Measure what is measurable: PET RANO 1.0 criteria for interpretation of amino acid PET of diffuse gliomas

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Magnetic resonance imaging (MRI) is the recommended method for radiological assessment, monitoring, and response assessment of gliomas within clinical trials and in clinical routine. Since 2011, the Response Assessment in Neuro-Oncology (RANO) group has published and iteratively updated criteria for standardized MRI-based response assessment in glioma trials, with RANO 2.0 being the most recent edition. These MRI-based RANO criteria have been widely accepted and are used in most clinical trials enrolling glioma patients. However, MR imaging has some limitations with regard to reliable delineation of glioma extent from CNS tissue, the differentiation of post-therapeutic changes (such as pseudo-progression, pseudo-response, or radionecrosis) from true tumor progression, and assessment of metabolic tumor activity, which may render the evaluation of glioma ambiguous. Positron emission tomography (PET) using amino acid tracers such as [11C]methionine ([11C]MET), [18F]-fluoroethyl-L-tyrosine ([18F]FET), or [18F]-dihydroxyphenylalanine ([18F]F-DOPA) allows tumor-specific visualization of metabolically active glioma tissue also in the absence of blood-brain barrier disruption. Consequently, amino acid PET is increasingly used for planning of biopsies and neurosurgical resections or radiotherapy, and as tool for disease monitoring of gliomas, including differentiation of tumor progression or shrinkage from treatment-related pseudo-effects. However, although joint procedure guideline for PET image acquisition and reconstruction protocols by the European Association of Nuclear Medicine, Society of Nuclear Medicine and Molecular Imaging, European Association of Neuro-Oncology, and RANO have been published, no criteria for standardized response assessment using amino acid PET have been available so far. The RANO group has now for the first time presented response criteria for evaluation of gliomas using amino acid PET, the PET RANO 1.0 criteria.

The PET RANO 1.0 publication provides a series of specific recommendations on imaging technologies, tracer use, rater qualification, imaging schedules, and, most importantly, concrete definitions of PET parameters and their interpretation for glioma baseline assessment and follow-up. As such, the PET RANO 1.0 criteria refer to the assessment of PET images alone, and do not incorporate MRI data or clinical information. In contrast to the 2-dimensional MRI-based RANO 2.0 response assessment criteria, PET RANO 1.0 uses 3-dimensional volumetric measurement of PET-positive lesions. In addition to the volume of PET-positive disease (defined as areas with a standardized uptake value ≥ 1.6 x mean background activity), 2 separate parameters for tracer uptake intensity, that is, the maximal and the mean target-to-background ratio (TBRmax and TBRmean), are assessed for the definition of measurable disease. PET RANO 1.0 recommends time points for optimal timing of baseline and follow-up PET investigations for newly diagnosed and recurrent gliomas per CNS WHO 2021 diagnosis. Finally, longitudinal changes of these parameters according to concrete thresholds define categorization of tumor behavior as PET-based progressive disease (PET-PD), stable disease (PET-SD), partial remission (PET-PR), or complete response (PET-CR).

PET RANO 1.0 defines a conceptual framework that is aiming to facilitate implementation of amino acid PET imaging into clinical trials enrolling patients with diffuse glioma, and eventually also routine clinical practice. A major challenge in this process will be the current lack of universal availability of amino acid PET imaging, even among specialized Neuro-Oncology centers worldwide. The regulatory and reimbursement situation is highly variable among countries in Europe, the United States, Asia-Pacific, and other regions of the world. However, current efforts will likely lead to regulatory approvals and broad availability of amino acid PET imaging, particularly also in the United States. To this end, the PET RANO 1.0 criteria will help to generate robust evidence of clinical benefit and thus facilitate coordinated efforts toward widespread implementation of amino acid PET imaging for patients with CNS tumors. Given the relative paucity of published information relevant for response assessment using amino acid PET imaging, especially from large and prospective data sets, PET RANO 1.0 criteria are based mainly on consensus among the multidisciplinary and international expert author group, similar to the initial development steps of the MRI-based RANO criteria. Therefore, systematic investigations are needed for...
validation of the proposed criteria and to inform future updates. Particularly important areas for dedicated research and development include the harmonization of PET imaging hardware and software components, the validation of thresholds defined for the PET-PD, PT-SD, PET-PR, and PET-CR response categories, and their correlation with clinical parameters including symptom burden, patient-reported outcomes, and survival times. Furthermore, multi-institutional efforts will be needed to confirm intra- and interrater, as well as intra- and intercenter reproducibility of PET RANO 1.0 response assessment. The relative contribution of PET-based in relation to MRI-based response assessment and the optimal integration of these different dimensions need to be elaborated through dedicated comparative studies. Ultimately, the incorporation of mandatory PET imaging in clinical trial protocols may help to improve the efficacy evaluation of novel experimental interventions through earlier or more accurate evaluation of response or nonresponse to treatment.

In summary, the PET RANO 1.0 publication defines for the first time criteria for response assessment of gliomas based on amino acid PET imaging and will enable structured investigation and widespread implementation of this advanced diagnostic modality with high potential to improve patient management into clinical research and practice.

**Conflict of interest**

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**References**

NOW ENROLLING
Phase 2b study of IGV-001 in patients with newly diagnosed glioblastoma (NCT04485949)

OBJECTIVES
- PRIMARY OBJECTIVE: Progression-free survival
- SECONDARY OBJECTIVE: Overall survival
- SAFETY OBJECTIVE: Safety and tolerability

CRITERIA
Key Inclusion Criteria
Patients who take part in the trial* must:
- Have newly diagnosed glioblastoma
- Be 18 to 70 years of age
- Have a KPS score ≥70 (unable to work but able to care for themselves overall)

Key Exclusion Criteria
Patients are not allowed to participate* in the trial if they have:
- A tumor that is on both sides of the brain
- Had previous surgery or anticancer treatment for glioblastoma
- Glioblastoma that came back
- Another cancer† while having glioblastoma or within the last 3 years that is not cured
- A weakened immune system (example: HIV, HBV, HCV) or an autoimmune disorder (example: Crohn’s disease)
- Heart disease or history of heart issues

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*Additional criteria apply. Please refer to protocol 14379-201 for full inclusion and exclusion criteria. †Patients can participate if they had some skin cancers, superficial bladder cancer (cancer that was only on the surface of the lining of the bladder), or carcinoma in situ (cancer that had not spread) of the cervix or breast that had been cured.

HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; IGF-1R, insulin-like growth factor 1 receptor; KPS, Karnofsky Performance Scale; RT, radiotherapy; SOC, standard of care; TMZ, temozolomide.

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