

# <sup>18</sup>F-FET PET prior to recurrent high-grade glioma re-irradiation—additional prognostic value of dynamic time-to-peak analysis and early static summation images?

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**Abstract** Most high-grade gliomas (HGG) recur after initial multimodal therapy and re-irradiation (Re-RT) has been shown to be a valuable re-treatment option in selected patients. We evaluated the prognostic value of dynamic time-to-peak analysis and early static summation images in O-(2-<sup>18</sup>F-fluoroethyl)-l-tyrosine (<sup>18</sup>F-FET) PET for patients treated with Re-RT ± concomitant bevacizumab. We retrospectively analyzed 72 patients suffering from recurrent HGG with <sup>18</sup>F-FET PET prior to Re-RT. PET analysis revealed the maximal tumor-to-background-ratio (TBR<sub>max</sub>), the biological tumor volume, the number of PET-foci and pattern of time-activity-curves (TACs; increasing vs. decreasing). Furthermore, the novel PET parameters early TBR<sub>max</sub> (at 5–15 min post-injection) and minimal time-to-peak (TTP<sub>min</sub>) were evaluated. Additional analysis was performed for gender, age, KPS, O6-methylguanine-DNA methyltransferase methylation status, isocitrate dehydrogenase 1 mutational status, WHO grade and concomitant bevacizumab therapy. The influence of PET and clinical parameters on post-recurrence survival (PRS) was investigated. Shorter TTP<sub>min</sub> was related to shorter PRS after

Re-RT with 6 months for TTP<sub>min</sub> < 12.5 min, 7 months for TTP<sub>min</sub> 12.5–25 min and 11 months for TTP<sub>min</sub> > 25 min (p = 0.027). TTP<sub>min</sub> had a significant impact on PRS both on univariate (p = 0.027; continuous) and multivariate analysis (p = 0.011; continuous). Other factors significantly related to PRS on multivariate analysis were increasing vs. decreasing TACs (p = 0.008) and Karnofsky Performance Score (p = 0.015; < 70 vs. ≥ 70). Early TBR<sub>max</sub> as well as the other conventional PET parameters were not significantly related to PRS on univariate analysis. Dynamic <sup>18</sup>F-FET PET with TTP<sub>min</sub> provides a high prognostic value for recurrent HGG prior to Re-RT, whereas early TBR<sub>max</sub> does not. Dynamic <sup>18</sup>F-FET PET using TTP<sub>min</sub> might help to personalize Re-RT treatment regimens in future through voxelwise TTP<sub>min</sub> analysis for dose painting purposes and PET-guided dose escalation.

**Keywords** High-grade glioma · Re-irradiation · <sup>18</sup>F-FET PET · Kinetic analysis · Prognostic value

## Introduction

Although there is ongoing research concerning the treatment of high-grade glioma (HGG), the prognosis remains poor, with e.g. a median survival of 12–14 months for patients with glioblastoma receiving standard multidisciplinary treatment [1, 2]. Besides surgical resection and chemotherapy, radiotherapy plays a key role in the therapeutic workup of patients suffering from primary and recurrent HGG. Despite those therapeutic efforts, tumor recurrence is the main issue in the following workup [3], hence, there is a clear need of highly effective therapeutic options concerning recurrent HGG [4]. One promising and very effective treatment option for recurrent high-grade glioma is

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represented by re-irradiation (Re-RT) with concurrent administration of bevacizumab in highly selected patients [5–7].

Several molecular biomarkers, such as the O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status, mutations in the cytosolic isocitrate dehydrogenase (IDH) 1 and 2 gene and the loss of heterozygosity in the chromosomes 1p and 19q have been shown to be prognostic during primary treatment of HGG patients [8–10], which just have a minor importance in case of tumor recurrence. In this scenario, recent studies indicated additional clinical value of PET for response assessment and prognostication [11–13] besides magnetic resonance imaging (MRI) [14–16].

Regarding PET in neuro-oncology, dynamic O-(2-<sup>18</sup>F-fluoroethyl)-l-tyrosine positron emission tomography (<sup>18</sup>F-FET PET) has shown clinical value in planning of surgery, biopsy guidance and radiotherapy in previous studies [17–20]. Therefore, amino acid tracers such as <sup>18</sup>F-FET have recently been recommended by the Response Assessment in Neuro-Oncology working group and the European Association for Neuro-Oncology providing a framework for the use of PET to assist in the management of patients with gliomas [21].

In a former study, <sup>18</sup>F-FET PET prior to Re-RT showed clinical value in the treatment of HGG recurrence [22]; increasing tumoral <sup>18</sup>F-FET uptake during the 40-min scan, reflected by increasing time-activity-curves (TACs) in the dynamic analysis, correlated significantly with longer survival after re-irradiation with 12 months for patients with increasing TACs, 10 months for patients with mixed TACs and only 7 months with decreasing TACs.

Additionally, dynamic <sup>18</sup>F-FET PET has recently shown remarkably high prognostic value in both newly diagnosed astrocytic HGG and low-grade glioma (LGG) [23, 24], especially using the newly established parameter minimal time to peak (TTP<sub>min</sub>). In particular TTP<sub>min</sub> was highly prognostic and may allow more explicit identification of aggressive tumor tissue than the mere qualitative classification of increasing vs. decreasing TACs [23].

Besides the value of static <sup>18</sup>F-FET PET for antiangiogenic therapy response assessment [25], TTP<sub>min</sub> has predictive value for the response assessment in patients with recurrent HGG undergoing bevacizumab therapy, where an early TTP<sub>min</sub> besides reduction of the biological tumor volume was predictive for a treatment failure [26].

Additionally, a recent study reported that early static <sup>18</sup>F-FET PET scans have a higher accuracy than the conventionally acquired scans at 20–40 min for the differentiation of HGG and LGG at the initial diagnosis, when comparing the early maximal tumor-to-background ratio (early TBR<sub>max</sub>) [21]. However, these newly established PET parameters (i.e. TTP<sub>min</sub>, early TBR<sub>max</sub>) were not yet

evaluated regarding their prognostic value prior to Re-RT of recurrent HGG with concomitant antiangiogenic therapy using bevacizumab.

Thus, the aim of this study was to determine the additional prognostic value of the newly derived TTP<sub>min</sub> and the novel assessment of the early summation images from 5 to 15 min post-injection in patients with recurrent HGG prior to Re-RT with bevacizumab.

## Methods

### Patients

Patients undergoing dynamic <sup>18</sup>F-FET PET examination prior to Re-RT were identified by searching the clinical database of the Department of Radiation Oncology, University hospital of Munich. Re-RT was performed at least 6 months after the initial radiotherapy in patients with recurrent HGG as diagnosed by MRI or proven histologically by stereotactic biopsy [27]. <sup>18</sup>F-FET PET with dynamic acquisitions performed in the routine management was used to confirm disease progression and to exclude radiation necrosis in cases of suspicious findings in the MRI scan. For all patients gadolinium-enhanced brain MRI, <sup>18</sup>F-FET PET as well as physical and neurological examination were performed prior to Re-RT. Treatment follow-up was evaluated by clinical examination and gadolinium-enhanced brain MRI, followed by <sup>18</sup>F-FET PET examination in the case of abnormal brain MRI findings.

### <sup>18</sup>F-FET PET acquisition and evaluation of kinetic parameters

40 min dynamic <sup>18</sup>F-FET PET scans were performed with an ECAT EXACT HR+ scanner (Siemens) according to standard protocols as described previously [28, 29]. Static and dynamic <sup>18</sup>F-FET PET parameters were evaluated on a Hermes workstation (Hermes Medical Solutions, Sweden) [28]. The consecutive semiquantitative evaluation consisted of the calculation of the maximal tumor-to-background-ratio (TBR<sub>max</sub>) (i.e. the standardized uptake value of the tumor divided by the mean background activity in the unaffected contralateral hemisphere) and the biological tumor volume (BTV) as calculated semiautomatically on a threshold basis of the volume of interest (TBR<sub>max</sub> ≥ 1.8) as described previously [30]. Volumes of interest were classified as a single focus, if the threshold was exceeded at only one coherent area or as multifocal, if the threshold was exceeded at multiple disconnected areas. Additionally to the standard assessment of the summation images 20–40 min post-injection, the early maximal

tumor-to-background ratio (early  $TBR_{max}$ ) was investigated using summation images 5–15 min post-injection.

As also described previously [28], dynamic PET data was evaluated according to the standardized clinical procedures using the software PET Display Dynamic which is implemented in the Hermes workstation: early summation images (10–30 min post-injection, frames 13–15) were used to define a 90% isocontour threshold region of interest (ROI), which was semiautomatically generated for the area of suspicious  $^{18}F$ -FET uptake on each slice (thickness 3 mm) of the tumor. The individual TACs of each tumor slice within these ROIs were extracted and used for the kinetic analysis. The TAC patterns of each tumor were evaluated and classified according to the predominant kinetic structure into increasing vs. decreasing TACs analogous to our previous study [22]. Solely (G1) and predominantly (G2) increasing TACs were classified as increasing, whereas mixed pattern (G3) TACs as well as predominantly (G4) and solely (G5) decreasing TACs were classified as decreasing TACs.

Additionally, for each ROI and corresponding TAC the frame presenting the peak uptake was determined as previously published [23]: the starting time of the particular frame plus half the frame duration, corresponding to the respective peak value, was set as time to peak (TTP). Accordingly, TTP accounted for 4 min in frame 11, 7.5 min in frame 12, 12.5 min in frame 13, 17.5 min in frame 14, 25 min in frame 15, and 35 min in frame 16. The shortest TTP presenting in at least 2 consecutive slices was set as minimal TTP ( $TTP_{min}$ ). In order to exclude noise artifacts at the beginning of the acquisition and due to low counting rates, only slices 11–16 (3–40 min post-injection) were analyzed in the dynamic evaluation.

### Re-irradiation and concomitant use of bevacizumab

Re-RT was applied as described before [31] with a total dose of 36 Gy in conventional fractions of 2 Gy.  $^{18}F$ -FET PET images and an analysis of the tracer uptake kinetics were demonstrated by a nuclear medicine physician in the interdisciplinary neurooncologic tumor board, before the start of re-irradiation planning.  $^{18}F$ -FET PET (3 mm slice thickness) and gadolinium-enhanced MRI images (3 mm slice thickness) were fused with the planning computer tomography scan images (3 mm slice thickness) and dynamic  $^{18}F$ -FET PET information was utilized in the planning process. Generally, the gross tumor volume plus a 10 mm margin accounted for the planning target volume. In patients receiving concomitant bevacizumab therapy, 10 mg/kg body weight was applied at days 1 and 15 of Re-RT. Maintenance therapy with bevacizumab was initiated on a patient-specific basis by the interdisciplinary

Neuro-Oncology Tumor Board of the University Hospital of Munich.

### Statistical analysis

Statistical analysis was performed with IBM® SPSS® Statistics for Microsoft® Windows®, Version 23, Armonk, NY, USA. Descriptive statistics were used for patients' characteristics and  $^{18}F$ -FET PET data including TACs,  $TTP_{min}$ ,  $TBR_{max}$ , early  $TBR_{max}$ , BTV and  $^{18}F$ -FET PET positive foci. Post-recurrence survival (PRS) was defined as first day of Re-RT until death or until the last day of follow-up. Kaplan–Meier estimators and Log-rank tests were used for survival and univariate analysis. Continuous variables were evaluated by Cox regression analysis. A Mann–Whitney U test was used to assess association between the dynamic PET parameters  $TTP_{min}$  and TACs. Multivariate analysis was performed by using a backward stepwise exclusion model, based on the likelihood ratio test. Statistical significance was considered for two-tailed p-values below 0.05.

### Consent

Written informed consent for scientific evaluation of  $^{18}F$ -FET PET and follow-up data was obtained for all patients before participating in the  $^{18}F$ -FET PET investigation.

### Results

#### Patient characteristics

72 HGG patients who received Re-RT at recurrence with preceding dynamic  $^{18}F$ -FET PET examination at the University hospital of Munich were retrospectively analyzed (Table 1) of which 52 were previously examined in a former study with a reduced number of parameters [22]. Duration between  $^{18}F$ -FET PET and Re-RT was intended to be 3 weeks on average, therefore the mean time duration was 22 days  $\pm$  standard deviation of 13 days. Exceptionally, three patients received  $^{18}F$ -FET PET shortly after beginning of Re-RT and one patient received  $^{18}F$ -FET PET two-and-a-half months before Re-RT. At the beginning of Re-RT median age of the patients was 49 years (range 18–73 years) and median Karnofsky performance score (KPS) was 80 (range 40–100). 57 patients (79.2%) suffered from WHO grade IV tumors at relapse. MGMT methylation status was available for 64 patients (88.9%) with methylated MGMT promoters in 37/64 (57.8%) patients and IDH1 mutational status was available for 42 patients (58.3%) with IDH1 mutation in 10/42 (23.8%) patients. Median prescribed radiation doses were 60 Gy at primary

**Table 1** Patient characteristics

Patient characteristics	
Median age at Re-RT and range (years)	49 (18–73)
Gender	
Male	28 (38.9%)
Female	44 (61.1%)
Median KPS	80 (40–100)
<70	16 (22.2%)
≥70	56 (77.8%)
WHO grade at initial diagnosis	
II	6 (8.4%)
III	15 (20.8%)
IV	51 (70.8%)
WHO grade at relapse	
III	15 (20.8%)
IV	57 (79.2%)
MGMT methylation status	
Methylated	37 (51.4%)
Not methylated	27 (37.5%)
Unknown	8 (11.1%)
IDH1 mutational status	
Mutated	10 (13.9%)
Not mutated	32 (44.4%)
Unknown	30 (41.7%)
Median dose of primary RT and range (Gy)	60 (39–78)
Median dose of Re-RT and range (Gy)	36 (30–46)
Concomitant bevacizumab therapy at Re-RT	
Yes	57 (79.2%)
No	15 (20.8%)
Adjuvant chemotherapy after Re-RT	
Begin within 8 weeks after Re-RT	29 (40.3%)
Begin at 8 or more weeks after Re-RT	11 (15.3%)
No adjuvant chemotherapy	32 (44.4%)
PET positive foci	
1	59 (81.9%)
2	9 (12.5%)
3	3 (4.2%)
4	1 (1.4%)
FET uptake kinetics	
Increasing	13 (18.1%)
Decreasing	59 (81.9%)
Median TTP <sub>min</sub> and range (min)	12.5 (4–35)
4.0 min	5 (6.9%)
7.5 min	3 (4.2%)
12.5 min	29 (40.3%)
17.5 min	14 (19.4%)
25.0 min	10 (13.9%)
35.0 min	11 (15.3%)
<12.5 min	8 (11.1%)
12.5–25 min	53 (73.6%)
>25 min	11 (15.3%)
Median early TBR <sub>max</sub> and range	3.7 (1.8–7.2)

**Table 1** (continued)

Patient characteristics	
Median TBR <sub>max</sub> and range	3.2 (1.6–7.0)
Median BTV 1.8 and range (cc)	11.1 (0.1–100.6)

radiotherapy and 36 Gy during Re-RT, both with 2 Gy single fractions. Bevacizumab was applied concomitantly to Re-RT in 57 patients (79.2%). PRS was 8 months (95% CI 6.5–9.5). Applying the reverse Kaplan–Meier method the median follow-up was not reached, consequently mean follow-up was 30.5 months (95% CI 26.4–34.7).

### <sup>18</sup>F-FET PET

<sup>18</sup>F-FET PET examination revealed a single focus in 59 patients (81.9%) and multifocal tumor recurrence in the remaining 13 patients (range 2–4). Median TBR<sub>max</sub> was 3.2 (range 1.6–7.0), median early TBR<sub>max</sub> 3.7 (range 1.8–7.2) and median size of the BTV 11.1 cc (range 0.1–100.6). On kinetic analysis median TTP<sub>min</sub> was 12.5 min with TTP<sub>min</sub> below 12.5 min in 8 patients (11.1%), TTP<sub>min</sub> in the range of 12.5 to 25 min in 53 patients (73.6%) and TTP<sub>min</sub> above 25 min in 11 patients (15.3%). Tumoral TAC pattern was increasing in 13 (18.1%) patients, while decreasing TACs were detected in 59 (81.9%) patients. As expected by its definition increasing TACs were associated with longer median TTP<sub>min</sub> values (35/12.5 min within the increasing/decreasing TAC groups,  $p < 0.001$  on Mann–Whitney U test). Due to technical reasons early TBR<sub>max</sub> could only be investigated in 71 of the 72 patients.

### Univariate analysis including Log-rank test and Cox regression

Univariate analysis with Log-rank test and Cox regression was performed according to PRS including the factors age groups, gender, KPS, MGMT methylation status, IDH1 mutational status, WHO grade at relapse, concomitant bevacizumab therapy to Re-RT, number of foci, TBR<sub>max</sub>, early TBR<sub>max</sub>, BTV, TACs and TTP<sub>min</sub> (Table 2).

Factors with statistically significant influence on PRS were number of foci ( $p = 0.025$ ), TTP<sub>min</sub> ( $p = 0.027$ ; continuous), TAC classifications ( $p = 0.019$ ; increasing vs. decreasing), and gender ( $p = 0.028$ ). In patients with one PET focus, PRS was 9 months (95% CI 6.8–11.2), whereas patients with two to four PET foci presented with a median PRS of only 6 months (95% CI 3.8–8.2,  $p = 0.028$ ). In patients with TTP<sub>min</sub> < 12.5 min median PRS was 6 months (95% CI 1.9–10.1), with TTP<sub>min</sub> 12.5–25 min 7 months (95% CI 5.3–8.7) and for TTP<sub>min</sub> ≥ 25 min 11 months

**Table 2** P-values for univariate analysis on post-recurrence survival (p-values are calculated for corresponding strata and, if possible, the respective variables are additionally treated as being continuous in the Cox proportional hazards model)

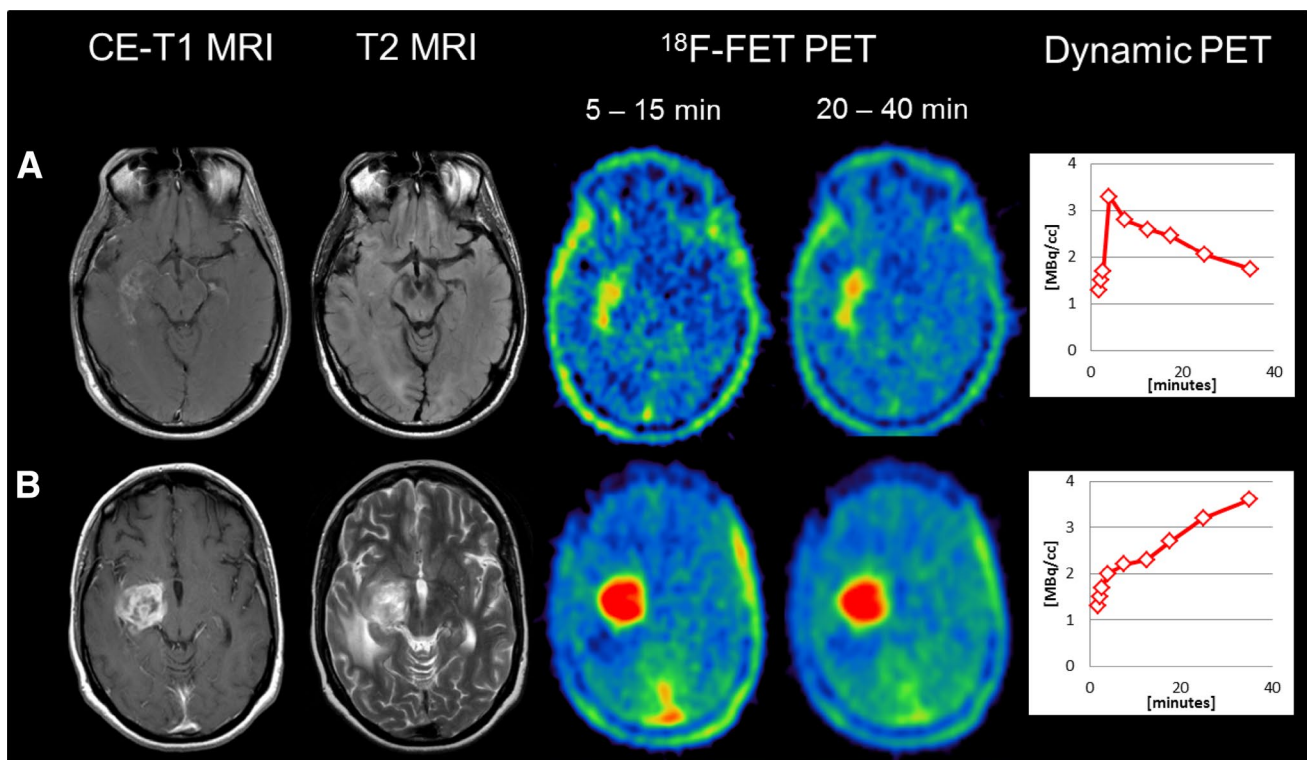
Stratum	Median CI	Univariate p-value LR	Univariate p-value Cox
Overall	8 (6.5–9.5)		
Age (years)			
<50	7 (5.0–9.0)	ns (p=0.956)	ns (p=0.652)
≥50	8 (6.3–9.7)		
Gender			
Female	10 (7.4–12.6)	p=0.028	
Male	7 (4.6–9.4)		
Karnofsky performance score			
<70	6 (0.1–11.9)	ns (p=0.076)	ns (p=0.140)
≥70	9 (7.4–10.6)		
MGMT methylation status			
Not meth.	8 (5.6–10.4)	ns (p=0.491)	
Meth.	7 (5.1–8.9)		
IDH1 mutation status			
Not mut.	8 (4.9–11.1)	ns (p=0.602)	
Mut.	10 (5.4–14.6)		
WHO grade at relapse			
III	7 (6.1–7.9)	ns (p=0.836)	
IV	9 (7.2–10.8)		
Bevacizumab concomitant			
No	7 (5.6–8.4)	ns (p=0.366)	
Yes	9 (6.9–11.1)		
Foci			
1	9 (6.8–11.2)	p=0.025	
2–4	6 (3.8–8.2)		
TTP <sub>min</sub>			
<12.5	6 (1.9–10.1)	p=0.027	p=0.027
12.5–25	7 (5.3–8.7)		
>25	11 (6.7–15.3)		
Time activity curves			
Increasing	11 (7.5–14.5)	p=0.019	
Decreasing	7 (6.0–8.0)		
Early TBR <sub>max</sub>			
≤3.7	8 (6.5–9.5)	ns (p=0.997)	ns (p=0.140)
>3.7	9 (6.1–11.9)		
TBR <sub>max</sub>			
≤3.2	8 (5.2–10.8)	ns (p=0.380)	ns (p=0.405)
>3.2	8 (5.6–10.4)		
BTV 1.8 (cc)			
≤11.1	9 (7.4–10.6)	ns (p=0.052)	ns (p=0.109)
>11.1	7 (5.2–8.8)		

(95% CI 6.7–15.3, p=0.027, Fig. 1). Similarly in patients with increasing TACs median PRS was 11 months (95% CI 7.5–14.5) compared to patients with decreasing TACs with only 7 months of median PRS (95% CI 6.0–8.0, p=0.019). Female patients presented with longer median PRS of 10 months (95% CI 7.4–12.6) than male patients with only 7 months (95% CI 4.6–9.4, p=0.028). No significant influence on PRS could be shown for age categories of younger than 50 years or 50 years and older, KPS, WHO grade, bevacizumab therapy, BTV size, TBR<sub>max</sub>. The early static parameter early TBR<sub>max</sub> did not show significance

in Log-Rank test (p=0.997, Fig. 2b) or on Cox regression (p=0.140). The time span between the <sup>18</sup>F-FET PET and the beginning of the re-irradiation did not show significant correlation with TTP<sub>min</sub> on Pearson’s correlation (p=0.205).

**Multivariate analysis**

Multifactorial analysis was performed for all factors with statistical significance or trend (p<0.1) according to PRS on univariate analysis including TTP<sub>min</sub>, TACs, number



**Fig. 1** Patient examples **a** A male glioblastoma patient (WHO grade IV, 48 years) at Re-RT: static  $^{18}\text{F}$ -FET PET images show recurrent tumor tissue in the right temporal lobe with pathologic  $^{18}\text{F}$ -FET uptake, a  $\text{TBR}_{\text{max}}$  of 3.37 and an early  $\text{TBR}_{\text{max}}$  of 3.49, dynamic images reveal decreasing TACs with a  $\text{TTP}_{\text{min}}$  of 4 min. The patient had a PRS of 3 months. **b** A female glioblastoma patient (WHO IV,

36 years) at Re-RT: static  $^{18}\text{F}$ -FET PET images present temporally located tumor recurrence with intense tracer uptake, a  $\text{TBR}_{\text{max}}$  of 4.73 and an early  $\text{TBR}_{\text{max}}$  of 4.65, but with increasing TACs in the dynamic analysis. The  $\text{TTP}_{\text{min}}$  was accordingly set as 35 min. The patient had a PRS of 17 months

of foci, gender, KPS, BTV and WHO grade (see Table 3). Early  $\text{TBR}_{\text{max}}$  was not included into the multivariate analysis, since it did not show statistical significance or trend according to PRS.

Since  $\text{TTP}_{\text{min}}$  and kinetic categories showed significant intercorrelation on Mann–Whitney U test three multivariate models were calculated separately. For all variables without TACs  $\text{TTP}_{\text{min}}$  ( $p=0.011$ ; continuous) and KPS ( $p=0.028$ ;  $\geq 70$  vs.  $<70$ ) were significant factors. For all variables without  $\text{TTP}_{\text{min}}$ , TACs ( $p=0.008$ ; increasing vs. decreasing) and KPS ( $p=0.015$ ;  $\geq 70$  vs.  $<70$ ) were significant. In the model including both TACs and  $\text{TTP}_{\text{min}}$  with an interaction variable of  $\text{TTP}_{\text{min}} \times \text{TACs}$ , merely one kinetic parameter (TACs  $p=0.008$ ) remained significant while the other was ruled out due to correlation effects.

## Discussion

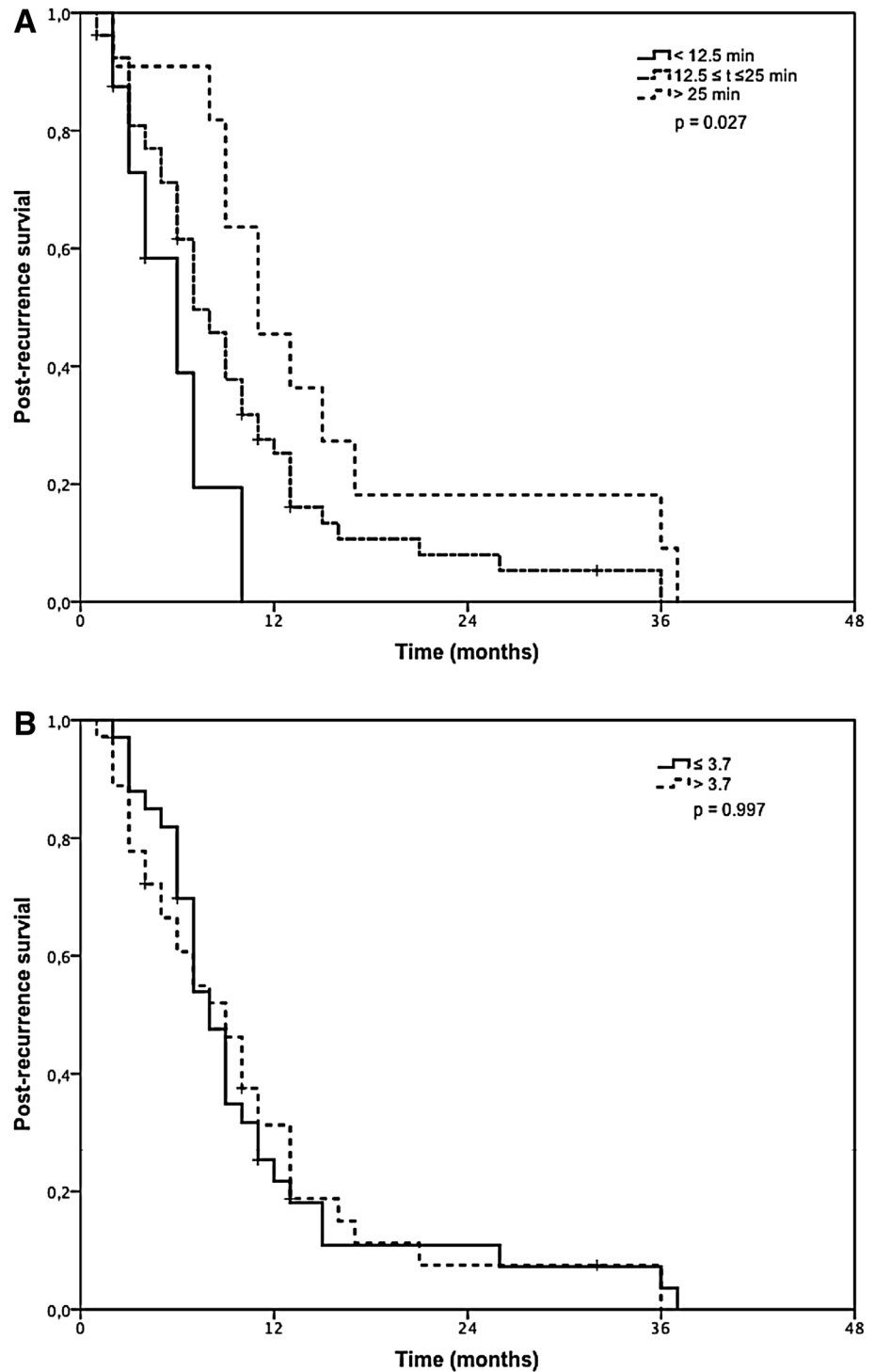
Molecular imaging with positron emission tomography (PET) visualizing metabolic pathways is increasingly used in the neurooncological treatment of patients suffering from

both high and low grade glioma [32]. Particularly radiolabeled amino acids such as  $^{18}\text{F}$ -FET are of special interest in the clinical workup because of a high uptake in biologically active tumor tissue and low uptake in normal brain tissue [33] which enables the identification of vital tumor tissue even after preceding therapies [22].  $^{18}\text{F}$ -FET PET implementation in the clinical routine helps to individualize and optimize the specific therapy because of its value in tumor grading, biopsy guidance and planning of surgery and radiotherapy [17–19, 29], therefore the Response Assessment in Neuro-Oncology working group and the European Association for Neuro-Oncology emphasize the clinical use of amino acid tracers such as  $^{18}\text{F}$ -FET PET [21].

Since conventional biomarkers such as MGMT promoter methylation status or IDH1 mutational status are lacking prognostic significance in the recurrence setting, there is an urgent need for novel imaging derived parameters with prognostic validity at this stage of the disease, especially as non-invasive methods have to be preferred in this treatment setting.

In this study,  $\text{TTP}_{\text{min}}$  in the pretherapeutic dynamic  $^{18}\text{F}$ -FET PET proved to be a strong prognostic factor in

**Fig. 2 a** Kaplan–Meier estimates for PRS by  $TTP_{min}$ . **b** Kaplan–Meier estimates for PRS by early  $TBR_{max}$



our cohort of patients with recurrent glioma treated with Re-RT. Patients with longer  $TTP_{min}$  value showed significantly longer PRS. Unlike the TACs, which only give qualitative information of the tracer uptake kinetics (increasing vs. decreasing) and usually refer to the entire tumor,  $TTP_{min}$  has the advantage of showing detailed information within the group of tumors with decreasing TACs by presenting

the time point of curve decrease. This is particularly useful when high-grade tumors are evaluated, as most HGG are characterized by decreasing TACs, which points out the need for a more detailed risk stratification by dynamic parameters within these tumors with decreasing TACs. Furthermore, by evaluating the TTP layer by layer within the entire tumor, one may receive spatial information on

**Table 3** P-values for multivariate analysis on post-recurrence survival

Stratum	Multivar. p-value Cox BStep HR (95% CI) without TAC	Multivar. p-value Cox BStep HR (95% CI) without TTPmin	Multivar. p-value Cox BStep HR (95% CI) all
-2 Log likelihood of last step of Cox BStep	423.75	422.57	422.57
Gender			
Female	ns (p=0.133)	ns (p=0.144)	ns (p=0.144)
Male			
Karnofsky performance score			
<70	p=0.028	p=0.015	p=0.015
≥70	0.51 (0.28–0.93)	0.47 (0.26–0.86)	0.47 (0.26–0.86)
Foci			
1	ns (p=0.131)	ns (p=0.088)	ns (p=0.088)
2–4			
TTP <sub>min</sub>			
Continuous	p=0.011 0.96 (0.94–0.99)	–	ns (p=0.980)
Time activity curves			
Increasing	–	p=0.008	p=0.008
Decreasing		2.54 (1.27–5.05)	2.54 (1.27–5.05)
BTV 1.8 (cc)			
Continuous	ns (p=0.139)	ns (p=0.159)	ns (p=0.159)
Interaction variable TTP <sub>min</sub> × TACs	–	–	ns (p=0.678)

tumor areas with a more aggressive biology, which would not be represented with the standard evaluation of increasing vs. decreasing TACs. This was particularly obvious in the observation, that there is a link between an early TTP<sub>min</sub> and a short PRS and vice versa. Exact localization of the most aggressive parts within the tumor is another advantage of TTP<sub>min</sub> over the TACs, which only describe the most prevalent kinetic type of the tumor in toto. As the study was conducted retrospectively, the timespan between the pre-therapeutic <sup>18</sup>F-FET PET and the Re-RT varied with a median of 22 days with a standard deviation of 13 days. A longer timespan could have added a certain confounding to our results, since some tumors might have had a shorter TTP<sub>min</sub>, if the PET had been conducted at a closer time to the radiation planning. Since some of the tumors could have been “understaged” in our retrospective analysis, we performed a Pearson’s correlation of the time span between the <sup>18</sup>F-FET PET and the beginning of the re-irradiation, which was not statistically significant.

Conversely, none of the static <sup>18</sup>F-FET PET parameters (i.e. TBR<sub>max</sub>, BTV) but only the number of tumor foci showed significance on univariate analysis. A possible explanation for the insignificance of static parameters prior to Re-RT might be, that the summation of the images from minutes 20–40, which are commonly used for clinical reading and the standard calculation of TBR<sub>max</sub>, were not able to represent tumors with a very aggressive tracer uptake accurately, because the peak uptake had already occurred at an earlier timepoint. Therefore, taking into account the high prognostic value of TTP<sub>min</sub>, one might hypothesize that the assessment of TBR<sub>max</sub> values in earlier time frames might be more promising for outcome prognostication than the standard evaluation in this recurrence scenario.

Nonetheless, the newly introduced static parameter early TBR<sub>max</sub>, which is assessed by the summation of the early images from minutes 5–15 of the dynamic scans, did not reveal any association with the patients’ PRS in this setting prior to recurrent HGG Re-RT. These data indicate that the main application of this interesting new parameter might be the differentiation of LGG and HGG, e.g. at the initial diagnosis, as already demonstrated [21]. Whether relative changes of PET parameters derived from early summation images after Re-RT and during the maintenance therapy with bevacizumab have an additional predictive or prognostic value, as demonstrated in conventional static parameters during bevacizumab therapy [25, 26], has to be evaluated in further prospective settings. Unlike after primary surgery [34], static parameters derived from a single <sup>18</sup>F-FET PET including early TBR<sub>max</sub>, do not seem to have a prognostic value prior to Re-RT, as also described previously [22].

One might hypothesize that the tumoral uptake intensity does not have an impact on the patients’ PRS, since the mere intensity is most likely related to the amount and density of the tumor cells, whereas the dynamic parameter TTP<sub>min</sub> enables to characterize the biological behavior in terms of tumoral aggressiveness, since patients with an early TTP<sub>min</sub> in the dynamic evaluation had a significantly poorer outcome regarding the PRS. Further fields of application for early TBR<sub>max</sub> have to be evaluated in future studies, e.g. the identification of malignant transformation in patients suffering from LGG. In the setting of HGG recurrence, this early static parameter does not seem to have a clinical impact so far.

On a future perspective, TTP<sub>min</sub> has the potential to further personalize retreatment of HGG by adding individually tailored radiation boosts to tumor areas with aggressive kinetic uptake behavior, i.e. a short TTP<sub>min</sub>. Additional voxelwise analysis of the tracer uptake and the quantitative TTP<sub>min</sub> might enable even more elaborate radiation planning approaches such as dose-painting, where areas with a short TTP<sub>min</sub> could be precisely treated with higher radiation doses, compared to areas with a late TTP<sub>min</sub>.



## Conclusion

The new dynamic parameter  $TTP_{min}$  has prognostic value prior to recurrent HGG Re-RT with concomitant bevacizumab; the earlier the  $TTP_{min}$  in the dynamic evaluation, the shorter the PRS after Re-RT and vice versa. In contrast, early  $TBR_{max}$  as derived from early summation images did not show prognostic value in this setting. Therefore, dynamic  $^{18}F$ -FET PET aims towards a future of personalized radiotherapy treatment planning in recurrent HGG with  $TTP_{min}$  as novel quantitative prognostic marker. Voxelwise  $TTP_{min}$  analysis with dose-escalation at aggressive tumor parts with short  $TTP_{min}$  as dose-painting could help to advance tumor control and survival in HGG in the future.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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