

## Prediction of progression-free and overall survival following temozolomide chemoradiation using FET PET-based parameters including radiomics in patients with glioblastoma

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### Abstract

**Background.** Early after surgery and completion of first-line radiotherapy with concomitant temozolomide, the prediction of progression-free and overall survival (PFS, OS) is of considerable interest for managing patients with glioblastoma.

**Methods.** Sixty-three newly diagnosed patients with glioblastoma (age range, 19-82 years) who received PET imaging using the radiolabeled amino acid *O*-(2-[<sup>18</sup>F]fluoroethyl)-L-tyrosine (FET) after surgery or biopsy and completion of radiotherapy with concomitant temozolomide were evaluated. Static FET PET parameters, that is, maximum and mean tumor-to-brain ratios ( $TBR_{max}$ ,  $TBR_{mean}$ ), metabolic tumor volumes (MTV), and the dynamic FET PET parameters time-to-peak (TTP) and slope were obtained. Additionally,  $n = 1,303$  FET PET radiomics features were extracted per patient, of which 15 robust features were selected for further evaluation based on test-retest analysis. The prognostic values of FET PET parameters and radiomics features were evaluated using receiver-operating-characteristic (ROC) analyses regarding a favorable PFS and OS. Subsequently, univariate and multivariate survival estimates were performed to assess the prognostic value of these parameters in predicting a significantly longer PFS and OS.

**Results.** ROC analyses revealed that static parameters (ie,  $TBR_{max}$ , MTV) and one radiomics feature were the most powerful parameters to predict a significantly longer PFS (all  $P = .002$ ) and OS (all  $P \leq .02$ ). In addition, the dynamic parameter TTP predicted a significantly longer OS ( $P \leq .03$ ) but not PFS ( $P > .05$ ).  $TBR_{max}$ , MTV, and one radiomics feature remained significant in multivariate survival analysis (all  $P \leq .03$ ).

**Conclusion.** Our results suggest that FET PET parameters, including radiomics, are highly prognostic in patients with glioblastoma at an early stage of first-line therapy.

### Key Points

- FET PET parameters, including radiomics features, help identify patients with longer PFS and OS.
- Prognostic information derived from FET PET may be helpful for patient counseling, enabling personalized, evidence-based discussions that guide treatment decisions and clarify expectations.

## Importance of the Study

The study highlights the prognostic significance of static and dynamic FET PET imaging parameters, combined with radiomic features, in newly diagnosed patients with glioblastoma. It underscores early and accurate predictions of PFS and OS early after initial surgery and chemoradiation, aiding effective clinical decision-making. In particular, FET PET parameters allow the identification of patient subgroups with

favorable outcomes, potentially facilitating patient counseling by individualized risk stratification and treatment strategies in terms of more personalized medicine approaches in neuro-oncology. Moreover, the research also reinforces the transformative potential of FET PET radiomics for enhanced prognostic assessment and patient management in glioblastoma.

Glioblastoma is the most malignant primary brain tumor in adults, with an incidence of 3 to 4 per 100,000 individuals.<sup>1</sup> Median survival from initial diagnosis is approximately 12-14 months for patients with tumors with an unmethylated O<sup>6</sup>-methylguanine-DNA-methyltransferase (*MGMT*) promoter,<sup>2-5</sup> and 22-29 months for patients with tumors with a methylated *MGMT* promoter.<sup>2,3,6,7</sup> The 5-year survival rate of patients with glioblastoma remains low at less than 10% despite multimodal therapy, including maximal safe surgical resection, radiotherapy, and alkylating chemotherapy.<sup>8</sup> Important clinical prognostic factors in patients with glioblastoma are age, the extent of resection, including the residual tumor after surgery, and the patient's overall clinical status as evaluated by the Karnofsky Performance Status (KPS) scale.<sup>9-12</sup> Efforts to evaluate the clinical status of patients with brain tumors for survival prediction using newer status scales, such as the Neurologic Assessment in Neuro-Oncology (NANO) scale<sup>13</sup> are currently ongoing.

Furthermore, integrated histomolecular diagnostics of gliomas according to the World Health Organization (WHO) classification of Tumors of the Central Nervous System (CNS) from 2016 and 2021 has refined diagnostic accuracy and prediction of prognosis.<sup>14,15</sup> Pivotal prognostic molecular markers are the mutation status of the isocitrate dehydrogenase (*IDH*) genes 1 or 2 and the chromosomal 1p/19q co-deletion status. Also contributing to the patient's prognosis is the response to alkylating chemotherapy, which is highly predicted by the methylation status of the *MGMT* gene.<sup>16</sup> A methylated *MGMT* promoter results in low *MGMT* expression and is associated with a better prognosis.<sup>16</sup> Besides its predictive value for response to alkylating agents, it appears that *MGMT* promoter methylation is also prognostic for overall survival in histomolecularly characterized glioblastomas.<sup>17</sup>

Moreover, besides estimating a patient's prognosis based on well-established clinical or molecular parameters, static and dynamic amino acid PET imaging parameters seem also provide further prognostic information in terms of overall survival in patients with gliomas, especially at initial diagnosis and the early postoperative phase using the radiolabeled amino acid *O*-(2-[<sup>18</sup>F]fluoroethyl)-L-tyrosine (FET).<sup>18,19</sup> This potential prognostic value is of considerable interest since FET PET is—despite its increasing routine use predominantly in European centers—mainly used for clinical purposes at a later stage of first-line

therapy, that is, after radiotherapy completion, especially for diagnosing pseudoprogression.<sup>20</sup>

Furthermore, little is known about the prognostic role of radiomics imaging features derived from FET PET at this stage of first-line treatment in glioblastoma. With the increasing use of neuroimaging techniques such as anatomical and advanced MRI in combination with amino acid PET, the amount of data available for individual patients has grown immensely. More recently, this has promoted the role and use of computers in decision support. In particular, radiomics allows the extraction of numerous quantitative features from medical images beyond human perception.<sup>21</sup> FET PET radiomics have demonstrated its potential in primary and secondary brain tumors, predominantly for the noninvasive prediction of molecular markers,<sup>22-24</sup> the differentiation between treatment-related changes and tumor relapse,<sup>25,26</sup> and the assessment of response to radiotherapy.<sup>27</sup>

Thus, the present study aims to demonstrate that static and dynamic FET PET imaging parameters, including radiomics features, may serve as independent prognostic factors after radiotherapy completion in patients with glioblastoma.

## Patients and Methods

### Patients' Characteristics and Treatment

From 2014 to 2024, we retrospectively identified 63 adult patients with newly diagnosed and histomolecularly characterized glioblastoma according to the CNS WHO classification of 2021<sup>15</sup> who had undergone FET PET imaging within four weeks after radiotherapy completion. At initial diagnosis, patients underwent a stereotactic biopsy (46%), a complete resection (29%), or a partial resection (25%). A complete tumor resection was defined as a lack of residual contrast enhancement in the early postoperative MRI performed within the first 48 h after surgery. After biopsy or surgery, the vast majority of patients (91%) had undergone radiotherapy with concomitant temozolomide chemotherapy (75 mg/m<sup>2</sup> body surface area) according to Stupp et al.<sup>2</sup> (*n* = 49) or Perry et al.<sup>11</sup> (*n* = 8). Four patients (6%) had undergone radiotherapy plus intensified alkylating chemotherapy with temozolomide plus lomustine, according to the CeTeG/NOA-09 trial.<sup>28</sup> After biopsy, one patient was treated only with radiotherapy alone. After radiotherapy,

the clinical status was evaluated using the Neurologic Assessment in Neuro-Oncology (NANO) scale<sup>29</sup> and the Karnofsky Performance Status (KPS) scale.

Before PET imaging, all patients had given written informed consent for the PET investigation and data usage for scientific purposes. The local ethics committee approved the retrospective analysis of neuroimaging data performed under the Declaration of Helsinki.

### Neuropathological Tumor Classification and Analysis of Molecular Markers

All tumors were histomolecularly classified at initial diagnosis, according to the CNS WHO classification of 2021.<sup>15</sup> For molecular biomarker analysis, tumor DNA was extracted from formalin-fixed and paraffin-embedded tissue samples with a histologically estimated tumor cell content of 80% or more. The *IDH1-R132H* mutation was evaluated by immunohistochemistry using a mutation-specific antibody in a standard immunohistochemical staining procedure as reported<sup>30,31</sup> to assess the *IDH* mutation status. If immunostaining for *IDH1-R132H* remained negative, the mutational hotspots at codon 132 of *IDH1* and codon 172 of *IDH2* were directly sequenced, as reported.<sup>32,33</sup> The *MGMT* promoter methylation status was evaluated by methylation-specific PCR, as described elsewhere.<sup>33</sup>

### Conventional MR Imaging

Following the International Standardized Brain Tumor Imaging Protocol (BTIP),<sup>34</sup> MR imaging was performed using a 1.5T or 3.0T MRI scanner with a standard head coil before and after administration of a gadolinium-based contrast agent (0.1 mmol/kg body weight). The imaging protocol comprised 3D isovoxels acquired in T1-weighted, 2D T2-weighted, and 2D fluid-attenuated inversion recovery-weighted sequences. The first (baseline) MRI was performed 8–12 weeks after radiotherapy completion. MRI changes at follow-up compared to the baseline scan were evaluated according to the RANO criteria.<sup>35</sup>

### FET PET Imaging

As described previously, the amino acid FET was produced via nucleophilic <sup>18</sup>F-fluorination with a radiochemical purity greater than 98%, molar radioactivity greater than 200 GBq/μmol, and a radiochemical yield of about 60%.<sup>36</sup> According to international guidelines for brain tumor imaging using radiolabeled amino acid analogs,<sup>37</sup> patients fasted for at least 4 h before the PET measurements. All patients underwent a dynamic PET scan from 0 to 50 min after injection of 3 MBq of FET per kg of body weight within the first 4 weeks after radiotherapy completion.

PET imaging was performed either on an ECAT Exact HR + PET scanner in 3-dimensional mode ( $n = 49$  scans; Siemens, Erlangen, Germany; axial field-of-view, 15.5 cm) or simultaneously with 3T MR imaging using a BrainPET insert ( $n = 14$  scans; Siemens, Erlangen, Germany; axial field of view, 19.2 cm). The BrainPET is a compact cylinder that fits into the bore of the Magnetom Trio MR scanner.<sup>38</sup>

Iterative reconstruction parameters were 16 subsets, 6 iterations using the OSEM algorithm for the ECAT HR + PET scanner and two subsets, and 32 iterations using the OPOSEM algorithm for the BrainPET. Data were corrected for random, scattered coincidences, dead time, and motion for both systems. Attenuation correction for the ECAT HR + PET scan was based on a transmission scan and, for the BrainPET scan, on a template-based approach.<sup>38</sup> The reconstructed dynamic data sets consisted of 16 time frames ( $5 \times 1$  minute;  $5 \times 3$  min;  $6 \times 5$  min) for both scanners. To optimize the comparability of the results related to the influence of the two different PET scanners, reconstruction parameters, and post-processing steps, a 2.5 mm 3D Gaussian filter was applied to the BrainPET data before further processing. In phantom experiments using spheres of different sizes to simulate lesions, this filter kernel demonstrated sufficient comparability between PET data obtained from the ECAT HR + PET and the BrainPET scanner.<sup>39</sup>

### FET PET Data Analysis

We used summed PET images over 20–40 min after injection to evaluate FET PET data. Mean tumoral FET uptake was determined by a 2D auto-contouring process using a tumor-to-brain ratio (TBR) of at least 1.6. This cutoff was based on a biopsy-controlled study in glioma patients and differentiated best between tumoral and peritumoral tissue.<sup>40</sup> A circular region-of-interest (ROI) with a diameter of 1.6 cm was centered on the maximal tumor uptake to evaluate the maximal FET uptake, as previously reported.<sup>41</sup> Maximum and mean TBRs ( $TBR_{max}$ ,  $TBR_{mean}$ ) were calculated by dividing the mean and maximum standardized uptake values (SUV) of the tumor ROI by the mean SUV of a larger ROI placed in the semioval center of the contralateral unaffected hemisphere, including white and gray matter.<sup>37</sup> The calculation of metabolic tumor volumes (MTV) was determined by a 3D auto-contouring process using a threshold of 1.6 using the PMOD software (version 4.3; PMOD Technologies LCC, Faellanden, Switzerland). Time-to-peak values (TTP) were defined as the time from the beginning of the dynamic acquisition to the maximum SUV of the lesion in minutes. In cases with steadily increasing FET uptake without an identifiable peak uptake, we defined the end of the dynamic PET acquisition as TTP. Furthermore, the slope of the time-activity curve in the late phase of FET uptake was assessed by fitting a linear regression line to the late phase of the curve (20–50 min post-injection). The slope was expressed as the SUV change per hour. This procedure allows for a more objective evaluation of kinetic data compared with an assignment of time-activity curves to earlier reported patterns of FET uptake during dynamic acquisition.<sup>41</sup>

### Radiomics Feature Extraction and Selection

For the extraction of radiomics features, segmentation of the MTV was carried out using the publicly available JuST\_BrainPET model, which uses a neural network trained on 699 FET PET scans to automatically determine the MTV.<sup>42</sup> In that study, resulting segmentation masks were validated by an expert, and incorrect predictions ( $n = 2$ ) were segmented

manually by a 3D auto-contouring process with a threshold of 1.6 using the PMOD software (version 4.3; PMOD Technologies LCC, Faellanden, Switzerland). Besides, brain extraction was performed using the open-access software package Heidelberg Brain Extraction (HD-BET).<sup>43</sup> The images were resampled to an isotropic voxel size of 1.25 mm<sup>3</sup> using the Python package TorchIO (version 0.19.5). Standardization was also carried out by subtracting the mean and dividing by the standard deviation of the brain-extracted voxels. The open source package PyRadiomics (version 3.1.0) was used to calculate radiomics features from the segmented FET PET tumor volumes. As recommended for PET radiomics analyses, a fixed bin width of 0.15 was used for image discretization.<sup>44,45</sup> The extracted features included  $n = 1$  shape feature,  $n = 18$  first-order features, and  $n = 75$  second-order features derived from gray level matrices such as the gray level co-occurrence matrix (GLCM) or the gray level dependence matrix (GLDM).<sup>46</sup> Features were calculated from the original images and from wavelet and Laplacian of Gaussian filtered images, resulting in a total of 1,303 radiomics features ( $n = 94$  original;  $n = 744$  wavelet;  $n = 465$  LoG).

To identify robust radiomics features, the framework proposed by Zwanenburg and colleagues was followed.<sup>47</sup> In brief, augmented versions of the original images (re-test images) were generated by applying image perturbations such as random deformation, random flipping, and random noise (TorchIO; version 0.19.5). The intraclass correlation coefficient from the package Pingouin (version 0.5.4) was used to assess the repeatability of features between the original image (test) and the augmented version of the image (retest). Features were considered repeatable if the 95% confidence interval of the intraclass correlation coefficient was greater than 0.9, resulting in 439 repeatable features.<sup>48</sup> Next, the Pearson correlation coefficient was computed to avoid redundant and identify important (ie, uncorrelated) features. A Pearson correlation coefficient below 0.8 was considered uncorrelated, resulting in a final set of 15 repeatable and uncorrelated features.

### Survival Times

The PFS was defined as the time in months between the date of biopsy or resection at initial diagnosis and *Progressive Disease* according to the RANO criteria for MRI.<sup>35,49</sup> The OS was defined as the interval between initial diagnosis and death in months. If no tumor relapse or death has not occurred at the end of the study (ie, May 2024), the respective event was marked as censored.

### Statistical Analysis

Descriptive statistics are provided as mean and standard deviation or median and range. To compare two groups, the Student's *t*-test was used. The Mann–Whitney rank sum test was applied if samples were not normally distributed. The prognostic value of the FET PET parameters  $TBR_{max}$ ,  $TBR_{mean}$ , MTV, TTP, slope, and the 15 repeatable and uncorrelated radiomics features was assessed by receiver-operating-characteristic (ROC) curve analyses using a favorable PFS and OS as reference. Favorable

outcomes were considered as PFS longer than 7 months and OS longer than 15 months. These favorable outcome thresholds were adopted from the results of the EORTC 22981/26981-NCIC CE3 trial (ie, median PFS of 6.9 months and median OS of 14.6 months).<sup>2</sup> Decision cutoff was considered optimal when the product of paired values for sensitivity and specificity reached its maximum. As a measure of the test's diagnostic quality, the area under the ROC curve (AUC), its standard error, and the significance level were determined. Univariate survival analyses were performed using Kaplan–Meier estimates. The log-rank test was used to compare the median PFS and OS between the subgroups. Multivariate Cox proportional hazards models were constructed to test the relationship between FET PET parameters and well-known general prognostic factors (ie, age, extent of resection, *MGMT* promoter methylation status, KPS). Only significant parameters in univariate analyses were included in the multivariate analysis. This analysis was done separately for each FET PET imaging parameter ( $TBR_{max}$ ,  $TBR_{mean}$ , MTV, TTP, slope, and the radiomics feature with the highest prognostic value). Hazard ratios (HR) and their 95% confidence intervals (CI) were calculated. *P*-values of .05 or less were considered statistically significant. Statistical analyses were performed using SPSS statistics, version 29.0.

## Results

### Patients' Survival

Sixty-three patients with glioblastoma (median age, 57 years; age range, 19–82 years; 49% females) were evaluated. The *MGMT* promoter was methylated in 44% of patients ( $n = 28$ ). Following first-line therapy, the median PFS was 8.1 months (range, 2.4–105.4 months), and the median OS was 13.7 months (range, 4.8–105.4 months). Further patient characteristics are summarized in [Table 1](#) and [Supplementary Table 1](#).

### Static and Dynamic FET PET Parameters after Completion of Radiotherapy

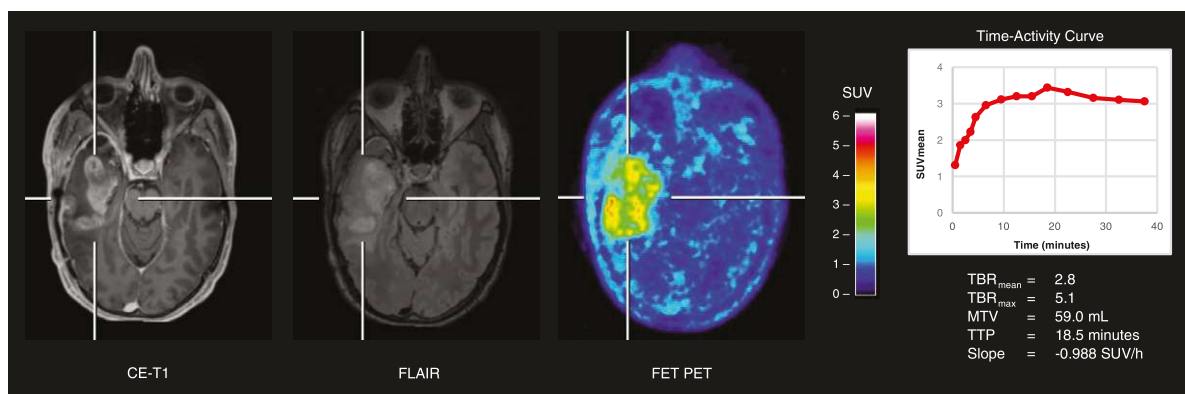
In lesions with FET uptake after radiotherapy completion ( $n = 59$  of 63 patients; 94%), the average  $TBR_{max}$  was 3.3 (range, 1.7–4.5), and the average  $TBR_{mean}$  was 2.1 (range, 1.4–3.0). The average MTV was 31.5 mL (range, 0.4–108.2 mL). The dynamic parameter slope had an average value of -0.051 SUV/h (range, -2.010–1.289 SUV/h), and the averaged TTP was 29.1 min (range, 9.5–47.5 min). An illustrative patient example is shown in [Figure 1](#). Static and dynamic FET PET parameters for each individual patient are summarized in [Supplementary Table 2](#).

### Value of Radiomics Features and Static and Dynamic FET PET Parameters for Prediction of Prognosis

Six radiomics features were statistically significant in the ROC analysis. The prognostic value was highest for the radiomics feature *GLCM Inverse Difference Moment*

**Table 1.** Patient Characteristics of the 63 Patients with Glioblastoma

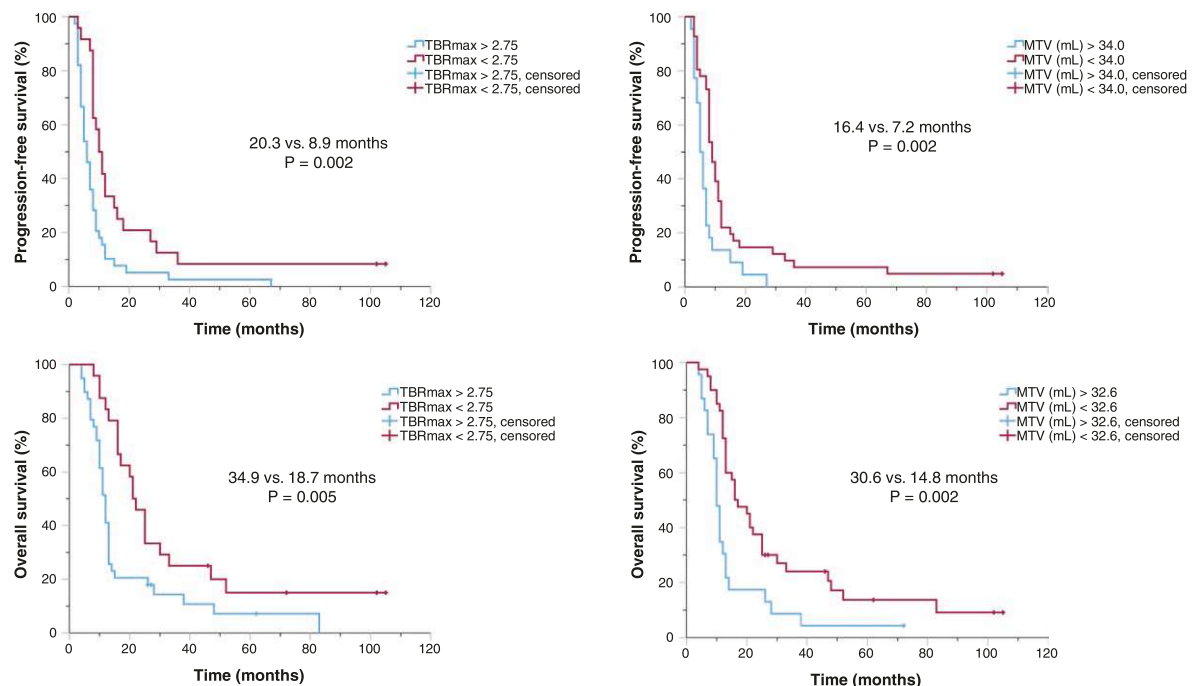
| Sex                                                                                                                                                                                                           |                |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| Female                                                                                                                                                                                                        | 49%            |
| Age at initial diagnosis in years                                                                                                                                                                             |                |
| Median (range)                                                                                                                                                                                                | 57 (19-82)     |
| MGMT promoter methylation status                                                                                                                                                                              |                |
| Unmethylated                                                                                                                                                                                                  | 56%            |
| Methylated                                                                                                                                                                                                    | 44%            |
| First-line treatment                                                                                                                                                                                          |                |
| RT (60 Gy) with concomitant and adjuvant TMZ, according to Stupp et al.                                                                                                                                       | 79%            |
| Hypofractionated RT (40 Gy) with concomitant and adjuvant TMZ, according to Perry et al.                                                                                                                      | 13%            |
| RT (60 Gy) combined with TMZ and CCNU, according to Herrlinger et al.                                                                                                                                         | 6%             |
| RT alone                                                                                                                                                                                                      | 2%             |
| Extent of resection at initial diagnosis                                                                                                                                                                      |                |
| Complete resection                                                                                                                                                                                            | 29%            |
| Partial resection                                                                                                                                                                                             | 25%            |
| Biopsy                                                                                                                                                                                                        | 46%            |
| Karnofsky Performance Status scale                                                                                                                                                                            |                |
| Median (range)                                                                                                                                                                                                | 90% (60-100%)  |
| NANO scale                                                                                                                                                                                                    |                |
| Median score (range)                                                                                                                                                                                          | 1 (0-5) points |
| <b>Abbreviations:</b> CCNU = lomustine; MGMT = O <sup>6</sup> -methylguanine-DNA-methyltransferase; NANO = Neurologic Assessment in Neuro-Oncology scale; RT = fractionated radiotherapy; TMZ = temozolomide. |                |



**Figure 1.** Illustrative MR and FET PET image including a time-activity curve of a 29-year-old patient (patient #60) with glioblastoma after completion of radiotherapy with concomitant temozolomide. **Abbreviations:** CE = contrast enhancement; MTV = metabolic tumor volume; SUV = standardized uptake value;  $TBR_{max}$  = maximum tumor-to-brain ratio;  $TBR_{mean}$  = mean tumor-to-brain ratio; TTP = time-to-peak

Normalized (*original\_glcml\_idmn*) derived from the unfiltered FET PET images, which predicted a favorable PFS of  $\geq 7$  months with a sensitivity of 85% and a specificity of 72% (AUC,  $0.767 \pm 0.07$ ;  $P < .0001$ ; threshold, 0.99045). A similar performance to predict a favorable OS of  $\geq 15$  months was observed with the same radiomics feature and threshold (sensitivity, 74%; specificity, 75%; AUC,  $0.764 \pm 0.07$ ;  $P < .0001$ ). In addition, ROC analyses revealed

that the static FET PET parameters  $TBR_{max}$  and MTV predicted both a favorable PFS and OS. Absolute values of the dynamic FET PET parameter TTP at radiotherapy completion predicted a favorable OS of  $\geq 15$  months, but not a favorable PFS of  $\geq 7$  months. Values for the radiomics feature *original\_glcml\_idmn* for each individual patient are summarized in [Supplementary Table 2](#). Results of the ROC analyses are summarized in [Supplementary Tables 3 and 4](#).



**Figure 2.** Progression-free and overall survival (PFS, OS) separated by the  $TBR_{max}$  (threshold for both PFS and OS, 2.75) and MTV (threshold for PFS, 34.0 mL; threshold for OS, 32.6 mL) in patients with glioblastoma after radiotherapy completion. **Abbreviations:** MTV = metabolic tumor volume;  $TBR_{max}$  = maximum tumor-to-brain ratio

## Univariate Analysis

Regarding general prognostic factors (ie, age, KPS score, extent of resection, *MGMT* promoter methylation status, NANO score), only age influenced survival. Patients not older than 65 years had a significantly longer PFS (15.6 vs. 6.8 months;  $P=.017$ ) and OS (28.7 vs. 14.1 months;  $P=.040$ ). In addition, the static FET PET parameters  $TBR_{max}$  and MTV predicted a significantly longer PFS and OS (all  $P \leq .005$ ) (Figure 2). The parameter TTP calculated from dynamic FET PET acquisition predicted a significantly longer OS (threshold, 25 min; 29.9 vs. 17.9 months;  $P=.027$ ). The radiomics feature *original\_glcml\_idmn* also predicted longer survival times. Below the threshold of 0.99045, patients had a significantly longer PFS (15.1 vs. 8.6 months;  $P=.002$ ) and OS (30.0 vs. 18.3 months;  $P=.002$ ). The results of the univariate survival analyses are summarized in Table 2.

## Multivariate Analysis

Besides age after radiotherapy completion, the static FET PET parameters  $TBR_{max}$  and MTV, and the radiomics feature *original\_glcml\_idmn* remained statistically significant in the multivariate survival analysis (all  $P < .05$ ), indicating an independent predictor for both PFS and OS. The dynamic FET PET parameter TTP also remained statistically significant in the multivariate survival analysis ( $P=.012$ ), indicating an independent predictor for OS but not for PFS.

The results of the multivariate survival analyses are summarized in Table 3.

## Subgroup Analyses

To exclude a potential bias by different first-line therapies, we re-analyzed the data after exclusion of patients treated according to the CeTeG/NOA-09 trial ( $n=4$ ). Accordingly, the prognostic value of the above-mentioned PET parameters remained statistically significant. In addition, a subgroup analysis of the prognostic value of these parameters in elderly glioblastoma patients older than 65 years ( $n=17$ ) remained also statistically significant. Furthermore, excluding patients who received tumor-treating fields ( $n=9$ ) did not change the results, which remained statistically significant. After stratification by the *MGMT* promoter methylation status (unmethylated,  $n=35$ ; methylated,  $n=28$ ), univariate analyses identified  $TBR_{max}$  as statistically relevant prognostic marker in both the methylated (PFS, 8.9 vs. 27.4 months,  $P=.030$ ) and unmethylated group (PFS, 8.8 vs. 12.0 months,  $P=.026$ ; OS, 13.4 vs. 25.6 months,  $P=.063$ ). In the unmethylated group, MTV and the dynamic FET PET parameter TTP remained also statistically significant predictors of PFS and OS (both  $P < .02$ ). Furthermore, the radiomics feature *original\_glcml\_idmn* remained statistically significant regarding PFS in both groups ( $P < .013$ ) and showed a highly significant association with OS in the methylated group (13.1 vs. 32.8 months,  $P=.002$ ).

**Table 2.** Univariate Survival Analyses Regarding FET PET Imaging Parameters Including Best-performing Radiomics Features and General Prognostic Factors

|                                         | Threshold                 | Univariate PFS analysis |                 | Threshold                 | Univariate OS analysis |                 |
|-----------------------------------------|---------------------------|-------------------------|-----------------|---------------------------|------------------------|-----------------|
|                                         |                           | P-value                 | PFS (months)    |                           | P-value                | OS (months)     |
| Sex                                     | female vs. male           | .419                    | 14.7 vs. 11.7   | female vs. male           | .486                   | 26.5 vs. 23.7   |
| Age (years)                             | < 65 vs. > 65             | .017                    | 15.6 vs. 6.8    | < 65 vs. > 65             | .040                   | 28.7 vs. 14.1   |
| MGMT promoter methylation status        | methyated vs. unmethyated | .127                    | 17.5 vs. 9.8    | methyated vs. unmethyated | .070                   | 30.7 vs. 20.4   |
| EoR                                     | CR vs. PR or B            | .411                    | 15.8 vs. 12.1   | CR vs. PR and B           | .534                   | 25.7 vs. 25.2   |
| KPS (%)                                 | 100 vs. < 100             | .778                    | 14.9 vs. 12.2   | 100 vs. < 100             | .309                   | 28.1 vs. 23.9   |
| NANO (points)                           | < 2 vs. ≥ 2               | .236                    | 16.0 vs. 7.7    | < 2 vs. ≥ 2               | .165                   | 28.7 vs. 17.3   |
| TBR <sub>max</sub>                      | < 2.75 vs. > 2.75         | .002                    | 20.3 vs. 8.9    | < 2.75 vs. > 2.75         | .005                   | 34.9 vs. 18.7   |
| TBR <sub>mean</sub>                     | < 1.85 vs. > 1.85         | .081                    | 16.7 vs. 11.7   | < 1.85 vs. > 1.85         | .217                   | 28.0 vs. 23.5   |
| MTV (mL)                                | < 34.0 vs. > 34.0         | .002                    | 16.4 vs. 7.2    | < 32.6 vs. > 32.6         | .002                   | 30.6 vs. 14.8   |
| TTP (minutes)                           | > 25 vs. < 25             | .082                    | 14.6 vs. 11.1   | > 25 vs. < 25             | .027                   | 29.9 vs. 17.9   |
| Slope (SUV/h)                           | < -0.097 vs. > -0.097     | .425                    | 13.95 vs. 12.08 | < 0.116 vs. > 0.116       | .694                   | 25.71 vs. 24.17 |
| Radiomics feature (original_glcml_idmn) | < 0.99045 vs. > 0.99045   | .002                    | 15.1 vs. 8.6    | < 0.99045 vs. > 0.99045   | .018                   | 30.0 vs. 18.3   |

**Abbreviations:** B = biopsy; CR = complete resection; EoR = extent of resection; KPS = Karnofsky Performance Status scale after completion of radiotherapy; MGMT = O<sup>6</sup>-methylguanine-DNA-methyltransferase; MTV = metabolic tumor volume; NANO = Neurologic Assessment in Neuro-Oncology scale; original\_glcml\_idmn = gray level co-occurrence matrix inverse difference moment normalized; OS = overall survival; PFS = progression-free survival; PR = partial resection; TBR<sub>max</sub> = maximal tumor-to-brain ratio; TBR<sub>mean</sub> = mean tumor-to-brain ratio; TTP = time-to-peak.

**Table 3.** Multivariate Survival Analyses Including Significant FET PET Imaging Parameters and Best-performing Radiomics Features Compared with General Prognostic Factors

|                                         | Multivariate PFS analysis |      |           |         | Multivariate OS analysis |      |           |         |
|-----------------------------------------|---------------------------|------|-----------|---------|--------------------------|------|-----------|---------|
|                                         | Threshold                 | HR   | 95% CI    | P-value | Threshold                | HR   | 95% CI    | P-value |
| TBR <sub>max</sub>                      | > 2.75                    | 1.41 | 1.06–1.88 | .020    | > 2.75                   | 1.96 | 1.11–3.47 | .021    |
| MTV (mL)                                | > 34.0                    | 1.92 | 1.07–3.43 | .028    | > 32.6                   | 2.14 | 1.23–3.72 | .007    |
| TTP (minutes)                           |                           |      |           |         | > 25                     | 0.49 | 0.29–0.85 | .012    |
| Radiomics feature (original_glcml_idmn) | > 0.99045                 | 1.99 | 1.14–3.49 | .016    | > 0.99045                | 1.77 | 1.01–3.09 | .048    |

**Abbreviations:** CI = confidence interval; HR = hazard ratio; MTV = metabolic tumor volume; original\_glcml\_idmn = gray level co-occurrence matrix inverse difference moment normalized; OS = overall survival; PFS = progression-free survival; TBR<sub>max</sub> = maximal tumor-to-brain ratio; TTP = time-to-peak.

## Discussion

This study's most relevant finding is that static and dynamic FET PET parameters, as well as radiomics features extracted from FET PET, were highly prognostic in patients with glioblastoma diagnosed according to the CNS WHO 2021 classification at an early stage of first-line therapy, that is, after completion of radiotherapy. In particular, imaging parameters obtained from FET PET seem to identify patients with a more favorable outcome within this patient group with a generally dismal outcome. Thus, FET PET may be of value for patient counseling and allows a

stronger emphasis on personalized treatment decisions. Furthermore, in clinical trials evaluating adjuvant therapy after radiotherapy completion, FET PET may assist in creating prognostically balanced treatment and control patient groups.

Our findings support the results of previous FET PET studies assessing prognosis in glioblastoma patients.<sup>18,19,50</sup> For example, Suchorska et al. demonstrated that especially the static FET PET parameter MTV obtained before initiation of chemoradiation with temozolomide is a powerful prognostic marker in patients with glioblastoma independent from MGMT promoter methylation status and mode of surgery.<sup>19</sup>

Furthermore, in patients with predominantly *IDH*-wildtype gliomas at initial diagnosis, Bauer and colleagues observed that the dynamic FET PET parameter TTP was highly prognostic for significantly longer PFS and OS.<sup>18</sup> Of note, the reported TTP threshold (ie, 25 min) for this prediction in that study was exactly the same as shown in the present study. For research purposes, these studies were performed at an early disease stage. In contrast, despite its increasing routine use predominantly in European centers, FET PET is mostly used for clinical purposes at a later stage of first-line therapy, that is, after radiotherapy completion, especially for diagnosing pseudoprogression.<sup>20</sup> Thus, the present study adds further information on FET PET and its prognostic value at this particular stage of disease.

Regarding the prognostic value of radiomics features extracted from amino acid PET, our findings are basically in line with and extend upon previous results.<sup>51,52</sup> In patients with newly diagnosed glioblastoma after surgery, the study by Shahzadi and co-workers revealed that the prognostication of the time-to-recurrence and OS could be obtained best using radiomics derived from postoperative [<sup>11</sup>C]-methyl-L-methionine (MET) PET combined with clinical parameters (ie, age and *MGMT* promoter methylation status).<sup>51</sup> Another study highlighted the prognostic value of FET PET radiomics before re-irradiation in 32 patients with glioblastoma in the recurrent setting.<sup>52</sup> In the present study, the radiomics signature *original\_glcml\_idmn* were identified as significantly prognostic for both a longer PFS and OS (both  $P = .002$ ). The authors suggested that FET PET radiomics may contribute to the prognostic assessment and selection of patients with glioblastoma recurrence benefiting from re-irradiation.<sup>52</sup> Besides these previously reported results, the radiomics feature *original\_glcml\_idmn* – a measure of the local homogeneity of an image – makes it possible to predict significantly longer survival time after radiotherapy completion using the tracer FET, which has considerable logistic advantages compared to MET due to radiolabeling with F-18.

The following limitations of our study need to be discussed. The study is based on retrospective data and should be regarded as a proof-of-concept analysis. The results warrant confirmation in a prospective study. Another putative weakness is the relatively small number of patients, which might explain why well-known prognostic factors such as a complete resection or a high KPS score did not predict a favorable outcome. Although the patient sample includes only patients with glioblastoma characterized according to the latest CNS WHO 2021 criteria, the clinical heterogeneity in terms of applied treatment regimens may represent a further limitation. Although multivariate analyses and subgroup analyses were performed, residual confounders cannot be fully excluded. Furthermore, practical considerations are that acquiring and analyzing dynamic FET PET scans is time-consuming and more complex than evaluating static parameters such as TBR and MTV. These practical considerations might hamper a more widespread use of this powerful imaging technique. In addition, it is a matter of debate that PET imaging protocols are not sufficiently standardized for widespread use in clinical routine, especially in the context of amino acid PET for brain tumors, which is not yet covered by

existing Quantitative Imaging Biomarker Alliance (QIBA) Profiles.<sup>53</sup> Notwithstanding, in 2019, major European and American medical societies for Nuclear Medicine and Neuro-Oncology (ie, the Society of Nuclear Medicine and Molecular Imaging, the European Association of Nuclear Medicine, the European Association of Neuro-Oncology, and the RANO group for PET) have published joint practice guidelines for amino acid PET addressing acquisition of images, data evaluation, and reporting of results<sup>37</sup> which may help to harmonize imaging protocols, especially in clinical trials.

In conclusion, our data suggest that in patients with glioblastoma characterized according to the CNS WHO 2021 classification who had completed radiotherapy combined with chemotherapy, FET PET parameters, including radiomics, provide critical information for assessing the probability of tumor relapse by predicting the PFS, predicting patient outcomes in terms of OS, guiding further treatment, and avoiding unnecessary interventions. Regarding the latter-mentioned point, especially in the subgroup of patients with reduced clinical condition (eg, older or frail patients with a considerably reduced KPS), our FET PET findings may be helpful for patient counseling, that is, to decide whether subsequent treatment with an increased risk of severe side effects should be administered or not. Accordingly, a prospective clinical trial is warranted to further improve the confidence level of the obtained initial data.

## Supplementary Material

Supplementary material is available online at *Neuro-Oncology Advances* (<https://academic.oup.com/noa>).

## Keywords:

glioma | prognosis | artificial intelligence

## Lay Summary

Glioblastoma is a fast-growing brain tumor that is difficult to treat. The authors of this study wanted to see if PET scans could help predict how long patients with glioblastoma might live after starting treatment. To do this, they analyzed PET scans and other imaging data from 63 patients who had surgery or a biopsy followed by radiation and chemotherapy. Their study found that specific PET scan features, including tumor activity and size, were linked to how long patients lived without the tumor getting worse and to overall survival. These results suggest that PET imaging could be a useful tool early in treatment planning for patients with glioblastoma.

**Conflict of interest statement.** NG received honoraria for lectures from Blue Earth Diagnostics, for advisory board

participation from Telix Pharmaceuticals and Servier, and for consultancy services from Telix Pharmaceuticals. PL received honoraria for lectures from Blue Earth Diagnostics and for advisory board participation from Servier. KJL and FM received honoraria for consultancy services from Telix Pharmaceuticals. JW received funding from the German Cancer Aid (Deutsche Krebshilfe). FM received institutional grants from the German Research Foundation (DFG) and Radiopharm Theranostics. FM received consulting fees from Novartis. GRF received honoraria for lectures of the Deutsche Gesellschaft für Neurologie and Forum Medizin Fortbildung (FOMF).

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## Ethics Statement

Before PET imaging, all patients had given written informed consent for the PET investigation and data usage for scientific purposes. The local ethics committee approved the retrospective analysis of neuroimaging data performed under the Declaration of Helsinki.

## Author Contributions

Study design: N.G., I.S. Data acquisition: I.S., J.-M.W., M.W., G.C., G.S., N.G. Data analysis, writing of manuscript drafts: I.S., K.G.C., P.L., N.G. Interpretation of data: I.S., G.R.F., K.-J.L., F.M.M., K.G.C., P.L., N.G. Revising manuscript, approving final content of manuscript: all.

## Data Availability

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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