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PET-based response assessment criteria for diffuse gliomas (PET RANO 1.0): a report of the RANO group

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Abstract

Response Assessment in Neuro-Oncology (RANO) response criteria have been established and were updated in 2023 for MRI-based response evaluation of diffuse gliomas in clinical trials. In addition, PET-based imaging with amino acid tracers is increasingly considered for disease monitoring in both clinical practice and clinical trials. So far, a standardised framework defining timepoints for baseline and follow-up investigations and response evaluation criteria for PET imaging of diffuse gliomas has not been established. Therefore, in this Policy Review, we propose a set of criteria for response assessment based on amino acid PET imaging in clinical trials enrolling participants with diffuse gliomas as defined in the 2021 WHO classification of tumours of the central nervous system. These proposed PET RANO criteria provide a conceptual framework that facilitates the structured implementation of PET imaging into clinical research and, ultimately, clinical routine. To this end, the PET RANO 1.0 criteria are intended to encourage specific investigations of amino acid PET imaging of gliomas.

Introduction

Gliomas represent the most common primary CNS tumours in adults and are associated with high morbidity, reduced quality of life, and poor outcomes. Standard therapy options include neurosurgical resection, radiotherapy, and chemotherapy.¹ In the past few decades, most efforts towards the development of new treatments have failed, although effective treatments for molecularly defined glioma types are emerging.^{2–4} Assessment of novel treatments and their implementation into clinical practice relies on prospective controlled clinical trials with standardised endpoints that allow accurate evaluation of treatment effects. Although overall survival is commonly regarded as the most robust endpoint, measurement of tumour response to an investigational intervention with neuroimaging remains a key endpoint in most clinical trials enrolling people with glioma. Such measurements are commonly expressed as objective radiological response rates or progression-free survival times on the basis of morphological neuroimaging changes.

According to contemporary guidelines,^{1,5–9} regular follow-up and response assessment in people with glioma is performed with anatomical MRI. The Response Assessment in Neuro-Oncology (RANO) working group published MRI-based response criteria for high-grade gliomas (RANO-HGG) in 2010⁵ and for low-grade gliomas (RANO-LGG) in 2011.⁶ Subsequent modifications of these criteria were introduced to account for challenges associated with pseudoprogression after radio-chemotherapy or immunotherapy, including the immunotherapy criteria (iRANO) in 2015¹⁰ and the modified RANO criteria (mRANO) in 2017.¹¹ Motivated by validation studies and the publication of the revised classification of CNS tumours by WHO in 2021, a single unified set of MRI-based response criteria for all gliomas was issued in 2023 (RANO 2.0).^{9,12,13} The MRI-based RANO criteria have been widely accepted and used in most glioma clinical trials over the past decade. However, anatomical MRI features of gliomas, including advanced MRI sequences, are prone to ambiguity, particularly regarding the delineation of glioma extent (including non-enhancing tumour regions) and differentiation of post-therapeutic changes (such as pseudoprogression or radionecrosis) from actual tumour progression. Furthermore, metabolic tumour activity is not captured by the MRI sequences included in the standardised anatomical brain tumour imaging protocols recommended for clinical trials.^{14,15}

Molecular imaging with PET has advanced considerably in the past few years, with increasing availability and sophistication of technologies, imaging tracers, and data analysis methods.¹⁶ PET imaging offers a multitude of relevant information for patients, including molecular, functional, and morphological data that can be highly relevant for clinical decision making.^{16,17} Currently, PET imaging with ¹⁸F-fluorodeoxyglucose ([¹⁸F]FDG) to visualise glucose metabolism is routinely used and recommended by international clinical practice guidelines in several tumour types, including lung cancer, melanoma, and lymphoma, for staging and monitoring purposes.^{18,19} For CNS tumours, [¹⁸F]FDG-PET is not the radiotracer of first choice because of the high physiological [¹⁸F]FDG uptake of the brain, which renders the lesion-to-background ratio unacceptably low. Conversely, radiolabelled amino acids, such as ¹¹C-methionine ([¹¹C]MET), ¹⁸F-fluoroethyl-L-tyrosine ([¹⁸F]FET), or ¹⁸F-dihydroxyphenylalanine ([¹⁸F]F-DOPA), show high uptake in glioma cells due to the overexpression of L-amino acid transporters and allow favourable contrast

for the visualisation of gliomas.^{20,21} In addition, the synthetic amino acid analog anti-1-amino-3-[¹⁸F]fluorocyclobutane-1-carboxylic acid (FACBC or Fluciclovine) has gained clinical interest particularly for the imaging of primary and secondary brain tumours since 2016, when Fluciclovine was approved for imaging of recurrent prostate cancer. It has since been repurposed for brain tumours. In the past decade, the 18-kDa translocator protein has been evaluated as a target in PET imaging of glioblastoma, with preliminary evidence for an association with survival.^{22,23} Other PET tracers visualising proliferative tumour cell activity (eg, [¹⁸F] fluorothymidine), cell membrane components (eg, [¹¹C] choline), or hypoxia (eg, [¹⁸F]fluoromisonidazol) are under investigation in gliomas and are not ready for clinical applications at present.^{24–26} Unlike conventional contrast enhancement in MRI, the uptake of radiolabelled amino acid PET tracers does not require disruption of the blood–brain barrier, and might therefore allow for more direct assessment of tumour extent, including diffuse infiltration, by visualising the non-enhancing glioma components. Amino acid PET imaging might also show sites of increased malignancy in non-contrast-enhancing tumour portions. Indeed, amino acid PET imaging is increasingly used in people with CNS tumours, for example for planning neurosurgical interventions, aiding tumour delineation for planning of radiotherapy, and as a tool for disease monitoring and response assessment (including differentiation of treatment-related effects from pseudoprogression and pseudoresponse).^{27–30} Moreover, amino acid PET imaging might be able to monitor effects induced by novel treatments such as various forms of immunotherapy, which are currently being evaluated in brain tumours.³¹ To this end, including PET in clinical trials for response evaluation would be both useful and important. However, no criteria for standardised response assessment of PET imaging are available and there is high variability in the methodologies, PET parameters, and response assessment thresholds used across available studies, most of which are small and retrospective (table 1).

To provide a framework for the standardised inclusion of amino acid PET imaging in clinical trials, the RANO/PET working group devised recommendations for PET-based response assessment criteria for diffuse gliomas (PET RANO 1.0). As with the MRI-based RANO 2.0 criteria, the PET RANO 1.0 response criteria are intended for use in clinical trials on diffuse gliomas as defined in the 2021 WHO classification of tumours of the central nervous system.¹² The recommendations in this first edition of the PET RANO response criteria are mainly based on expert opinion and currently available published data, and systematic studies for validation and refinement are needed to inform future updates (panel).

The process of developing PET RANO 1.0

The RANO working group is an international group of neuro-oncologists, neuroradiologists, neurosurgeons, nuclear medicine physicians, radiation oncologists, statisticians, and experts in clinical outcomes assessments working in collaboration with patient advocacy groups, academic study groups, neuro-oncological societies, industry, and regulatory agencies to improve response criteria and outcome assessments in neuro-oncology. The RANO/PET working group developed the PET RANO 1.0 criteria through literature review and consensus finding among the multi-disciplinary and international expert group.

The recommendations provided in this Policy Review were elaborated in consensus-finding meetings and communications among coauthors between June 2 and Aug 31, 2023. The project was first presented on June 2, 2023, at the RANO meeting during the Annual Meeting of the American Society of Clinical Oncology. NLA and MP drafted recommendation statements that were elaborated on during a number of subsequent virtual consensus findings meetings, and which were then critically reviewed and adapted by the expert coauthor panel until unequivocal agreement was achieved. All authors approved the final set of criteria.

Method of measurements

Imaging technology

Brain amino acid PET imaging can be performed with stand-alone PET scanners or combined multimodality technologies, such as PET-CT or PET-MRI.¹⁶ The PET RANO 1.0 criteria refer to the interpretation of the PET component only. For PET imaging in clinical trials, acquisition and reconstruction processes should be standardised according to the most recent procedure guidelines.⁵⁸ To ensure comparability in multicentre studies, PET scanning procedures need to be harmonised across investigator sites and between scans.^{59,60} PET RANO 1.0 criteria use static PET parameters.⁵⁸ Dynamic PET images might provide additional information with regard to prognosis or differential diagnostic considerations, but are mostly only available in specialised centres.²⁹

Tracers

The amino acid tracer most commonly used for PET imaging of gliomas is the amino acid analog [¹⁸F]FET (table 1). Other amino acid tracers include [¹¹C]MET, [¹⁸F]F-DOPA, and [¹⁸F]FACBC. In clinical trials, the specific PET tracers used for response evaluation need to be clearly defined in the study protocol and should be used consistently (eg, the type of amino acid PET tracer should not be switched during longitudinal assessments, unless this is required to address a specific study rationale).

Rater qualification and training

The interpretation of PET findings and the application of PET RANO 1.0 criteria in the framework of clinical trials should be performed by board-certified nuclear medicine physicians with more than 1 year of experience in amino acid PET imaging of brain tumours to ensure the consistency and accuracy of scan interpretation.⁶¹ Our present recommendations will result in more standardised data, which will enable the investigation of machine-learning and artificial intelligence applications for potential future incorporation into revised PET RANO criteria.^{62,63}

Two-dimensional versus volumetric assessment

The MRI-based RANO 2.0 criteria use two-dimensional measurements (maximal cross-sectional diameters of contrast-enhancing or non-contrast-enhancing lesions) for response assessment, although there is an option for volumetric assessment if resources are available. In contrast, the PET RANO 1.0 criteria base disease monitoring on three-dimensional measurement of PET-positive lesions, as tumour volume provides more information on

tumour extent and behaviour and is based on a threshold and semi-automatically calculated by imaging analysis software packages already available in clinical use. In addition, measures of PET tracer uptake intensity with target-to-background ratios (TBRs) (ie, TBR_{max} and TBR_{mean}) are an integral part of the PET RANO 1.0 criteria. More advanced quantification methods, such as parametric response mapping, are not covered in the criteria but should be an area of investigation in future studies.⁶⁴ In order to overcome potential issues related to the use of various software packages with unknown reproducibility at different investigator sites, assessment by central review is recommended for multicentre clinical trials in which PET imaging contributes to the definition of primary or secondary endpoints.

Relation to MRI-based and clinical response assessment

The PET RANO 1.0 criteria are designed to evaluate PET imaging alone and do not integrate information from MRI and clinical presentation or steroid consumption. The relative contribution of PET findings in relation to MRI, handling of discordant results between MRI and PET, clinical findings (symptom burden) and corticosteroid requirement for outcome assessment, and the optimal integration of these different dimensions need to be elaborated through future, optimally prospective, systematic studies.

Implementation in clinical trials

The PET RANO 1.0 criteria are intended to be incorporated into protocols of clinical trials enrolling people with diffuse glioma. Although systematic validation studies are still needed, the PET RANO 1.0 criteria can potentially aid in individual decision making in routine clinical practice outside of clinical trials. The RANO/PET working group recommends that the PET RANO 1.0 response categories be used as secondary or exploratory endpoints in clinical trials to generate prospective data on their correlation with clinical parameters, MRI-based response criteria, and patient outcomes. Interpretation of PET findings with the application of the PET RANO 1.0 criteria in central core centres in clinical trials should be considered. Effective implementation of PET imaging in clinical trials requires multicentre and international efforts towards the standardisation of regulatory frameworks, multimodality imaging workflows, PET camera harmonisation and credentialing, PET tracer availability and distribution, hardware and software components, and the involvement of nuclear medicine specialists during the planning and conduct of clinical trials.

Definitions

PET parameters

A PET image acquisition and reconstruction protocol based on the recommendations given in the joint procedure guideline of the European Association of Nuclear Medicine (EANM), Society of Nuclear Medicine and Molecular Imaging (SNMMI), European Association of Neuro-Oncology (EANO), and RANO⁵⁸ should be employed for prospective clinical trials, and initial and follow-up PET scans should preferably be performed with the same scanner and protocol. Background activity on amino acid PET is assessed in the contralateral healthy-appearing cerebral CNS tissue including grey and white matter, preferentially within

a crescent-shaped volume of interest in the frontal lobe⁶⁵ as recommended by EANM, SNMMI, EANO, and RANO (figure 1).⁵⁸ PET-positive disease is defined as volumes with a standardised uptake value (SUV) of $1.6 \times$ the mean background activity or higher. Although only a few studies with histological correlations are available, the expert RANO panel recommends pragmatically applying a threshold of $1.6 \times$ the mean background activity for standardised assessment irrespective of the amino acid tracer used.^{58,66–68} The volume of PET-positive disease is assessed semi-automatically with $1.6 \times$ the background SUV as the lower threshold and serves as a measure of tumour volume. To ensure that structures with physiologically high uptake (eg, vasculature, muscles, choroid plexus, and striatum in the case of [¹⁸F]F-DOPA) are not encompassed in the volume of interest, a visual plausibility check and manual correction are recommended. The maximal SUV and the mean SUV in the PET-positive volume are evaluated as a ratio to the mean SUV of the healthy background and serve as two separate measures for uptake intensity (maximal and mean target-to-background ratio; TBR_{max} and TBR_{mean}). Evaluation of TBR_{max} and TBR_{mean} cannot be obtained if no PET-positive volume can be delineated.

Measurable and non-measurable disease

Measurable disease in amino acid PET imaging is defined as PET-positive disease with a volume exceeding 0.5 mL (ie, a volume based on a diameter of more than 1 cm in accordance with RANO 2.0).⁹ Non-measurable disease in PET imaging is defined as visible lesions with intensity values below a TBR_{max} of 1.6 (when no PET-positive volume can be assessed), or lesions with a PET-positive volume below 0.5 mL. No measurable disease is defined as the absence of any visually increased signal abnormality in amino acid PET imaging. In accordance with RANO 2.0, people without measurable disease (eg, after gross total resection or in case of PET-negative glioma) cannot show a partial or complete response to subsequent treatment and can therefore only have stable disease or progressive disease as their PET-based outcome. Although objective responses (partial or complete responses) cannot be achieved in patients without measurable disease, outcomes such as time to event endpoints (eg, progression-free survival and overall survival) and clinical status can be evaluated. The definitions of no measurable disease, non-measurable disease, and measurable disease according to the PET RANO 1.0 criteria are shown in figure 2.

Target lesions

Generally, the lesion or lesions with the highest uptake intensity or largest PET-positive volume should be selected as the target lesion or lesions. In accordance with the RANO 2.0 criteria, in the case of multiple measurable lesions, at least two (and no more than three) lesions should be identified as target lesions.⁹

Baseline PET

Newly diagnosed glioma—Baseline amino acid PET is recommended in newly diagnosed gliomas at study entry within 14 days before the start of any postoperative treatment (but as late as possible after surgery due to potential non-specific uptake in the early postoperative period). In cases for which no postoperative treatment is planned after surgery (ie, surveillance), the baseline PET should be performed 4–6 weeks after surgical

intervention. In cases for which no surgical resection is performed (ie, biopsy only), a preoperative PET can be used as the baseline scan, but the time interval until the start of a subsequent therapeutic intervention should not exceed 14 days.

Recurrent glioma—In recurrent glioma, the baseline PET scan of the recurrent tumour should be performed as close as possible before the initiation of therapeutic intervention, with an interval not exceeding 14 days. In cases for which surgical resection of recurrent disease is performed, a postoperative PET should be similarly acquired within 14 days before the start of any subsequent postoperative treatment (but as late as possible after surgery).

Follow-up schedule in clinical trials

In the case of CNS WHO 2021 grade 4 diffuse glioma (isocitrate dehydrogenase [*IDH*] wild-type or *IDH* mutant), PET imaging should be performed at intervals of 2–3 months, preferentially in parallel to MR imaging. In cases of CNS WHO 2021 grades 2 or 3 diffuse glioma, PET imaging should be performed at intervals of 3–6 months, preferentially in parallel to MR imaging. For assessment of early metabolic response, an additional PET scan 2–4 weeks after initiation of treatment can be considered for implementation in clinical trial protocols. In the case of clinical deterioration, additional PET imaging should be performed in parallel to MR imaging when possible. If PET imaging findings are equivocal (eg, the appearance of lesions with only slight tracer uptake or non-measurable PET-positive disease), with the result that it is unclear whether the individual has stable or developed progressive disease, PET imaging should be repeated in closer intervals—eg, after one to two treatment cycles.

PET-based response and progression

The assessment of PET response should be established by comparison with the tumour measurement obtained at baseline or nadir (ie, in the case of a response of target lesions from baseline after initiation of therapy, the best response serves as the new baseline). A summary of the PET RANO 1.0 response criteria is provided in figure 3 and table 2.

Measurable PET-positive disease at baseline—PET-based progressive disease is defined as an increase of 30% or more (in analogy to the PET response criteria in solid tumours [PERCIST] criteria)⁶⁹ in TBR_{max} , or of 10% or more (per expert consensus) in TBR_{mean} , or of 40% or more (in analogy to the RANO 2.0 criteria)⁹ in PET volume. Furthermore, the appearance of any new measurable lesion (local or distant) is considered as PET-based progressive disease. In the case of multiple lesions, the progression of at least one target lesion is considered as PET-based progressive disease. PET-based partial response is defined as a decrease of 30% or more in TBR_{max} , or of 10% or more in TBR_{mean} , or of 40% or more in PET volume if no PET-based progressive disease definition is fulfilled. In the case of multiple lesions, for PET-based partial response, each target lesion must fulfil the partial response criteria or there can be a complete response for all but one target lesion if no PET-based progressive disease or PET-based stable disease definition is fulfilled. PET-based complete response is defined as the complete disappearance of all previously detectable PET-positive disease and no new lesions. A change of lesion status

from measurable disease to non-measurable disease or no measurable disease is considered PET-based partial response or PET-based complete response, respectively. For assessment of durability of PET-based partial response or PET-based complete response, a confirmatory PET scan at least 4 weeks later can be implemented in the clinical trial protocol, but feasibility and radiation protection regulations need to be considered. PET-based stable disease is defined as not being PET-based progressive disease, PET-based partial response, or PET-based complete response (ie, a $<30\%$ decrease or increase in TBR_{max} , a $<10\%$ decrease or increase in TBR_{mean} , and a $<40\%$ decrease or increase in PET volume).

No measurable (PET-negative) or non-measurable (low uptake or small PET-positive volume) disease at baseline—PET-based progressive disease is defined as the appearance of at least one measurable PET-positive lesion. PET-based stable disease is defined as no appearance of measurable PET-positive lesions and is the best possible response. In accordance with RANO 2.0, individuals without measurable disease (eg, after gross total resection or PET-negative glioma) cannot show an objective response to subsequent treatment and can therefore only have stable disease (PET-based stable disease) as their best PET-based outcome due to the absence of a target lesion. PET-based partial response or PET-based complete response therefore cannot be outcomes with PET-negative disease at baseline. The same is true for non-measurable disease.

Consistent with the RANO 2.0 criteria, optional continuation of treatment and confirmation of progression are allowed if PET imaging changes are equivocal (eg, appearance of non-measurable PET-positive disease), making whether the individual is stable or has developed progressive disease unclear. In such cases, individuals should be observed closely, for example after another one to two treatment cycles. If a subsequent PET scan confirms progression, the date of progression should be backdated to the time that initial tumour progression was suspected.

Key recommendations for future research

The PET RANO 1.0 criteria are largely based on expert opinion and literature review. These criteria provide a conceptual framework that facilitates structured implementation of PET imaging into clinical research and ultimately routine clinical practice in the future. To this end, the PET RANO 1.0 criteria are intended to stimulate and foster specific investigations on amino acid PET imaging of gliomas. Priority should be given to larger prospective and multicentre studies, although these are challenging to design and operationalise, to overcome the current limitations and data gaps related to the availability of mainly retrospective and smaller single-centre studies.

Conclusion

Amino acid PET imaging is a promising tool to measure tumour tissue and provides additional information regarding tumour extent and activity compared with MRI. PET RANO 1.0 defines response criteria that can serve as a standardised assessment of treatment response in clinical trials enrolling participants with glioma in addition to conventional

response criteria. Systematic studies are needed to validate and refine the PET RANO 1.0 criteria in future updates.

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Panel: Key recommendations for future research

- Validation of thresholds for definitions of PET-positive disease, measurable or non-measurable disease, and response categories (ie, PET-based stable disease, PET-based progressive disease, PET-based partial response, and PET-based complete response)
- Confirmation of the intrarater and inter-rater and intracentre and intercentre reproducibility of the PET Response Assessment in Neuro-Oncology (RANO) 1.0 assessments
- Correlation of the PET RANO 1.0 response criteria with MRI-based response criteria (RANO 2.0)
- Comparison of the prognostic value of the PET RANO 1.0 criteria with the MRI-based RANO 2.0 criteria
- Correlation of the PET RANO 1.0 response criteria with clinical presentation (eg, symptom burden, concomitant medications, and corticosteroid requirements)
- Correlation of the PET RANO 1.0 response criteria with patient-reported outcome measures (eg, quality of life and neurocognitive function)
- Correlation of tumour samples and liquid biopsy findings (eg, molecular parameters, circulating proteins, or tumour DNA) with the PET RANO 1.0 response categories
- Harmonisation of hardware and software components used for PET imaging and data analysis

Search strategy and selection criteria

Relevant literature was selected by all authors. References were identified through searches of PubMed with the search terms “PET”, “positron emission tomography”, “tracer”, “amino acid”, “glioma”, “glioblastoma”, “response”, “assessment”, “progression”, “surgery”, “radiotherapy”, “chemotherapy”, and “imaging” in various combinations and including full journal articles published between Jan 1, 2003, and Aug 31, 2023. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the scope of this Policy Review.

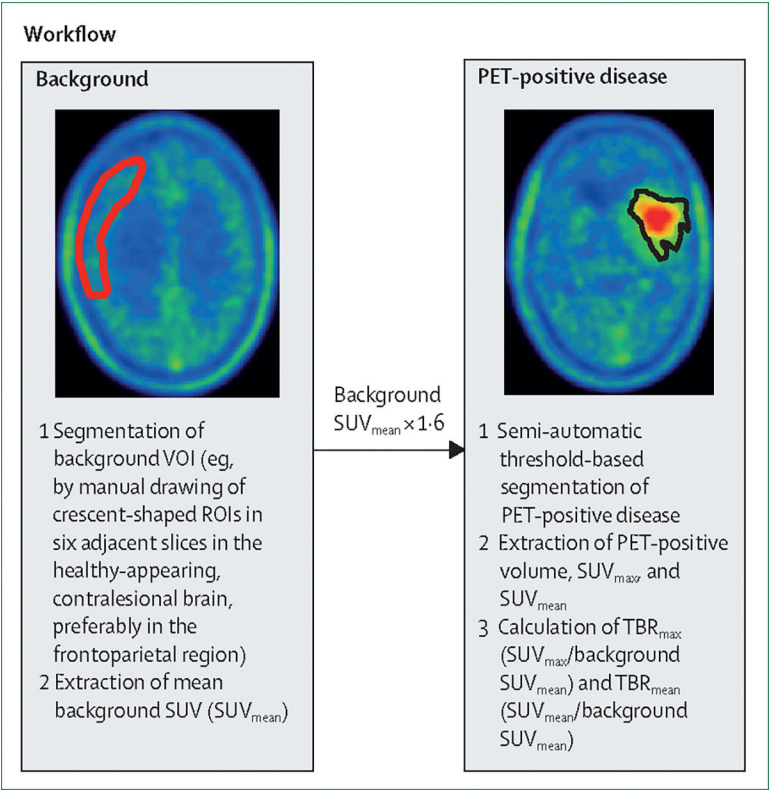


Figure 1: Exemplary definition of a crescent-shaped VOI and of the PET-positive volume
VOI=volume of interest. ROI=region of interest. SUV=standardised uptake value.
TBR=target-to-background ratio.

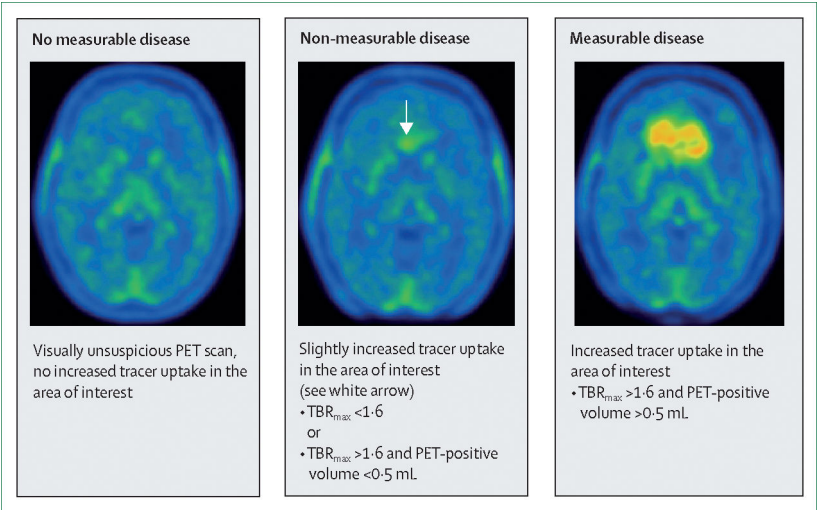


Figure 2: Definitions of no measurable disease, non-measurable disease, and measurable disease per the PET RANO 1.0 criteria
RANO=Response Assessment in Neuro-Oncology. TBR=target-to-background ratio.

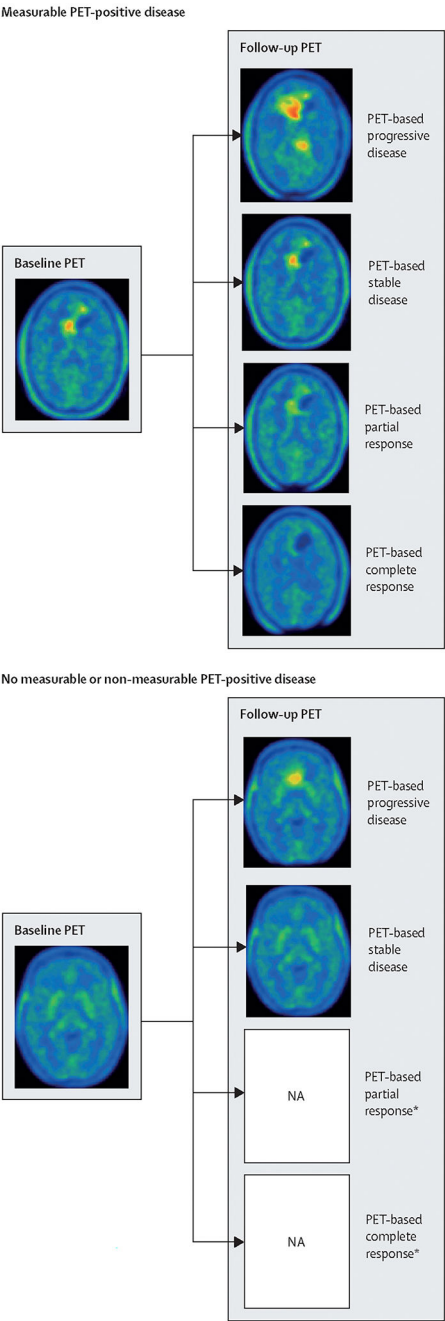


Figure 3: Visualisation of the PET RANO 1.0 criteria
NA=not applicable. RANO=Response Assessment in Neuro-Oncology. *Not a possible outcome.

Table 1:

Overview of published data on amino acid PET tracers in gliomas

Tracer	Tumour type	n	Study type	Diagnosis or recurrence	Timepoints (baseline and follow-up)	Thresholds	Parameters	Therapy	Previous treatment	Clinical endpoints
Nuutinen et al (2000) ³²	Diffuse glioma (grades 2 or 3)	14	Prospective	Diagnosis (n=10) and recurrence (n=4)	Baseline (before radiotherapy) and 3, 6, 12, and 24 months after radiotherapy	NA	TBR _{mean} and median SUV	Radiotherapy (with or without chemotherapy and resection)	Resection (and radiotherapy with or without chemotherapy in recurrent patients)	Different SUV according to the disease status at the timepoint (stable vs progressive vs dead); no detailed quantitative data reported
Galldiks et al (2006) ³³	Diffuse glioma (grades 2, 3, or 4)	15	Prospective	Diagnosis or first surgery (high grade; n=14), or recurrence (low grade; n=1)	Baseline (before temozolomide)	NA	TBR _{max} and MTV	Temozolomide	Resection and radiotherapy	Time to progression was longer in individuals with decreasing uptake than in individuals with increasing uptake (23 months vs 3.5 months; p=0.01)
Wyss et al (2009) ³⁴	Diffuse glioma (grade 2)	11	Prospective	Recurrence or progression	Baseline (before temozolomide) and after cycle 6 (group A) or cycles 3, 9, and 15 (group B)	≥10% MTV decrease to baseline	MTV (voxels >110% of mean cerebellar FET uptake), and TBR _{mean}	Temozolomide	Resection	Longest progression-free survival in individuals with both PET and MRI responses (median 38 months) compared with individuals without MRI response (median 15 months)
Hutter et al (2011) ³⁵	Diffuse glioma (grades 3 or 4)	11	Retrospective	Recurrence or progression	Baseline (before start of treatment), followed by PET every 8–12 weeks	≥25% or 45% MTV decrease to baseline	TBR _{mean} , SUV _{mean} , and MTV	Bevacizumab plus irinotecan	Resection, radiotherapy and chemotherapy	Mean progression-free survival was longer in responders than in non-responders (10.2 months vs 4.1 months; p=0.015)
Galldiks et al (2012) ³⁶	Glioblastoma	25	Prospective	Diagnosis or after first surgery	Baseline (after surgery) and 7–10 days and 6–8 weeks	As established by ROC analysis for progression-	TBR _{mean} , TBR _{max} , and MTV	Temozolomide plus radiotherapy	Resection	Multivariate analysis: progression-free survival (follow-

Tracer	Tumour type	n	Study type	Diagnosis or recurrence	Timepoints (baseline and follow-up)	Thresholds	Parameters	Therapy	Previous treatment	Clinical endpoints
[¹⁸ F]FET	Glioblastoma	79	Retrospective	Diagnosis or after first surgery	after completion of radiochemotherapy	free survival: >10% TBR _{max} decrease and >20% TBR _{max} decrease to baseline	NA	Recurrence pattern or location (in-field vs marginal)	Resection	up 1 vs baseline): TBR _{max} (HR 0.122; p=0.017), TBR _{mean} (HR 0.216; p=0.035); follow-up 3 vs baseline: MTV (HR 0.142; p=0.007); overall survival (follow-up 1 vs baseline): TBR _{max} (HR 0.197; p=0.028), TBR _{mean} (HR 0.195; p=0.05)
[¹⁸ F]FET	Glioblastoma	79	Retrospective	Diagnosis or after first surgery	Baseline (4–6 weeks after end of concurrent radiochemotherapy), then every 3 months	NA	Recurrence pattern or location (in-field vs marginal)	Temozolomide plus radiotherapy	Resection	Different recurrence pattern according to MGMT promoter methylation status
[¹⁸ F]FET	Diffuse glioma (grades 3 or 4)	10	Prospective	Recurrence or progression	Baseline (before start of treatment), followed by PET after two administrations (ie, 4–6 weeks)	≥45% MTV (TBR ≥1.6) reduction to baseline	TBR _{mean} , TBR _{max} , SUV _{mean} , SUV _{max} and MTV	Bevacizumab plus irinotecan	Resection, radiotherapy, and chemotherapy	Median progression-free survival was longer in responders than in non-responders (9 months vs 3 months; p=0.001); median overall survival was longer in responders than in non-responders (23 months vs 3.5 months; p=0.001)
[¹⁸ F]FET	Glioblastoma	25	Prospective	Diagnosis or after first surgery	Baseline (after surgery; FET-1), early after completion of radio-chemotherapy (FET-2), and 6–8 weeks after completion of radiochemotherapy (FET-3)	≥10% TBR _{max} or ≥5% TBR _{mean} decrease between baseline (FET-1) and FET-2	Time to peak and slope of time or activity curves	Temozolomide plus radiotherapy	Resection	Median progression-free survival was longer in responders than in non-responders (TBR _{max} : 9.3 months vs 4.2 months; p=0.002; and TBR _{mean} : 10.3 months vs 5.1 months;

Tracer	Tumour type	n	Study type	Diagnosis or recurrence	Timepoints (baseline and follow-up)	Thresholds	Parameters	Therapy	Previous treatment	Clinical endpoints
Santoni et al (2014) ⁴⁰	Diffuse glioma (grades 2,3, or 4)	53	Retrospective	Diagnosis or after first surgery	Regular follow-up after surgery or radiochemotherapy	NA	SUV _{mean}	No treatment (follow-up after completion of first-line treatment)	Resection (with or without radiotherapy and temozolomide)	p=0.001; median overall survival was longer in responders than in non-responders (TBR _{max} : 18 months vs 8.5 months; p<0.01; and TBR _{mean} : 22.8 months vs 9.3 months; p<0.001); no correlation of kinetic parameters with survival
Schwarzenberg et al (2014) ⁴¹	Diffuse glioma (grades 3 or 4)	30	Prospective	Recurrence or progression	Baseline (before start of treatment), followed by PET after 2 weeks and 6 weeks	≥35% MTV reduction to baseline	SUV _{mean} , SUV _{max} and MTV	Bevacizumab	Resection, radiotherapy, and chemotherapy	At 2 weeks, mean overall survival was longer in responders than non-responders (13.7 months vs 7 months; p=0.02); at 6 weeks, mean overall survival was longer in responders than non-responders (14.1 months vs 7.6 months; p=0.02)
Roelcke et al (2016) ⁴²	Diffuse glioma (grade 2)	33	Retrospective	Not reported	Baseline (within 1 month before initiation of temozolomide) and follow-up 2–6 months after initiation	≥10% MTV reduction from baseline at at least two subsequent timepoints after temozolomide initiation; ROC analyses: ≥80.5% decrease in MTV for progression-	TBR _{mean} , TBR _{max} and MTV	Temozolomide	Resection	No difference in median progression-free survival between metabolic responders* and non-responders (34.3 months vs 27.6 months; p=0.605); ROC analyses showed higher thresholds

Tracer	Tumour type	n	Study type	Diagnosis or recurrence	Timepoints (baseline and follow-up)	Thresholds	Parameters	Therapy	Previous treatment	Clinical endpoints
						free survival at ≥60 months; ≥64.5% decrease in MTV for progression-free survival at ≥48 months				for prediction of progression-free survival (see thresholds)
Beppu et al (2016) ⁴³	Glioblastoma	20	Prospective	Recurrence or progression	Baseline (before treatment) and at 4 weeks and 8 weeks after treatment initiation	TBR <1.6 at follow-up	TBR _{mean}	Temozolomide plus bevacizumab	Resection, radiotherapy, and chemotherapy	Longer progression-free survival in responders than in non-responders at 8 weeks (no values given; p<0.01)
Kebir et al (2016) ⁴⁴	Glioblastoma	26	Retrospective	Recurrence or progression	At progression (increasing contrast-enhancing lesions in MRI)	TBR _{max} >1.9 (according to ROC analysis)	TBR _{mean} and TBR _{max}	NA	Resection, radiotherapy, and chemotherapy	Mean TBR _{max} and TBR _{mean} were higher in individuals with true progression than in individuals with pseudoprogression (TBR _{max} : 2.4 vs 1.5; p=0.003; TBR _{mean} : 2.1 vs 1.5; p=0.0012)
Deuschl et al (2017) ⁴⁵	Glioblastoma	11	Prospective	Recurrence or progression	Baseline (before treatment) and at 25–60 days after treatment	TBR reduction ≥25% compared with baseline	TBR _{max}	Bevacizumab	Not reported	Longer progression-free survival (p=0.048) and overall survival (p=0.009) in responders than in non-responders (according to PET at follow-up)
Suchorska et al (2018) ⁴⁶	Diffuse glioma (grades 2 or 3, and not contrast-enhancing in MRI)	61	Retrospective	Recurrence or progression	Baseline (before treatment) and 6 months after treatment	≥25% PET-positive volume reduction, TBR _{max} reduction ≥10%, or both (responsive disease), ≥25% PET-positive volume increase, TBR _{max}	TBR _{max} change in MTV, and time-activity kinetics	Temozolomide, or lomustine or procarbazine	Subtotal resection of biopsy	Responders had significantly longer time to treatment failure (78.5 months) than individuals with stable disease (24.6 months) or progressive disease (24.1 months; p=0.001); postchemotherapy

Tracer	Tumour type	n	Study type	Diagnosis or recurrence	Timepoints (baseline and follow-up)	Thresholds	Parameters	Therapy	Previous treatment	Clinical endpoints
Wang et al (2018) ⁴⁷	Glioblastoma	18	Prospective	Diagnosis or after first surgery	Baseline (after surgery), follow-up (4 weeks after completion of radiochemotherapy)	NA	Changes in SUV _{max} , SUV _{mean} , TBR, and volume	Temozolomide plus radiotherapy	Surgery	Mean decrease in SUV _{max} : 40%; mean decrease in SUV _{mean} : 35%; mean decrease in volume: -64%; no correlation with outcome performed
Galidiksetal (2018) ⁴⁸	Glioblastoma	21	Prospective	Recurrence or progression	Baseline (before treatment) and after 8–10 weeks	Reduction of TBR _{max} >27%, reduction of TBR _{mean} >17%, and reduction of MTV >27% (according to ROC analysis)	Changes in TBR _{max} , TBR _{mean} , and MTV	Bevacizumab plus lomustine	Surgery and temozolomide-based radiochemotherapy	Absolute MTV at follow-up used as an independent prognostic factor (HR 0.158; p=0.006); relative changes of parameters were not significant
Kawasaki et al (2019) ⁴⁹	Glioblastoma	30	Retrospective	Diagnosis or first surgery	Baseline (before radiotherapy) and every 3 months after radiotherapy	SUV _{max}	Changes in SUV _{max}	No treatment (follow-up)	Surgery and temozolomide-based radiochemotherapy	Variation rate of SUV _{max} between baseline and 3 months after radiotherapy was associated with survival (p=0.016)
Hirono et al (2019) ⁵⁰	Glioblastoma	44	Retrospective	Diagnosis or after first surgery	After completion of first-line treatment	TBR _{max} ≥2.0	TBR _{max}	No treatment (follow-up)	Surgery and temozolomide-based radiochemotherapy (extended temozolomide treatment for 12 months)	Individuals with a TBR _{max} ≥2.0 had higher odds of progression within 12 months (OR 147; p<0.001) than individuals with a TBR _{max} of less than 2.0
Ceccon et al (2021) ⁵¹	Diffuse glioma	40	Prospective	Diagnosis or after	Baseline (before adjuvant temozolomide) and	Baseline: absolute MTV ≤28.2 mL and	Absolute MTV and	Temozolomide (adjuvant phase)	Surgery and radiochemotherapy	Reduction in TBR _{max} was used

Tracer	Tumour type	n	Study type	Diagnosis or recurrence	Timepoints (baseline and follow-up)	Thresholds	Parameters	Therapy	Previous treatment	Clinical endpoints
	(grades 2,3, or 4)			first surgery	after 2 cycles of temozolomide	$TBR_{max} \leq 2.0$ (progression-free survival), absolute MTV 13.8 (overall survival); relative changes: no threshold	TBR_{max} and relative MTV and TBR_{max} compared with the baseline		(concomitant phase)	as an independent prognostic factor for progression-free survival (HR 2.92; p=0.012); reduction in TBR_{max} (HR 2.66; p=0.023) and MTV (3.61, p=0.005) was used as an independent prognostic factor for overall survival
Wirsching et al (2021) ⁵²	Glioblastoma (individuals older than 65 years)	67	Post-hoc analysis of a prospective trial	Diagnosis or after first surgery	Baseline (pretreatment), follow-up (4 weeks after completion of radiotherapy)	Cutoffs for TBR established by ROC analysis but not reported	Absolute TBR at baseline and follow-up	Bevacizumab plus hyp of ractionated radiotherapy	Surgery	High pretreatment TBR in contrast-enhancing tumour regions was associated with overall survival independent of the treatment arm (HR 2.53,95% CI 1.17-5.49), MRI contrast-enhancing volume, and ADC (HR 3.54, 95% CI 1.12-11.16); high TBR at first follow-up (on treatment) in contrast-enhancing tumour regions was associated with longer overall survival in the radiotherapy arm (p=0.44; median survival not reported)
Werner et al (2021) ⁵³	Glioblastoma	23	Retrospective	Diagnosis or after first surgery	Baseline (after radiotherapy)	$TBR_{mean} < 1.95$ at baseline	Absolute TBR_{mean} at baseline, relative changes of TBR_{mean} and	No treatment (follow-up)	Surgery, radiotherapy, temozolomide, and lomustine (according to the CeTeG/N0A-09 trial) ⁵⁴	Accuracy of 87% in identifying pseudoprogression at a $TBR_{mean} < 1.95$ (p=0.029), with improved accuracy (91%) when integrating

Tracer	Tumour type	n	Study type	Diagnosis or recurrence	Timepoints (baseline and follow-up)	Thresholds	Parameters	Therapy	Previous treatment	Clinical endpoints
Beppu et al (2023) ⁵⁵	¹¹ C]MET IDH-mutant, lower-grade glioma (grades 2 or 3)	30	Not reported	Diagnosis or after first surgery	Baseline (after adjuvant temozolomide)	TBR _{mean} ≥1.27 at baseline	dynamic parameters TBR _{mean} at baseline	No treatment (follow-up)	Surgery, and temozolomide with or without radiotherapy	relative changes and specificity (100%) with dynamic parameters TBR _{mean} >1.27 associated with shorter progression-free survival (univariate log-rank p=0.002; multivariate HR 8.44; p=0.002)
Wollring et al (2023) ⁵⁶	Diffuse glioma (grades 3 or 4)	36	Retrospective	Recurrence or progression	Baseline and followup (not later than 2 cycles of chemotherapy)	Cutoffs for relative changes established with ROC analysis (progression-free survival: MTV0%, TBR _{mean} 0%, TBR _{max} 0%, and time to progression -7%; overall survival: MTV 0%, TBR _{mean} -4.7%, TBR _{max} 0%, and time to progression -7%).	TBR _{max} , TBR _{mean} , MTV, time to progression, and new hotspot with a TBR _{mean} >1.6	Lomustine, or lomustineor procarbazine	At least one line of pretreatment including resection, alkylating radiotherapy, and chemotherapy, or combinations of thethree	Multivariate analysis (progression-free survival): TBR _{max} change (HR 2.909; p=0.029), MTV change (HR 4.546; p=0.001), new hotspots (HR 3.155; p=0.019); multivariate analysis (overall survival): new hotspots (HR 8.578; p<0.001); all independent from MRI-based RANO criteria, TBR _{mean} change, and time to progression change
Darcourt et al (2023) ⁵⁷	[¹⁸ F]-FDOPA Diffuse glioma (grades 3 or 4)	107	Prospective	Recurrence or progression	Baseline (once after inconclusive MRI during follow-up)	Cutoff for PD according to ROC analysis: TBR _{max} of 1.94	TBR _{max} and TSR _{max}	No treatment (follow-up)	Surgery with or without radiotherapy and chemotherapy	Tumour board decision changed in 26.8% of participants (diagnosis) and 22.5% of participants (management) if PET was considered; sensitivity (86% vs 83%), specificity (64% vs 58%), and

Tracer	Tumour type	n	Study type	Diagnosis or recurrence	Timepoints (baseline and follow-up)	Thresholds	Parameters	Therapy	Previous treatment	Clinical endpoints
										accuracy (71% vs 66%) all higher if PET was considered

ADC= Apparent diffusion coefficient. [¹¹C]MET=¹¹C-methionine. [¹⁸F]-F-DOPA=¹⁸F-dihydroxy-fluoro-L-phenylalanine. [¹⁸F]FET=¹⁸F-fluoroethyl-L-tyrosine. HR=hazard ratio. MGMT=O⁶-methylguanine-DNA-methyltransferase. MTV =metabolic tumour volume. NA =not available. OR=odds ratio. PD=progressive disease. RANO=Response Assessment in Neuro-Oncology. ROC=receiver operating characteristics. SUV=standardised uptake value. TBR=tumour-to-background ratio. TSR=tumour-tostriatum ratio.

* As defined by a priori threshold of tumour volume change ≥10%.

Summary of the PET RANO 1.0 response criteria

Table 2:

Measurable PET-positive disease		No measurable or non-measurable PET-positive disease
Progressive disease (PET-PD)	At least one of the following: ≥30% increase in TBR _{max} of at least one target lesion ≥10% increase in TBR _{mean} of at least one target lesion ≥40% increase in PET volume of at least one target lesion Appearance of a new measurable PET-positive lesion or lesions	Appearance of a new measurable PET-positive lesion or lesions
Stable disease (PET-SD)	No definition of PET-PD, PET-PR, or PET-CR is fulfilled	No appearance of a new measurable PET-positive lesion or lesions
Partial response (PET-PR)	At least one of the following and no definition of PET-PD, PET-SD, or PET-CR is fulfilled (in the case of multiple lesions, each target lesion must fulfil at least one of these criteria): ≥30% decrease in TBR _{max} in a target lesion or lesions ≥10% decrease in TBR _{mean} in a target lesion or lesions ≥40% decrease in PET volume in a target lesion or lesions; or Complete response of all target lesions but one, and no PET-PD or PET-SD definition is fulfilled	Not applicable
Complete response (PET-CR)	Complete disappearance of all PET-positive disease	Not applicable

RANO=Response Assessment in Neuro-Oncology. TBR=target-to-background ratio.