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Assessment of ^{18}F-FET PET-based response in patients with gliomas using the PET RANO 1.0 criteria

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Abstract

Background. We evaluated the amino acid PET-based response assessment criteria (PET RANO 1.0) for their proficiency in predicting longer survival in patients with gliomas undergoing adjuvant temozolomide chemotherapy.

Methods. In a previous study, 38 patients with newly diagnosed grade 4 gliomas according to the World Health Organisation classification underwent *O*-(2-[^{18}F]fluoroethyl)-l-tyrosine (^{18}F-FET) PET at baseline and after the second cycle of adjuvant temozolomide chemotherapy. The ability of PET parameter changes to predict favorable progression-free and overall survival (PFS, OS) of ≥9 and ≥15 months was evaluated. Here, we performed a post hoc analysis of these PET data to evaluate the PET RANO 1.0 criteria. In addition, the value of the RANO 2.0 criteria for MRI to predict response was evaluated and compared with the PET RANO 1.0 criteria.

Results. According to the PET RANO 1.0 criteria, patients with *Stable Disease* (n=16), *Partial Response* (n=9), or *Complete Response* (n=0) had a significantly longer OS than patients with *Progressive Disease* (n=13) (16.8 vs 12.0 months; P=.016). This difference remained significant in the multivariate survival analysis (HR, 4.185; 95% CI, 1.715-10.530, P=.002). In contrast, PFS was not significantly different between the two groups (9.7 vs 8.1 months; P=.147). PET RANO 1.0 criteria could not identify patients with a PFS ≥ 9 months (P=.503) or OS ≥ 15 months (P=.722). RANO 2.0 criteria for MRI were unable to predict a longer PFS (8.8 vs 9.8 months; P=.565) or OS (16.4 vs 16.8 months; P=.625).

Conclusions. Our data suggest that PET RANO 1.0 criteria identify survival differences between predefined groups. Despite many efforts in recent years, the treatment of gliomas remains restricted to maximally safe cytoreductive surgery, radiotherapy, alkylating chemotherapy, and, in case of disease relapse, antiangiogenic agents and other more experimental approaches.[1]

Key Points

- Recently, the PET RANO 1.0 criteria for assessment of treatment response in patients with diffuse gliomas using amino acid PET have been proposed
- When applied in newly diagnosed patients with CNS WHO grade 4 gliomas undergoing adjuvant chemotherapy with temozolomide, PET RANO 1.0 criteria seem to identify survival differences between predefined groups but not to predict patients with favorable outcomes (ie PFS ≥ 9 months and OS ≥ 15 months)
- Further studies validating the PET RANO 1.0 criteria are warranted.

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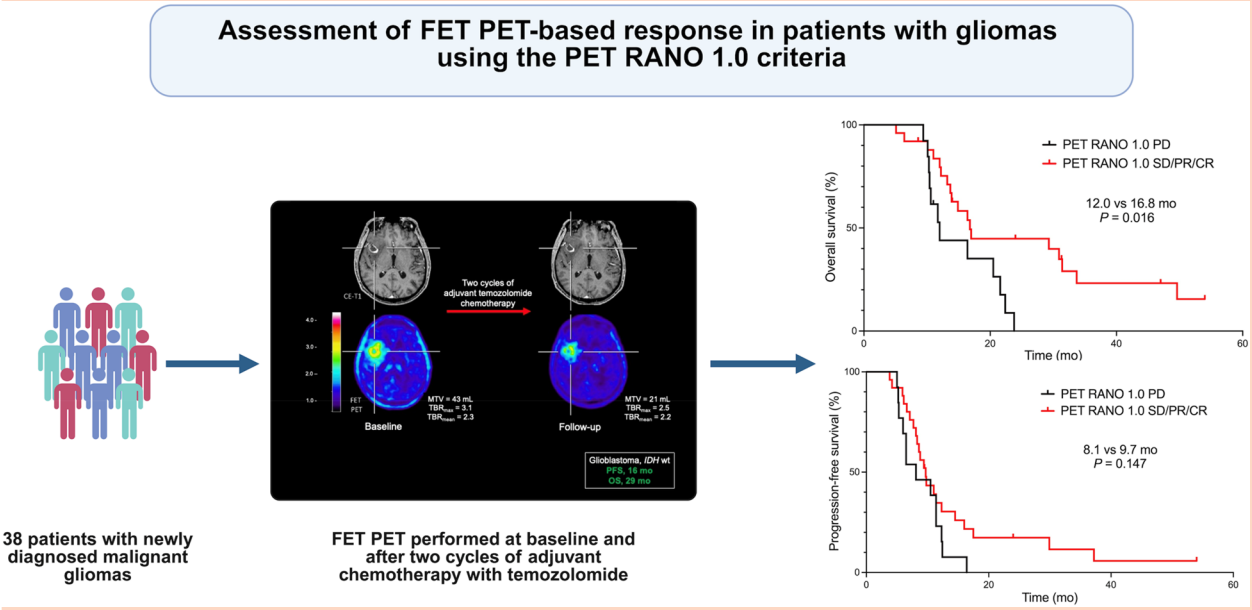
Graphical Abstract



Importance of the Study

The RANO group has recently proposed amino acid PET-based criteria for response assessment. However, these thresholds were defined mainly by consensus, and validation is needed in real-life patients. Our results suggest that the PET RANO 1.0 criteria can significantly predict longer overall survival in patients with newly diagnosed CNS WHO grade 4 gliomas undergoing chemoradiation with temozolomide, but not progression-free survival. Further studies validating these response criteria are warranted.

During follow-up of glioma patients, contrast-enhanced anatomical MRI is the method of choice for response assessment and detecting disease relapse.[2–6] Of note, this diagnostic approach has shortcomings, for example, a limited specificity for neoplastic tissue and a limited capability for discriminating disease relapse from treatment-related changes.[7,8] Notably, MRI cannot reliably identify pseudoprogression and radiation necrosis following chemoradiation with alkylating agents. Pseudoprogression is characterized by a self-limiting contrast enhancement, typically occurring within 12 weeks after completion of chemoradiation.[2,3,9,10] In contrast, radionecrosis occurs months or even years after radiotherapy.[7,11] Furthermore, antiangiogenic agents (eg bevacizumab) may induce a rapid decrease of contrast enhancement, suggesting erroneously high response rates on anatomical MRI, related to normalizing abnormally permeable blood vessels and partial restoration of the blood-brain barrier.[12] In sum, these treatment-related changes may affect response assessment with MRI.

Various studies highlighted the value of PET using radiolabeled amino acids such as [^{11}C]-methyl-l-methionine (^{11}C-MET), 3,4-dihydroxy-6-[^{18}F]-fluoro-l-phenylalanine (FDOPA), and *O*-(2-[^{18}F]fluoroethyl)-l-tyrosine (^{18}F-FET) for response assessment.[13–25] The uptake of ^{11}C-MET, ^{18}F-FDOPA, and ^{18}F-FET is mediated by large neutral amino acid transporters of the l-type (LAT) in gliomas and brain metastases (ie subtypes LAT1 and LAT2).[26] In contrast, the recently introduced tracer for brain tumor imaging anti-1-amino-3-[^{18}F]fluorocyclobutane-1-carboxylic acid (^{18}F-fluciclovine) is primarily transported by the sodium-dependent alanine-serine-cysteine transporter-type 2 (ASCT-2).[27]

Until recently, the evaluation of amino acid PET parameter changes for response assessment lacked standardization, and several thresholds were utilized. Similar to the recent update of the response criteria for MRI published by the Response Assessment in Neuro-Oncology (RANO) Working Group (RANO criteria 2.0),[3] a corresponding set of criteria for amino acid PET-based response assessment was defined (PET RANO criteria 1.0).[28] For example, a *Partial Response* based on amino acid PET parameter change in the follow-up scan relative to the baseline is considered when each measurable target lesion fulfills at least one of the following criteria: (1) a ≥30% decrease in the maximum tumor-to-brain ratio (TBR_{max}), (2) a ≥10% decrease in the mean tumor-to-brain ratio (TBR_{mean}), or a ≥40% decrease in the metabolically active tumor volume. The PET RANO criteria 1.0 also define *Progressive Disease*, *Stable Disease*, and *Complete Response* (Table 1).

However, these criteria are solely based on expert consensus defining thresholds for treatment-induced amino acid PET parameter changes, indicating response. Therefore, retrospective and prospective evaluation of these criteria is warranted. Furthermore, whether the PET RANO 1.0 criteria are applicable in the first-line and recurrent setting and

Table 1. Univariate survival analysis regarding ^{18}F-FET PET parameter changes evaluated according to the PET RANO 1.0 criteria

	Threshold	months	*P* value
PFS	SD/PR/CR vs PD	9.7 vs 8.1	.147
OS	SD/PR/CR vs PD	16.8 vs 12.0	.016

Abbreviations: CR, *Complete Response*; OS, overall survival; PFS, progression-free survival; PD, *Progressive Disease*; PR, *Partial Response*; SD = *Stable Disease*.

transferable to each therapeutic regime (eg radiotherapy, alkylating chemotherapy, antiangiogenic agents) is unclear.

As a first step, we evaluated the proficiency of the radiolabeled amino acid *O*-(2-[^{18}F]fluoroethyl)-l-tyrosine (^{18}F-FET) to predict a longer progression-free and overall survival (PFS, OS) using the PET RANO 1.0 criteria in a first-line setting. This evaluation was based on previously published data in patients with newly diagnosed CNS WHO grade 4 gliomas undergoing adjuvant temozolomide chemotherapy after surgery or biopsy and completion of radiotherapy with concomitant temozolomide chemotherapy. In addition, the value of the RANO 2.0 criteria for MRI to predict response was evaluated and compared with the PET RANO 1.0 criteria.

Materials and Methods

Patients

PET data from an already published study of our group were used to evaluate the PET RANO 1.0 criteria.[21] In that study, 38 patients (glioblastoma, *n*=34; H3K27-mutated midline glioma, *n*=1; astrocytoma CNS WHO grade 4, *n*=3) underwent PET imaging using the radiolabeled amino acid *O*-(2-[^{18}F]fluoroethyl)-l-tyrosine (^{18}F-FET) at baseline and after the second cycle of adjuvant temozolomide chemotherapy. All patients were treated according to the EORTC/NCIC 22981/26981 trial.[29] In more detail, after resection or stereotactic biopsy and completion of concomitant radiochemotherapy, ^{18}F-FET PET imaging was performed before initiation of adjuvant temozolomide chemotherapy (baseline) and after the second cycle. The timing after 2 cycles of adjuvant temozolomide chemotherapy was chosen because this is a well-established time point in clinical routine. In particular, the first MRI follow-up scan after completion of radiotherapy with concomitant temozolomide is usually performed at this time. More importantly, this time point allows the assessment of response to temozolomide chemoradiation early after its initiation. Table S1 provides details on the patients' characteristics. Before PET imaging, all patients had given written informed consent for the PET investigation and for the use of their data for scientific purposes. There was no conflict with the Declaration of Helsinki.

Treatment and Follow-up

In that study, patients were closely monitored by a neurological examination and MRI imaging every 8-12 weeks. PFS was defined as the time between initial diagnosis (eg the time of biopsy or surgery) and tumor progression according to the RANO criteria.[3] OS was defined as the time between initial diagnosis and death.

^{18}F-FET PET Acquisition and Data Evaluation

As described in the paper by Ceccon et al., summed ^{18}F-FET PET images over 20-40 minutes after injection were used.[21] The metabolically active tumor volume was delineated using a 3D auto-contouring method with a minimum tumor-to-brain ratio (TBR) of 1.6. This cutoff discriminates between tumoral and nontumoral tissue.[30] Mean TBR was calculated by dividing the mean SUV of the tumor ROI by a spherical ROI (diameter, 30 mm) placed in the contralateral unaffected hemisphere, including white and grey matter.[31] Maximum TBR was calculated using the maximum SUV of the tumor, accordingly. The software used was PMOD (version 3.505; PMOD Technologies Ltd).

Subsequently, a post hoc analysis of these PET data was performed to evaluate the PET RANO 1.0 criteria. According to these criteria, ^{18}F-FET PET parameter changes were classified as follows: *Progressive Disease*, *Stable Disease*, *Partial Response*, and *Complete Response*.[28]

We first performed a univariate survival analysis (Kaplan-Meier estimates) using the log-rank test to compare median PFS and OS in 2 groups (ie patients with *Progressive Disease* compared to patients with *Stable Disease*, *Partial Response*, or *Complete Response*). Multivariate Cox proportional hazards models were used to test the relationship between the PET RANO 1.0 criteria and other prognostic factors (ie the extent of resection, age, O^6-methylguanine-DNA-methyltransferase (*MGMT*) promoter methylation) to confirm the independence of the PET RANO 1.0 criteria to identify significantly different PFS and OS. Hazard ratios and 95% confidence intervals were calculated.

In a second step, we evaluated whether the PET RANO 1.0 criteria can predict a favorable outcome using 2 × 2 contingency tables (Fisher's exact test). As described earlier, favorable outcome was defined as PFS ≥ 9 months and OS ≥ 15 months.[20] In that study, [20] the median progression-free survival (PFS) was 7.2 months, and the median OS was 14.1 months, aligning closely with the survival outcomes reported in the EORTC-NCIC 22981/26981 trial (PFS, 6.9 months; OS, 14.6 months).[1] Thus, slightly higher PFS and OS values were defined as favorable outcome thresholds.

MR Imaging Acquisition and Data Analysis

The acquisition of anatomical contrast-enhanced MRI was performed as described earlier.[21] MRI changes at first follow-up compared with the baseline scan were evaluated according to the RANO 2.0 criteria.[3] The criteria for *Stable Disease*, *Partial Response*, and *Complete Response* were considered to define response to treatment.

Statistical Analyses

For statistical analyses, the Fisher's Exact test, 2 × 2 contingency tables, univariate and multivariate analysis were

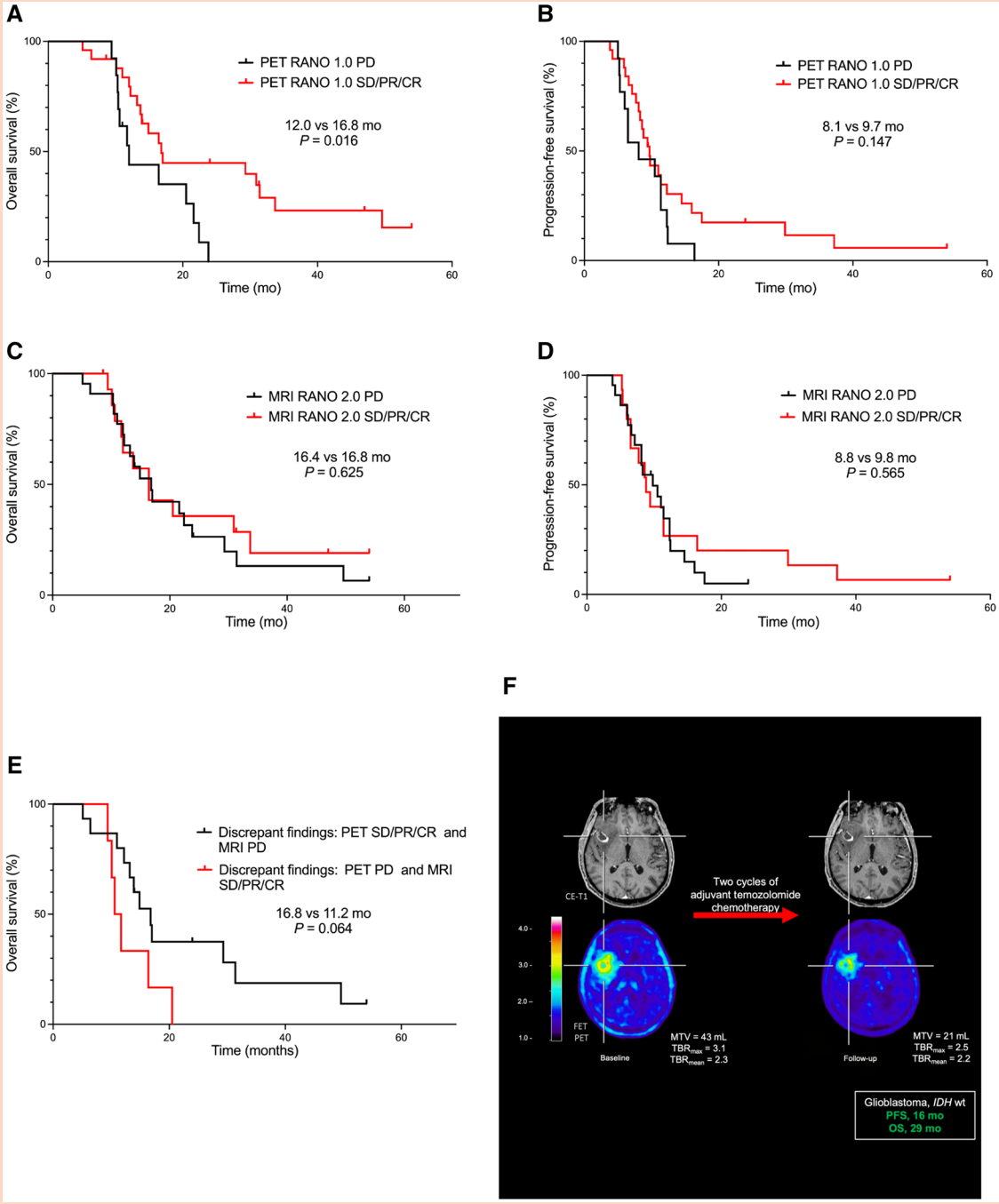


Figure 1. (A) Kaplan-Meier curves for the overall survival (OS) of patients with ^{18}F-FET PET findings consistent with *Stable Disease* (SD), *Partial Response* (PR), or *Complete Response* (CR) compared with patients with *Progressive Disease* (PD) according to the PET RANO 1.0 criteria (16.8 vs 12.0 months; $P = .016$). (B) Kaplan-Meier curves for the progression-free survival (PFS) of patients with ^{18}F-FET PET findings consistent with SD, PR, or CR compared with patients with PD according to the PET RANO 1.0 criteria (9.7 vs 8.1 months; $P = .147$). (C) Kaplan-Meier curves for the OS of patients with MRI findings consistent with SD, PR, or CR compared with patients with PD according to the RANO 2.0 criteria for MRI (16.4 vs 16.8 months; $P = .625$). (D) Kaplan-Meier curves for the PFS of patients with MRI findings consistent with SD, PR, or CR compared with patients with PD according to the RANO 2.0 criteria for MRI (8.8 vs 9.8 months; $P = .565$). (E) Kaplan-Meier curves for the OS of patients with discrepant findings (^{18}F-FET PET findings consistent with SD, PR, or CR and MRI results corresponding to PD compared with ^{18}F-FET PET consistent with PD and MRI findings with SD, PR, or CR (16.8 vs 11.2 months; $P = .064$). (F) Contrast-enhanced MRI and *O*-(2-[^{18}F]fluoroethyl)-l-tyrosine (^{18}F-FET) PET of a patient with glioblastoma at baseline and after two cycles of adjuvant temozolomide chemotherapy (patient #30). Compared to baseline, ^{18}F-FET PET shows a decrease of the metabolic tumor volume (MTV), consistent with *Partial Response* according to the PET RANO 1.0 criteria, that is, the MTV decreased by more than 40% by 51%. In contrast, the contrast-enhancing lesion on MRI is unchanged. The patient had a favorable PFS of 16 months and an OS of 29 months.

performed using GraphPad Prism (Release 10, GraphPad Software Inc., San Diego, CA, USA). *P* values ≤ .05 were considered statistically significant.

Results

Patients

Thirty-eight patients (mean age, 52 years; age range, 20-79 years; *n*=19 females) with gliomas were evaluated. The diagnoses were based on the 2021 edition of the World Health Organization (WHO) Classification of Tumors of the Central Nervous System.[32] The diagnoses included CNS WHO grade 4 glioblastoma (*n*=36), CNS WHO grade 4 astrocytoma (*n*=1), and CNS WHO grade 4 H3-K27 mutant diffuse midline glioma (*n*=1). During follow-up, tumor progression occurred in 35 patients (92%), and 33 patients (94%) deceased. Median PFS and OS were 9.5 months and 16.4 months, respectively. Details of the patients' clinical information are listed in Table S1.

Univariate Survival Analysis Regarding ^{18}F-FET PET Results Evaluated According to the PET RANO 1.0 Criteria

After completion of 2 cycles of temozolomide chemotherapy, patients with a ^{18}F-FET PET result consistent with *Stable Disease* (*n*=16), *Partial Response* (*n*=9), or *Complete Response* (*n*=0) had a significantly longer OS (16.8 vs 12.0 months; *P*=.016) than patients with *Progressive Disease* (*n*=13) (Figure 1A; Table 1). In contrast, PFS was not significantly different between the two groups (9.7 vs 8.1 months; *P*=.147) (Figure 1B; Table 1).

In the subgroup analysis of patients with methylated *MGMT* promoter (*n*=13), OS was significantly longer when changes in ^{18}F-FET PET were with consistent with *Stable Disease* (*n*=3), *Partial Response* (*n*=5), or *Complete Response* (*n*=0), compared with *Progressive Disease* (*n*=5) (not reached vs 16.4 months; *P*=.001). PFS was also significantly prolonged (23.0 vs 11.4 months; *P*=.039). In contrast, in patients without *MGMT* promoter methylation (*n*=25), neither OS (13.9 vs 11.2 months; *P*=.326) nor PFS (8.6 vs 7.3 months, *P*=.834) differed significantly.

Multivariate Survival Analysis Regarding ^{18}F-FET PET Results Evaluated According to the PET RANO 1.0 Criteria

Compared to age, extent of resection, and *MGMT* promoter methylation status, multivariate survival analysis remained significant (HR, 4.185; 95% CI, 1.715-10.530, *P*=.002) (Table 2).

Prediction of Favorable Survival Using ^{18}F-FET PET-Based Response Criteria

The PET RANO 1.0. criteria could not identify patients with a favorable PFS ≥9 months (*P*=.503) or OS ≥15 months (*P*=.722) (Tables 3 and 4).

Table 2. Multivariate survival analysis regarding ^{18}F-FET PET parameter changes evaluated according to the PET RANO 1.0 criteria

	Threshold	HR	95% CI	*P* value
OS	SD/PR/CR vs. PD	4.185	1.715-10.530	.002

Abbreviations: CI, confidence interval; CR, *Complete Response*; HR, hazard ratio; OS, overall survival; PD, *Progressive Disease*; PR, *Partial Response*; SD, *Stable Disease*.

Table 3. 2 × 2 contingency table regarding favorable PFS of ≥9 months

	PFS ≥ 9 months	PFS < 9 months	Total
PET RANO 1.0 PD (*n* patients)	6	7	13
PET RANO 1.0 SD/PR/CR (*n* patients)	13	9	22
Total *n* (patients)	19	16	35

Abbreviations: CR, *Complete Response*; PFS, progression-free survival; PD, *Progressive Disease*; PR, *Partial Response*; SD, *Stable Disease*.

Table 4. 2 × 2 contingency table regarding favorable OS of ≥15 months

	OS ≥ 15 months	OS < 15 months	Total
PET RANO 1.0 PD (n patients)	5	7	12
PET RANO 1.0 SD/PR/CR (*n* patients)	9	9	18
Total (*n* patients)	14	16	30

Abbreviations: CR, *Complete Response*; PFS, progression-free survival; PR, *Partial Response*; PD, *Progressive Disease*; SD, *Stable Disease*.

Prediction of Favorable Survival Using MRI Findings Evaluated According to the RANO 2.0 Criteria

MRI changes evaluated according to the RANO 2.0 criteria could not identify patients with a favorable PFS ≥ 9 months (*P*=.738) or OS ≥15 months (*P*>.999).

Univariate Survival Analysis Regarding MRI Results Evaluated According to the RANO 2.0 Criteria

The criterion *Progressive Disease*, according to the RANO 2.0 criteria, was not associated with a significantly shorter PFS (9.8 vs 8.8 months, *P*=.565) or OS (16.8 vs 16.4 months, *P*=.625) (Figure 1C and D; Table 5).

Table 5. Univariate survival analysis regarding MRI evaluated according to the RANO 2.0 criteria

	Threshold	Months	*P* value
PFS	SD/PR/CR vs PD	8.8 vs 9.8	.565
OS	SD/PR/CR vs PD	16.4 vs 16.8	.625

Differences Between MRI and ^{18}F-FET PET Changes According to the RANO 2.0 and PET RANO 1.0 Criteria

After 2 adjuvant temozolomide cycles, changes in MRI according to the RANO 2.0 criteria and ^{18}F-FET PET to the PET RANO 1.0 Criteria differed in 21 patients. MRI indicated *Progressive Disease* in 15 patients, while ^{18}F-FET PET showed either *Partial Response* (n=6) or *Stable Disease* (n=9). In the remaining 6 patients, MRI was consistent with *Stable Disease*, whereas ^{18}F-FET PET fulfilled the criterion for *Progressive Disease.*

Univariate Survival Analysis Regarding Discrepant ^{18}F-FET PET and MRI Changes According to the PET RANO 1.0 and RANO 2.0 Criteria

In the 21 patients with discrepant results, the median OS was longer in patients with *Partial Response* or *Stable Disease* according to the PET RANO 1.0 criteria and *Progressive Disease* according to the MRI RANO 2.0 criteria (16.8 months) than in patients with MRI RANO 2.0 criteria consistent with *Partial Response* or *Stable Disease* and PET RANO 1.0 criteria consistent with *Progressive Disease* (11.2 months) (Figure 1E). This difference showed only a trend towards significance (P=.064).

Discussion

The present study aimed to validate the PET RANO 1.0 criteria using a previously published data set.[21] We evaluated whether these response criteria can predict a significantly longer survival in terms of PFS and OS. The main finding of the present study is that patients with ^{18}F-FET PET parameter changes consistent with *Complete Response*, *Partial Response*, or *Stable Disease* had a significantly longer OS than patients with *Progressive Disease*. In contrast, PFS did not significantly differ between these 2 groups. Of note, the OS benefit was largely confined to patients with *MGMT* promoter methylation, in whom these parameter changes were also associated with a significant prolongation of PFS. This likely reflects a true biological effect of alkylating chemotherapy rather than an influence of *MGMT* status on FET uptake, as described previously.[33] Furthermore, the PET RANO 1.0 criteria could not reliably identify patients with a favorable survival, that is, a PFS of ≥9 months or an OS of ≥15 months.

Another main finding is that in comparison to the PET RANO 1.0 criteria, the RANO 2.0 criteria for MRI were unable to identify patients with a significantly longer OS. Moreover, after 2 adjuvant temozolomide cycles, changes in MRI and PET were discrepant in 21 patients, highlighting the added value of amino acid PET. In the majority of patients (n=15), MRI showed *Progressive Disease*, whereas ^{18}F-FET PET indicated either *Stable Disease or even Partial Response*. One possible explanation for this discrepancy is most probably related to pseudoprogression. The rate of pseudoprogression in our data set (39%) is in line with the rate reported in the literature.[34,35] This may have led to the misinterpretation of MRI, particularly in the first weeks following completion of radiotherapy with concomitant temozolomide, but was identified by ^{18}F-FET PET, as previously described.[6]

The reasons for the varying predictive performance of the PET RANO 1.0 criteria remain unclear. At first impression, the recommended criteria for defining *Progressive Disease* may appear rather strict (with an increase of at least 10%, 30%, or 40% in TBR_{mean}, TBR_{max}, and metabolic tumor volume relative to baseline, respectively). Furthermore, the recommendations are mainly based on consensus rather than on thresholds reported in previous amino acid PET studies. For example, the threshold for TBR_{max} was extrapolated from the PERCIST 1.0 criteria, used for response assessment in extracranial solid tumors.[36] Concerning the metabolic tumor volume for defining *Progressive Disease*, the recommended cutoff is based on the RANO 2.0 criteria for MRI (ie ≥ 40% increase in total volume of enhancing target lesions).[3] In addition, the threshold for TBR_{mean} defining *Progressive Disease* does not originate from previously reported results but on expert consensus.[28]

Another explanation could be that thresholds may be used with less strictness in clinical routine settings. For example, an increase in contrast enhancement below 25% in MRI at follow-up may already be considered as a *Progressive Disease* by clinicians, despite the fact that an increase of at least 25% is required according to the RANO criteria. For example, in patients with considerable clinical deterioration, *Progressive Disease* is frequently considered even if this threshold criterion is not yet fulfilled. Translating these considerations to the PET RANO 1.0 criteria, it may be discussed whether a lower TBR_{max} threshold should be preferred. For instance, in previous studies, lower thresholds for the reduction of TBR_{max} or metabolically active tumor volume obtained from serial amino acid PET imaging were shown to significantly predict a prolonged PFS and OS.[18,22]

This was also observed in our previous publication.[21] In that study, any reduction of both the parameters metabolic tumor volume (MTV) and TBR_{max} predicted a significantly longer PFS and OS. Moreover, changes in TBR_{max} values remained statistically significant in the multivariate analysis, independent of various other prognostic factors. One possible explanation for this observation is that the thresholds for MTV and TBR_{max} were defined using a survival time-based receiver operating characteristic (ROC) curve analyses instead of using a predefined threshold as suggested by the PET RANO 1.0 criteria. One might speculate that the survival time-based ROC approach seems to be more precise for response assessment. Moreover, that study established absolute prognostic thresholds, that is, metabolic tumor volume ≤ 28.2 ml and TBR_{max} ≤ 2.0 at baseline for favorable PFS, and metabolic tumor volume ≤ 13.8 ml for favorable OS, providing prognostic insight even from a single amino acid PET scan.

To apply the PET RANO 1.0 criteria, serial amino acid PET scans are mandatory, indicating that the number of serial

examinations will probably increase in the future. Besides response assessment, this offers the opportunity to investigate the possible advantage of serial PET imaging compared to single PET scans. For example, for the diagnosis of treatment-related changes, various TBR thresholds obtained from single amino acid PET scans have been proposed by several working groups.[37–42] It is tempting to speculate that serial amino acid PET may improve the diagnostic accuracy for this important clinical indication.

A suggestion for updates of the PET RANO 1.0 criteria could be the definition of thresholds based on meta-analysis-derived data of the most important studies evaluating amino acid PET for response assessment using thresholds for PET parameter changes derived from ROC analyses in patients with gliomas. In addition, the focus should be on prospective studies with larger patient cohorts to define thresholds more precisely and provide a solid data basis.

A possible weakness of this study is the number of patients evaluated using the PET RANO 1.0 criteria. On the other hand, this subset of patients with CNS WHO grade 4 gliomas is relatively homogenous and represents a "real-life" setting, where the presence of 2 sequential amino acid PET scans remains usually scarce. Another shortcoming is the retrospective nature of the collected data, which necessitates a prospective re-evaluation in the near future. One might argue that corticosteroids have affected the present results. In individual patients, corticosteroids may have an influence on TBR_{mean} and TBR_{max} values (ie by increasing the ^{18}F-FET uptake in the reference region of the healthy-appearing brain tissue).[43] Nevertheless, in the largest available study on this topic so far, in 160 patients with gliomas (n=80 with corticosteroids, and n=80 without corticosteroids) no significant differences in TBR_{mean} and TBR_{max} were reported.[43] Therefore, a relevant influence on the results of this study cannot be assumed.

Conclusion

After completion of radiotherapy with concomitant temozolomide chemotherapy, our results suggest that the evaluation of ^{18}F-FET PET parameter changes according to the PET RANO 1.0 criteria can significantly predict a longer OS already after 2 cycles of temozolomide chemotherapy in patients with newly diagnosed CNS WHO grade 4 gliomas. Further prospective studies with a higher number of patients, including patients at different stages of disease treated with agents other than temozolomide chemotherapy, for example, in the recurrent setting, are warranted.

Keywords

alkylating chemotherapy | amino acid PET | metabolic responders

Supplementary material

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

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Conflict of Interest Statement

N.G. received honoraria for lectures from Blue Earth Diagnostics, for advisory board participation from Telix Pharmaceuticals and Servier, and for consultancy services from Telix Pharmaceuticals. G.R.F. serves as an editorial board member of Cortex, Neurological Research and Practice, NeuroImage: Clinical, Zeitschrift für Neuropsychologie, Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie, and Info Neurologie & Psychiatrie; receives royalties from the publication of the books Funktionelle MRT in Psychiatrie und Neurologie, Neurologische Differentialdiagnose, SOP Neurologie, and Therapiehandbuch Neurologie; receives royalties from the publication of the neuropsychological tests KAS, NP-KiSS, and KöpSS; received honoraria for speaking engagements from the Deutsche Gesellschaft für Neurologie (DGN) and Forum für medizinische Fortbildung FomF GmbH. K.J.L. received honoraria from Telix Pharmaceuticals for consultancy services. P.L. received honoraria for lectures from Blue Earth Diagnostics, and for advisory board participation from Servier. All other authors reported no potential conflicts of interest.

Author Contributions

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

Ethical Approval

This research study was conducted retrospectively from data obtained for clinical purposes. The local Ethics Committee has confirmed that no ethical approval is required.

Data Availability

Upon reasonable request, the data can be provided by the corresponding author.

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