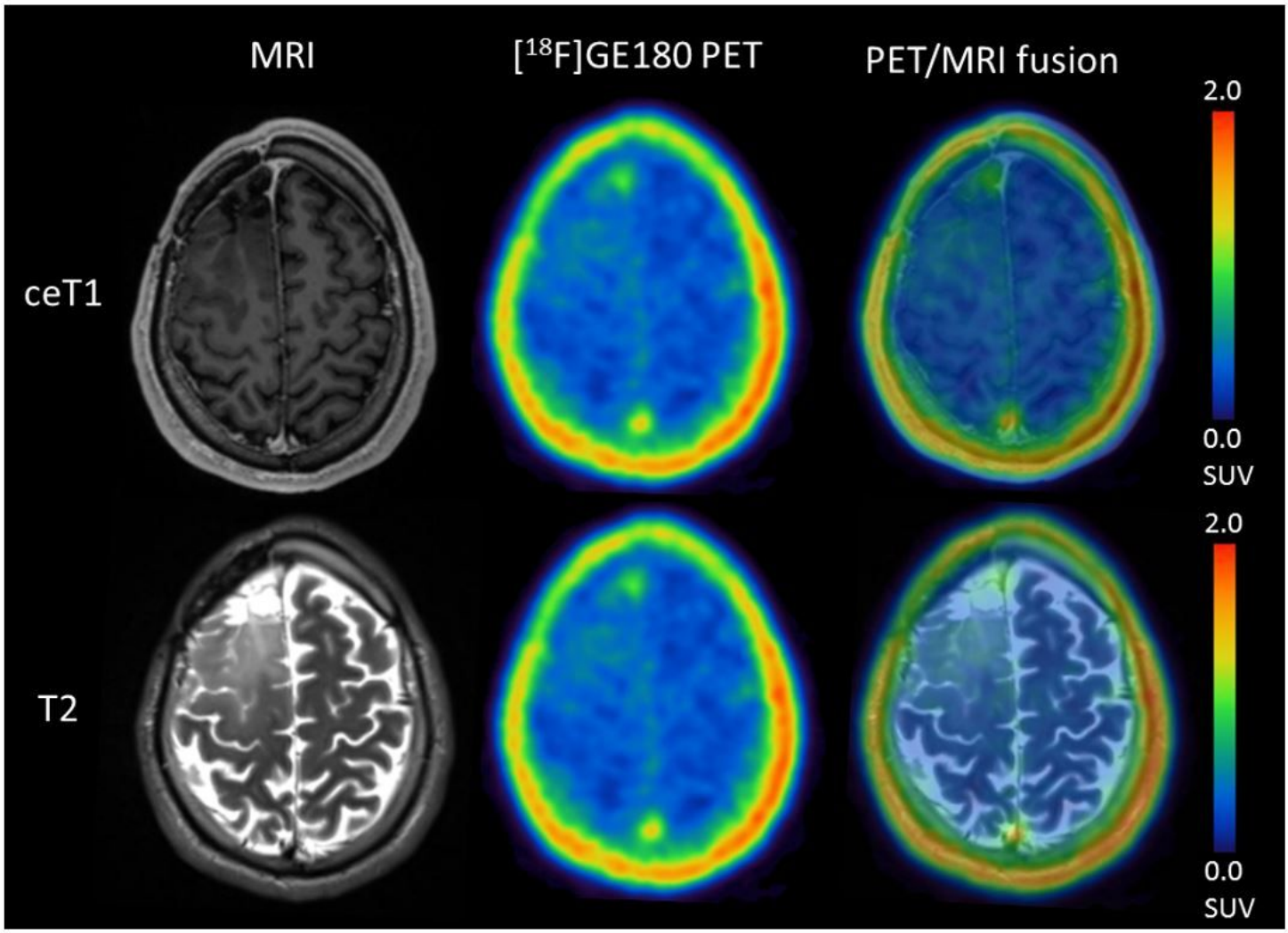

Figure 4

Exemplary case of a 31.0 year-old patient with histologically verified recurrent recurrent astrocytoma, IDH-mutant, CNS WHO grade 3 (SUV_{max} 0.79, Ki67 at recurrence 20%). The patient remained stable 15 months after recurrence and re-radiochemotherapy.

Supplementary Files

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- floatimage1.png
- SFig1.jpg