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# Amino acid positron emission tomography to monitor chemotherapy response and predict seizure control and progression-free survival in WHO grade II gliomas

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## Abstract

### Background

Patients with WHO grade II glioma may respond to chemotherapy that is currently not standardized regarding timing and treatment duration. Metabolic changes during chemotherapy may precede structural tumor volume reductions. We therefore compared time courses of amino acid PET and MRI responses to temozolomide (TMZ) and assessed whether responses correlated with seizure control and progression-free survival (PFS).

### Methods

PET and MRI were performed before and during TMZ chemotherapy. Tumor volumes were calculated using regions-of-interest analysis. Amino acid uptake was also quantified as metabolically active tumor volume and tumor-to-cerebellum uptake ratio.

### Results

One hundred twenty-five PET and 125 MRI scans from 33 patients were analyzed. Twenty-five patients showed metabolic responses that exhibited an exponential time course with a 25% reduction of the active volume on average after 2.3 months. MRI responses followed a linear course with a 25% reduction after 16.8 months. Reduction of metabolically active tumor volumes, but not reduction of PET uptake ratios or MRI tumor volumes, correlated with improved seizure control following chemotherapy ( $P = .012$ ). Receiver-operating-characteristic curve analysis showed that a decrease of the active tumor volume of  $\geq 80.5\%$  predicts a PFS of  $\geq 60$  months ( $P = .018$ ) and a decrease of  $\geq 64.5\%$  a PFS of  $\geq 48$  months ( $P = .037$ ).

### Conclusions

Amino acid PET is superior to MRI for evaluating TMZ responses in WHO grade II glioma patients. The response delay between both imaging modalities favors amino acid PET for individually tailoring the duration of chemotherapy. Additional studies should investigate whether this personalized approach is appropriate with regard to outcome.

**Keywords:** chemotherapy, epilepsy, low-grade glioma, MRI, PET

Diffuse cerebral WHO grade II gliomas often present with epileptic seizures and show insidious tumor growth.<sup>1</sup> The natural history and response to treatment of these tumors are predominantly determined by genetic alterations such as co-deletion on chromosomal arms 1p and 19q, isocitrate dehydrogenase 1 (IDH1/2) mutation, and methylation of the *O*<sup>6</sup>-methylguanine-DNA methyltransferase (*MGMT*) promoter.<sup>2,3</sup>

Alkylating agent chemotherapy is effective in patients with WHO grade II glioma. Once given at tumor progression or recurrence, it yields objective response rates up to 60% and response durations of several years.<sup>4</sup> In addition, chemotherapy can reduce the frequency of seizures. However, the evaluation of chemotherapy response based on MRI with T<sub>2</sub>-weighted and fluid-attenuated inversion recovery (FLAIR) MRI sequences is difficult.<sup>5</sup> Accordingly, a reduction in seizure frequency has been proposed as a surrogate marker for a clinical benefit from chemotherapy.<sup>6,7</sup> There is no current standard for the optimal drug choice, timing, or duration of chemotherapy. The European Organization for Research and Treatment of Cancer trial 22033-26033 prescribed 12 cycles of temozolomide (TMZ) chemotherapy, while other groups treated patients as long as MRI showed at least evidence of stable disease.<sup>4</sup> Interestingly, tumors may continue to shrink on MRI even after termination of chemotherapy.<sup>8,9</sup> We have previously reported WHO grade II glioma patients who experienced rapid metabolic deactivation in response to TMZ, which was confirmed by using PET with the amino acid O-(2-[18F]fluoroethyl)-L-tyrosine (FET).<sup>10</sup> Our current study aimed to investigate metabolic responses in a large multicenter participant cohort treated with TMZ. We also assessed whether metabolic responses on PET correlate with seizure control and progression-free survival (PFS).

## Materials and Methods

### Clinical Data

Participants were retrospectively identified according to the following criteria: (i) supratentorial cerebral WHO grade II glioma at progression after surgery; (ii) no contrast enhancement on T<sub>1</sub>-weighted MRI; (iii) no previous radio- or chemotherapy; (iv) measurable disease on T<sub>2</sub>-

weighted MRI before chemotherapy with 2 perpendicular diameters  $\geq 10$  mm; and (v) MRI and amino acid PET schedule including baseline evaluation and at least 2 examinations during and at the end of chemotherapy. Participant data were extracted from the hospital medical records and included demographic as well as tumor and treatment characteristics, PFS, and overall survival (OS). Seizure frequencies before chemotherapy were documented during postsurgical surveillance in every 3 months. Seizure frequencies were recorded monthly during chemotherapy. We defined seizure control groups during chemotherapy as: group I = 0–50% seizure frequency reduction and group II =  $>50\%$  reduction or seizure free.

## Chemotherapy

TMZ chemotherapy was administered according to local policies (Table 1). Adverse effects were scored according to the Common Terminology Criteria for Adverse Events (CTCAE, version 4.0).

| ID | Age | Sex | Histology    | Survival |
|----|-----|-----|--------------|----------|
| 1  | 37  | A   | WHO grade II | 2020     |
| 2  | 48  | A   | WHO grade II | 2020     |
| 3  | 36  | A   | WHO grade II | 2020     |
| 4  | 33  | A   | WHO grade II | 2020     |
| 5  | 36  | A   | WHO grade II | 2020     |

Table 1.

Clinical data, histology and molecular genetic status, imaging response, and survival

## Imaging Data Acquisition

Baseline imaging was performed within one month before chemotherapy initiation, and follow-up imaging started between 2 and 6 months thereafter. MRI examinations included T<sub>2</sub>-weighted and gadolinium-enhanced T<sub>1</sub>-weighted sequences according to clinical routine protocols on 1.5 or 3.0 Tesla MRI scanners. PET data were acquired after intravenous administration of 150–240 MBq FET (Switzerland, Austria, Germany) or ~650 MBq L-[methyl-11C]methionine (MET, Italy). Grosu et al reported that both tracers yield virtually identical amino acid uptake values in gliomas.<sup>11</sup> Their whole cohort of patients with WHO grade II–IV gliomas showed mean tumor-to-brain uptake ratios of 2.5 for FET and of 2.6 for MET, which represent a difference of 4%. Uptake ratios differed by 1% for the subgroup of WHO II gliomas.<sup>11</sup> We therefore consider both MET and FET suitable to comparably characterize low-grade gliomas on amino acid PET. Static emission scans were acquired at the following time periods after tracer administration: 40–60 minutes (Switzerland; Discovery LS, GE Medical Systems), 30–45 minutes (Austria; Advance, GE Healthcare), 20–40 minutes (Germany; ECAT Exact HR+, Siemens), and 30–45 minutes (Italy; Discovery LS, GE Healthcare). After correction for random and scattered coincidences and dead time, images were reconstructed with the specific scanner software. The reconstructed image resolution was ~5.5 mm.

## Image Data Analysis, Determination of Response, and Progression

Response assessment on PET and MRI was centrally performed by M.Wy. (nuclear medicine) and U.R. and N.G. (neuro-oncologists) with long-standing experience in PET and MRI analysis. Each participant served as his or her own control, and values during chemotherapy were expressed as percent from baseline (ie, before the start of chemotherapy). Quantification of PET and MRI data was performed on co-registered images using PMOD (PMOD Technologies Ltd).<sup>12</sup> MRI tumor volumes were measured on T<sub>2</sub>-weighted axial sequences by manually outlining regions-of-interest (ROIs) around tissue exhibiting T<sub>2</sub>-hyperintensity. Finally, all tumor-containing slices were summed. Values during chemotherapy were expressed as percent change from baseline MRI before the initiation of chemotherapy. Response was also determined according to the Response Assessment in Neuro-Oncology (RANO) criteria, which quantify the product of the perpendicular tumor diameters on the slice showing the largest tumor area (mm<sup>2</sup>).<sup>5</sup> The RANO criteria categorize size reductions between 25% and 50% as minor response,  $\geq 50\%$  as partial response, and disappearance of the lesion on T<sub>2</sub>-weighted or FLAIR MR imaging as complete response. Objective response is defined as the sum of minor response, partial response, and complete response. Size increases  $\geq 25\%$  were scored as progressive disease. Stable disease was defined when MRI changes did not qualify for progression or for complete, partial, or minor response. We also diagnosed progression if new contrast enhancement on T<sub>1</sub>-weighted sequences or clinical signs (eg, recurrence or new onset of seizures) were accompanied by tumor size increase  $<25\%$ .

Amino acid uptake was also quantified using ROI analysis. The cerebellum served as reference region. ROIs covering the whole cerebellum were drawn for each slice. Counts of all cerebellar ROIs were then averaged to produce the mean cerebellar amino acid uptake. Three measures were used for tumors. First, the metabolically active volume (cm<sup>3</sup>) was calculated as the tumor volume containing pixels  $>110\%$  of the mean cerebellar amino acid uptake. We derived this threshold from our earlier methodological study.<sup>13</sup> It corresponds well with the visual impression of active WHO grade II gliomas on PET.<sup>14</sup> Second, the tumor amino acid uptake (counts) was determined by placing a ROI over the tumor on the PET slice with the largest extent, which was normalized to the mean cerebellar uptake (mean T-to-CBL ratio, unit-less). Third, peak uptake ratios were calculated by averaging all counts from tumor voxels that exhibited  $\geq 95\%$  of the maximum tumor radioactivity. In participants without active tumor volume, ROIs were placed on the T<sub>2</sub>-weighted MR images and then transferred to the corresponding PET planes. In line

with our previous study,<sup>10</sup> we defined a metabolic treatment response as a reduction of  $\geq 10\%$  from the initial tumor volume (active PET volume) on at least 2 subsequent time points at least 4 weeks apart after the initiation of chemotherapy.

## Molecular Genetics

1p/19q co-deletion was assessed by fluorescence in situ hybridization and MGMT promoter methylation by methylation-specific PCR. IDH1 status was determined by immunohistochemistry or gene sequencing.

## Statistics

We used descriptive statistics to characterize the patient population. To test group-to-group differences, the Mann-Whitney U test for independent samples was applied. The association between baseline imaging parameters and PFS was assessed using the Spearman rank test. The prognostic value of the metabolically active tumor volume on PFS was assessed by receiver-operating-characteristic (ROC) curve analyses. Participants were divided into responders (PFS  $\geq 12, 24, 36, 48,$  or 60 months) and nonresponders (PFS  $< 12, 24, 36, 48,$  or 60 months). Decision cutoff was considered optimal when the product of paired values for sensitivity and specificity reached its maximum. Moreover, we determined the area under the ROC curve (AUC), its standard error, and level of significance as measures of diagnostic quality. In addition, we used uni- and multivariate analyses including logistic regression to test for associations of histology, PET and MRI response, and total dose of TMZ as well as 1p/19q co-deletion, IDH1, and MGMT status with PFS. PFS and OS were calculated from the start of chemotherapy. Analyses were performed using SigmaStat software (version 3.5; Systat Software, Inc.).

## Ethics

Amino acid PET examinations are part of routine clinical investigations in WHO grade II glioma participants in Austria, Italy, Switzerland, and Germany. All participants gave written informed consent before each FET or MET PET investigation. Signed consent is not required to perform clinical PET scans in Switzerland. The local ethics committee of Innsbruck Medical University approved this retrospective study. In Italy, local ethics committee approval or patients' signed consent is not required for retrospective data evaluation.

## Results

Thirty-three participants with WHO grade II astrocytoma ( $n = 6$ ), oligodendroglioma ( $n = 20$ ), or oligoastrocytoma ( $n = 7$ ) were enrolled (21 male and 12 female, mean age:  $37 \pm 8$  [SD] y, range: 20–53 y). Prior to chemotherapy, 29 participants underwent one, and 4 participants underwent 2 surgical procedures (gross total resection in 6, partial resection in 18, biopsy in 9 participants, Table 1). During the entire study, no participant received steroids, and no participant was treated with either previous radiotherapy or PCV (procarbazine-lomustine-vincristine) chemotherapy.

## Chemotherapy

TMZ chemotherapy started  $40 \pm 36$  months (range: 1–126 mo) after the last operation because of radiological progression. Chemotherapy was completed as scheduled in 17 participants and was interrupted because of participant request, toxicity, or progression in 1, 7, and 8 participants, respectively. Hematological adverse effects of CTCAE grades 1, 2, or 3 were noted in 5, 3, and 8 participants, respectively. Nonhematological adverse effects consisted of nausea in 8 participants (grades 1–3), fatigue in 6 (grades 2–3), anorexia in 2 (grades 1–2), pruritus in 2 (grade 2), and local skin infection/zoster in 2 (grades 2–3). No secondary neoplasias were observed after a median follow-up of 74 months.

## Imaging

All participants from Italy were imaged with MET-PET ( $n = 9$ ). Participants from all other countries were imaged with FET-PET ( $n = 24$ ). One-hundred twenty-five PET scans and 125 MRI scans were available for evaluation. On MRI, 14 participants achieved an objective response (9 minor responses, 5 partial responses) (Table 1). Baseline tumor volumes on T<sub>2</sub>-weighted MRI ranged from 4.3–450.3 cm<sup>3</sup> ( $75.7 \pm 103.9$  cm<sup>3</sup>). Among those 30 participants with baseline active tumor defined by PET, volumes ranged from 1.4–269.9 cm<sup>3</sup> ( $51.2 \pm 51.2$  cm<sup>3</sup>). In line with previous work,<sup>11</sup> we found similar baseline mean tumor uptake ratios for MET ( $1.43 \pm 0.27$ ) and FET ( $1.42 \pm 0.20$ ). For histological subtypes, the following numbers were found: T-to-CBL ratios were  $1.43 \pm 0.24$  in oligodendrogliomas,  $1.43 \pm 0.27$  in oligoastrocytomas, and  $1.28 \pm 0.14$  in astrocytomas. Peak T-to-CBL ratios were  $2.34 \pm 2.29$  in oligodendrogliomas,  $2.49 \pm 1.99$  in oligoastrocytomas, and  $1.80 \pm 1.58$  in astrocytomas. We found no active tumor volume at baseline in 3 participants. In these patients, the median T-to-CBL ratio was  $1.04 \pm 0.02$ .

We identified 25 metabolic responders and 5 nonresponders. Examples of individual PET and MRI responses are presented in Figure 1A. Metabolic responses during chemotherapy were best described by an exponential time course, which yielded a reduction of 25% after 2.3 months (Fig. 1B). In contrast, MRI responses on T<sub>2</sub>-weighted images of the same participants were delayed, followed a linear decrease, and showed a volume reduction of 25% at 16.8 months after initiation of chemotherapy (Fig. 1C). During chemotherapy, the mean and peak T-to-CBL ratios in PET responders were reduced in 7 participants by 10%–21%. The remaining participants showed decreases of  $< 7\%$ , most likely indicating that

successful chemotherapy reduced the spatial extent of tumor burden (ie, the active tumor volume) but not the histology or WHO tumor grade. In contrast to the responses of the active tumor volume, T-to-CBL ratios did not follow a linear or exponential fit (data not shown).

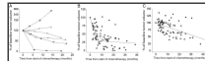


Fig. 1.

Time course of imaging responses. (A) Examples of individual responses as measured with PET (filled symbols) and MRI (open symbols). Square: oligoastrocytoma (#12); triangle: oligodendroglioma (#16); diamond: astrocytoma (#6). (B and C) Data points represent ...

In PET, nonresponding participants' active tumor volumes increased within 6 months up to 354% from baseline. The mean T-to-CBL ratios increased by 7%–11%, and the peak T-to-CBL ratios increased by 14%–36%. All tumors without active volume remained metabolically inactive during chemotherapy, and T-to-CBL ratios remained in a range between 96% and 103% from baseline.

## Molecular Genetic Data

Information on IDH1 status and LOH1p/19q was available for 26 participants each, and MGMT promoter methylation was available for 24 participants (Table 1). Twenty-two (85%) tumors showed IDH1 mutation, 13 (50%) had 1p/19q co-deletion, and 20 (83%) had MGMT promoter methylation. PET responders exhibited IDH1 mutation in 17 (77%) participants, 1p/19q co-deleted tumors in 11 (85%) participants, and MGMT promoter methylation in 17 (85%) participants.

## Seizures

Twenty-two participants presented with seizures before chemotherapy. Tumor size on MRI, active PET tumor volume, and tumor uptake ratios at baseline were balanced between the 2 seizure response groups (Table 2). During chemotherapy, antiepileptic drug doses were changed to account for low drug serum concentration or for persisting seizures in 5 participants, and were stable in 17 participants. No participant experienced an increase in seizure frequency during chemotherapy. Nine participants experienced seizure frequency reductions by 0%–50% and 6 participants by >50%, while 7 participants were seizure-free. Among the 17 participants under stable antiepileptic drug doses, TMZ reduced the active tumor volumes by  $22\% \pm 27\%$  in group I participants and by  $64\% \pm 28\%$  in group II participants (Fig. 2A,  $P = .012$ , Mann-Whitney test). In contrast, neither T-to-CBL ratio changes nor volume changes on T<sub>2</sub>-weighted MRI images corresponded with seizure frequency reductions (Fig. 2B and C).

|  | Group I | Group II |
|--|---------|----------|
| Number of participants                               | 9       | 13       |
| Median age   | 4       | 5        |
| Sex (male/female)                                    | 4/5     | 6/7      |
| Median tumor size (mm)                               | 21      | 21       |
| Median active PET volume (ml)                        | 10      | 10       |
| Median T-to-CBL uptake ratio                         | 1.00    | 1.00     |
| Median T <sub>2</sub> -weighted MRI lesion size (mm) | 2.0     | 2.0      |
| Median T-to-CBL uptake ratio                         | 1.00    | 1.00     |

Table 2.

Baseline characteristics according to seizure frequency reduction groups

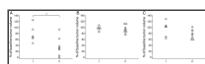


Fig. 2.

Seizure control and imaging responses. Best imaging responses on active PET volume (A), mean T-to-CBL uptake ratio (B), MRI T<sub>2</sub> lesion size (C) in patients under stable antiepileptic drug doses ( $n = 17$ ). Seizure control group I = reduction of seizure frequency ...

## Survival

At the time of last follow-up, 25 participants were alive, 7 had died, and one was lost to follow-up. Twenty-six participants progressed at  $33 \pm 22$  months (range: 6–85 mo) after the start of chemotherapy, while 7 participants were free from progression at  $42 \pm 22$  months (range: 6–68 mo). Progression was characterized by neurological deterioration in 23 participants, by increase of the T<sub>2</sub> lesion in 24 participants, and by appearance of new contrast enhancement in 14 participants, respectively. Nine participants underwent re-operation for progressive tumor (Table 1). Of the progressing participants, 7 died  $45 \pm 19$  months (range: 21–75 mo) after starting chemotherapy.

Neither the mean nor the peak T-to-CBL ratio nor the magnitude of active tumor volumes prior to chemotherapy was predictive for PFS ( $P = .551$ ,  $P = .748$ , and  $P = .622$ , respectively). In participants with active tumor volume ( $n = 30$ ), the median PFS was not significantly different between metabolic responders ( $34.3 \pm 21.8$  mo, range: 6–85 mo) and nonresponders ( $27.6 \pm 27.2$  mo, range: 6–67 mo) ( $P = .605$ ). In contrast, ROC analysis yielded a decrease of the active tumor volume of  $\geq 80.5\%$  as an optimal cutoff for the prognostication of a PFS  $\geq 60$  months (sensitivity 67%, specificity 90%, accuracy 83%, AUC  $0.78 \pm 0.02$ ,  $P = .018$ ). For the prognostication of a PFS  $\geq 48$  months, a decrease of the active tumor volume of  $\geq 64.5\%$  was the optimal threshold (sensitivity 70%, specificity 58%, accuracy 62%, AUC  $0.74 \pm 0.11$ ,  $P = .037$ ). The prognostication of a PFS  $\geq 36$  months ( $P = .154$ ),  $\geq 24$  months ( $P = .369$ ), and  $\geq 12$  months ( $P = .057$ ), respectively, was not significant.

The PFS in participants without active tumor volume was  $29.1 \pm 12.4$  months (range: 17–41 mo). None of the following parameters correlated with PFS, either on univariate or multivariate analysis: histology (oligodendroglial/oligoastrocytic vs astrocytic tumor,  $P = .988$ ), PET (responder vs nonresponder,  $P = .734$ ), MRI (objective response [RANO],  $P = .276$ ), total TMZ dose ( $P = .100$ ), IDH1 status ( $P = .088$ ), 1p/19q co-deletion ( $P = .331$ ), MGMT promoter methylation status ( $P = .672$ ) ( $P$  values shown for univariate analysis). In addition group-to-group comparisons (imaging responses) did not show differences between tumors with or without IDH mutation, between tumors with or without co-deletion 1p19q, or between tumors with methylated or unmethylated MGMT promoter (Mann-Whitney U test,  $P > .5$  for all comparisons). This may, in part, be explained by the small subgroups compared within this test.

## Discussion

In line with previous reports on patients with diffuse cerebral WHO grade II gliomas, we have observed that chemotherapy responses on MRI occur with variable delay from the initiation of treatment.<sup>8,9</sup> We noticed a 25% tumor volume reduction on MRI after 16.8 months, whereas a 25% reduction of the metabolically active tumor volume on PET was observed as early as 2.3 months after initiation of chemotherapy. We excluded participants with enhancing tumors on MRI because blood-brain barrier disruption contributes to nonspecific imaging results through passive radiotracer influx into the tumor. Thus, we can assume that the amino acid PET signal in our participants is specific for active amino acid uptake,<sup>15,16</sup> which for MET and FET is largely mediated by the L-amino acid transport system.<sup>17</sup> Accordingly, TMZ chemotherapy appears to downregulate active amino acid transport in WHO grade II gliomas as an early response indicator. Altogether, 83% of our participants with active tumor volume were PET responders following exposure to TMZ. The long delay between PET and MRI responses may reflect that amino acid transporters represent a sensitive nutritional part of tumor cell metabolism, whereas signal abnormalities on MRI T<sub>2</sub>-weighted sequences, which may relate to tumor cell densities, edema, and alteration of the extracellular matrix, respond slowly to cytotoxic therapy.

Apart from tumor control, TMZ chemotherapy resulted in improved seizure control. To the best of our knowledge, this is the first study showing that seizure control corresponds to the magnitude of active tumor volume reductions on amino acid PET. Of note, seizure control was neither paralleled by changes in amino acid uptake ratios nor by decreases of tumor volumes as measured by MRI. The latter is in line with recent observations in patients with WHO grade II gliomas treated with either radiotherapy<sup>18</sup> or TMZ.<sup>7</sup> Thus, improved seizure control may not rely exclusively on reduced compression of neuronal structures by the tumor but also on the reduction of magnitude and spatial extent of local metabolic disequilibrium. The mechanisms behind improved seizure control may involve the glutamatergic system. Gliomas release glutamate as an excitatory neurotransmitter and activate neuronal glutamate receptors.<sup>19,20</sup> FET uptake is increased during status epilepticus in the cortex adjacent to gliomas and resolves after cessation of epileptic activity.<sup>21</sup> Whether transport of both types of amino acids, which use different transport systems under physiological conditions, relates to each other in gliomas remains to be evaluated.

The main limitation of our study is its retrospective nature and small sample size. Moreover, there was heterogeneity of TMZ regimens and PET and MRI scanners, and molecular data were not available for all participants. The variability of TMZ regimens reflects the current lack of evidence-based recommendations regarding the optimal regimen and duration of chemotherapy.<sup>22</sup> However, based on our results, we assume that the time delay between amino acid PET and MRI response may be clinically meaningful. Individual PET-guided determination of chemotherapy duration in patients showing an early metabolic response and response plateau could reduce the risk of toxicity and lower treatment burden and costs. Moreover, one should be cautious about overtreating patients with alkylating chemotherapy, which can exert a mutagenic effect influencing the risk of malignant transformation.<sup>23,24</sup> In conclusion, here we have characterized the patterns of chemotherapy response on amino acid PET in a cohort of patients with diffuse cerebral WHO grade II gliomas and report a positive correlation between active tumor volume responses, PFS, and seizure control. A prospective study should validate our findings including MRI, dynamic amino acid PET,<sup>25</sup> and molecular markers to determine whether personalized PET-guided management has impact on survival. With regard to the choice of amino acid PET tracer, FET currently seems to be the most promising.<sup>26</sup> For the purpose of assessing response to chemotherapy, FET uptake should be quantified as metabolically active volume. This may represent a useful approach to patients with WHO grade II gliomas, a rare disease with substantial variation of the clinical course and treatment response.

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