Response Assessment in Neuro-Oncology working group and European Association for Neuro-Oncology recommendations for the clinical use of PET imaging in gliomas


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This guideline provides recommendations for the use of PET imaging in gliomas. The review examines established clinical benefit in glioma patients of PET using glucose (18F-FDG) and amino acid tracers (11C-MET, 18F-FET, and 18F-FDOPA). An increasing number of studies have been published on PET imaging in the setting of diagnosis, biopsy, and resection as well radiotherapy planning, treatment monitoring, and response assessment. Recommendations are based on evidence generated from studies which validated PET findings by histology or clinical course. This guideline emphasizes the clinical value of PET imaging with superiority of amino acid PET over glucose PET and provides a framework for the use of PET to assist in the management of patients with gliomas.

Keywords: amino acid PET, glioma, guideline, PET imaging, recommendations.

Gliomas are the second most common primary brain tumors, with an incidence of 4–5/100 000 individuals. Gliomas are the second leading cause of cancer mortality in adults under the age of 35, the fourth leading cause in those under the age of 54, and result in death in approximately 13 770 individuals per year in the United States.1 Median survival of glioblastoma, the most aggressive variant, is 16 months in patients treated with maximum safe resection, radiotherapy, and concurrent and adjuvant temozolomide in clinical trial populations.2–4

MRI is the mainstay of imaging of gliomas to monitor both treatment and response. T1-weighted MRI without and with contrast medium, T2-weighted as well as fluid-attenuated inversion recovery (FLAIR) MRI sequences are used for anatomic imaging. However, many brain tumors (particularly World Health Organization [WHO] grade II and a significant number of WHO grade III gliomas) do not enhance with contrast-agent administration, reducing the ability of contrast imaging to accurately quantify tumor burden. The challenge to accurately determine brain tumor response by MRI both in daily practice and in clinical trials has led to the introduction of updated guidelines by the Response Assessment in Neuro-Oncology (RANO) working group.5

Functional molecular imaging such as positron emission tomography (PET) uses various tracers to visualize biological processes such as cell proliferation, membrane biosynthesis, glucose consumption, and uptake of amino acid analogs.6 Hence, PET provides additional insight beyond MRI into the biology and treatment response of gliomas which may be used for
noninvasive grading, differential diagnosis, delineation of tumor extent, surgical and radiotherapy treatment planning, posttreatment surveillance, and prognostication.

Analogous to the RANO effort regarding MRI use in gliomas, an initiative was undertaken by a group of clinicians and nuclear medicine physicians to similarly define standards of molecular imaging for gliomas using PET with respect to interpretation and validation as well as to define its role in clinical practice. In this paper, evidence-based recommendations are proposed for the use of PET imaging in the clinical management of glioma patients. Accordingly, the review discusses tracers which image glucose metabolism—18F-2-fluoro-2-deoxy-D-glucose (18F-FDG)—and amino acid transport ([11C]-methylmethionine (11C-MET), O-[2-18F]-fluoroethyl-L-tyrosine (18F-FET) and 3,4-dihydroxy-6-[18F]-fluoro-L-phenylalanine (18F-FDOPA)), since these compounds have already entered clinical practice.

The current guidelines aim to serve medical professionals of all disciplines involved in the diagnosis and care of patients with gliomas. A separate procedural guideline focusing on the standardization of technical aspects of PET imaging for glioma will be the subject of another paper prepared by the ENAON (European Association of Nuclear Medicine)/EANO (European Association of Neuro-Oncology)/RANO groups.

Levels of Validation and Clinical Evidence Search Strategy and Selection Criteria

The information retrieved from a PubMed search of the published literature with the combination of the search terms “glioma,” “glioblastoma,” “brain tumor,” “PET,” “FDG,” “FET,” “MET,” and “DOPA” until September 2015 as well as from articles identified through searches of the authors’ own files was evaluated by the working group with respect to the level of evidence and the grade of validation of the PET studies examined.

Any study that correlated the PET findings with histopathology was considered to represent the highest degree of validation. Next, correlation with MRI (when applicable, according to RANO criteria) and with the patient’s clinical course was used for the second level of validation. Only papers constituting levels 1–3 evidence according to the Oxford Centre for Evidence-based Medicine (OCEBM Levels of Evidence Working Group: “The Oxford 2011 Levels of Evidence”) were included.

General Recommendations

Recommendations for clinical use and diagnostic performance of differing PET tracers compared with MRI are presented in Tables 1 and 2 and in Fig. 1.

Specific Recommendations

Primary Diagnosis/Differential Diagnosis

18F-FDG PET may provide useful information for distinguishing WHO grade III/IV gliomas from other malignant brain tumors, but its specificity is limited. Importantly, maximum standardized uptake values (SUVmax) were significantly higher in primary CNS lymphomas than in glioblastomas.1,15 However, corticosteroid medication may reduce uptake.

The differential diagnosis by 18F-FDG PET between WHO grades III/IV gliomas and brain metastases is limited, since considerable overlap of SUVmax exists between these tumor types.1,15 18F-FDG PET also has limited specificity for distinguishing glioma from other nonneoplastic lesions, such as brain abscesses, demyelinating tumefactive (“tumor-like”) lesions, fungal infections, and neurosarcoidosis9 due to increased 18F-FDG metabolism in inflammatory tissue.

Amino acid PET is useful for the noninvasive differentiation of tumor and nontumoral processes, as tumors have significantly higher uptake than nonneoplastic tissue.10,11 However, moderately increased uptake can also be seen in acute inflammatory lesions such as active multiple sclerosis and brain abscesses.12,13 Conversely, lack of 18F-FET uptake does not exclude a glioma, as approximately one-third of WHO grade II gliomas and most dysplastic/embryonal tumor-like telangiectatic tumors (WHO grade I) are 18F-FET negative.14 However, among WHO grades III and IV gliomas, the vast majority (>95%) show increased uptake11,12,15 with a resultant high sensitivity for the detection of these tumors. A recent meta-analysis revealed that for brain tumor diagnosis, 18F-FET PET performed much better than 18F-FDG PET and consequently would be the preferred PET tracer when assessing patients with a newly diagnosed brain tumor.16 Furthermore, numerous studies validated by histology have demonstrated higher diagnostic accuracy of additional amino acid PET compared with anatomic MRI alone for the differentiation of gliomas from nonneoplastic lesions.11,12,17-19

- In cases of diagnostic uncertainty, amino acid PET improves sensitivity, specificity, and accuracy and is markedly superior to 18F-FDG PET in differentiating between glioma and nonneoplastic tissue.

Tumor Grading

The value of 18F-FDG PET for grading of gliomas is hampered by the poor tumor-to-background contrast due to physiologically increased glucose uptake of cortical and subcortical (basal ganglia, thalamus) structures in brain and high variation of uptake and overlap of uptake values between tumors of different WHO grades, especially in oligodendrogliomas.20,21 However, WHO grades III and IV gliomas generally have higher 18F-FDG values than WHO grade II gliomas, which often appear as a hypometabolic lesion, particularly when compared with the uptake in the cortex.

Characteristically, amino acid uptake is higher in gliomas of WHO grades III/IV compared with WHO grade II gliomas. However, uptake intensities may vary, and tumor-to-brain ratios show a considerable overlap between different WHO grades as well as histological subtypes.11,12,22-24 For 18F-FET, accuracy for tumor grading can be markedly improved by evaluating dynamic (kinetic) PET data, which typically show steadily increasing time-activity curves in WHO grade II gliomas, as opposed to an early activity peak around 10–20 min after injection, followed by a decrease of 18F-FET uptake in WHO grades III/IV gliomas.22,25 This is particularly valuable in the clinical setting of patients with MRI non-contrast-enhancing gliomas suspected of harboring a WHO grade II glioma. In approximately 40% of such cases, an anaplastic focus is demonstrated.14,26 In these patients, kinetic analysis provides a higher sensitivity and specificity for the detection of WHO grades III/IV gliomas (95%).14 This method
of kinetic analysis does not work for $^{11}$C-MET$^{24}$; and for $^{18}$F-FDOPA, data are still controversial.$^{27,28}$

- Although $^{18}$F-FDG and amino acid uptake are usually higher in WHO grades III/IV gliomas than in WHO grade II gliomas, tumor grading is limited due to significant overlap in uptake values.

- Dynamic analysis of $^{18}$F-FET PET uptake further improves differential diagnosis between WHO grade II and WHO grades III/IV gliomas.

### Delineation of Glioma Extent

Multiple histopathological and postmortem series demonstrate the limitations of conventional MRI in defining the extent of glioma.$^{29,30}$ Moreover, the usefulness of $^{18}$F-FDG PET in tumor delineation, given high uptake in normal brain cortex and low uptake in WHO grade II gliomas, is particularly limited for cortical or pericortical tumors, even when dual-timepoint images are performed.$^{31}$ In contrast, amino acid PET imaging more accurately identifies infiltrating regions of tumor extending beyond the MRI contrast-enhancing lesion and often distinguishes among tumor, nontumoral edema, and normal brain.$^{32}$ In addition, amino acid PET provides functional and metabolic information about the tumor and may identify tumor regions with different biological and clinical behavior. In both WHO grade II and WHO grades III/IV gliomas, amino acid PET complements conventional MRI by providing additional information about tumor extent and biology.

### WHO grades III/IV glioma

Both the uptake and image contrast between tumor and normal tissue of amino acid tracers such as $^{11}$C-MET and $^{18}$F-FET.
Table 2. Overview of histologically validated amino acid PET studies in gliomas

<table>
<thead>
<tr>
<th>Clinical Problem</th>
<th>MET</th>
<th>PET</th>
<th>FDOPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differentiation of neoplastic from nonneoplastic lesions</td>
<td>Stereotactic biopsy</td>
<td>Stereotactic biopsy and hot-spot guided resection</td>
<td>n.a.</td>
</tr>
<tr>
<td>Differentiation between WHO grades II and WHO grades III/IV glioma</td>
<td>Hot-spot guided resection</td>
<td>In a subset of patients stereotactic biopsy</td>
<td>In a subset of patients stereotactic biopsy and hot-spot guided resection</td>
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<tr>
<td>Delineation of glioma extent</td>
<td>Stereotactic biopsy and hot-spot guided resection</td>
<td>Stereotactic biopsy</td>
<td>Stereotactic biopsy and hot-spot guided resection</td>
</tr>
<tr>
<td>Detection of glioma recurrence from treatment-induced changes (eg, radionecrosis)</td>
<td>Stereotactic biopsy and hot-spot guided resection</td>
<td>Stereotactic biopsy</td>
<td>Stereotactic biopsy</td>
</tr>
<tr>
<td>Detection of malignant tumor parts in MRI findings suggestive for WHO grade II glioma</td>
<td>Stereotactic biopsy</td>
<td>Stereotactic biopsy and hot-spot guided resection</td>
<td>n.a.</td>
</tr>
<tr>
<td>Assessment of prognosis in untreated gliomas</td>
<td>Histological confirmation of glioma only</td>
<td>Histological confirmation of glioma only</td>
<td>Histological confirmation of glioma only</td>
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Abbreviation: n.a., not available.

Indications for amino acid PET

Suspected primary glioma on MRI → Resection or biopsy → Radiotherapy or chemotherapy or both → Maintenance therapy → Follow-up

Rationale for AA PET during follow-up:
- Diagnosis of treatment-induced changes (e.g., radionecrosis) versus treatment relapse
- Follow-up AA PET for adjuvant therapy monitoring
- Delineation of tumor extent for resection planning

Rationale for AA PET within first 12 weeks after radio(chemo)therapy:
- Diagnosis of treatment-induced changes (e.g., pseudoprogression) versus treatment relapse
- Follow-up AA PET for monitoring of radio(chemo)therapy
- Baseline AA PET for adjuvant therapy monitoring

Rationale for AA PET after surgery:
- Assessment of resection extent
- Planning of radiotherapy
- Baseline AA PET for monitoring of radio(chemo)therapy
- Prognostication

Rationale for initial AA PET:
- Differentiation neoplastic vs. non-neoplastic tissue
- Delineation of tumor extent for resection planning
- „Hot-Spot“ localization for biopsy planning
- Prognostication

Fig. 1. Overview of indications for amino acid PET.
are similar. PET-based tumor volumes have been shown to extend beyond the contrast-enhancing volume on conventional MRI by 2–3.5 cm for different tracers. In addition, amino acid PET identifies tumor extent within non-specific regions of T2/FLAIR signal abnormality.

**WHO grade II glioma**

Most WHO grade II gliomas are nonenhancing with infiltrating tumor borders that are difficult to delineate by conventional MRI. Several studies have demonstrated the usefulness of amino acid PET in defining tumor extent. This has been demonstrated in histology-validated series for [11]C-MET, [18]F-FET, and [18]F-FDOPA PET.

- [18]F-FDG is not suitable for glioma volume delineation.
- Delineation of tumor borders by amino acid PET is superior to standard MRI both in contrast-enhancing as well as non-contrast-enhancing gliomas.

**Value for Treatment Planning: Biopsy and Resection**

Implementation of PET into biopsy and resection planning is advantageous, as PET better delineates tumor extent compared with standard MRI and additionally identifies intratumoral heterogeneity, including malignant foci in non-contrast-enhancing gliomas.

Numerous studies have investigated the benefit of incorporating [18]F-FDG or amino acid PET into biopsy target planning. The identification of malignant foci (“hot spots”) in MRI heterogeneous gliomas is essential for biopsy planning to ensure that the biologically most aggressive portion of the tumor, which determines the patient’s prognosis as well as treatment, is not undersampled. There are several reports that illustrate the advantages of amino acid PET-based resection planning, of considerable importance whenever functional, eloquent areas may be involved, and which demonstrate a higher probability of detecting more highly malignant areas within an MRI heterogeneous glioma as well as decreased risk of incomplete resection.

- Integration of amino acid PET into surgical planning allows better delineation of the extent of resection beyond margins visible with standard MRI. This is of considerable importance whenever functional eloquent areas of brain are involved.
- For biopsy planning, amino acid PET is particularly helpful in identifying malignant foci within non-contrast-enhancing gliomas.

**Value for Treatment Planning: Radiation**

Beyond MRI-based morphologic gross tumor volume delineation, a biological tumor volume may be defined by radiotracer uptake on amino acid PET that identifies tumor beyond the extent visible with standard MRI. In addition, the biologic and metabolic information provided by PET may identify subregions of tumor at higher risk of recurrence, which can be included in the radiation boost volume. The ability to better define tumor extent and biology may be used to improve the therapeutic ratio of radiation treatment. The current recommendations focus on the role of PET for radiation planning of WHO grades III/IV gliomas, as the role of PET imaging in irradiation of WHO grade II gliomas is not well established.

Small, prospective studies systematically comparing contrast MRI tumor volume (the “standard” radiation boost target) and [18]F-FDG uptake abnormality generally demonstrate a smaller region of [18]F-FDG uptake contained within the MRI abnormality, with only occasional extension outside of the MRI target. Although small studies have demonstrated the feasibility of radiation boost planning using [18]F-FDG PET, its utility is limited by the low contrast between tumor and normal cortex.

Studies analyzing patterns of failure following conventional chemoradiotherapy based on standard MRI-defined tumor volumes suggest that amino acid PET-defined tumor volumes may yield a more appropriate radiation target volume. In these small studies, a proportionate increase in marginal or noncentral tumor recurrences were seen when regions of [11]C-MET and [18]F-FET abnormality were not adequately covered by high-dose radiation. Prospective, single-arm studies evaluating the use of amino acid PET for radiation treatment planning of recurrent WHO grades III/IV glioma suggest the feasibility of this approach, and most studies suggest an improvement in outcome compared with radiation planning based on conventional MRI alone. However, the inclusion of amino acid PET-based tumor volumes in standard-dose radiation therapy and reirradiation protocols continue to demonstrate a predominance of in-field tumor recurrences, highlighting the need for more effective therapies.

- Amino acid PET may improve the delineation of a biological tumor volume beyond conventional MRI and identify aggressive tumor subregions that may be targeted by radiation therapy.
- While [18]F-FDG PET is of limited utility in radiation treatment planning of WHO grades III/IV gliomas, radiation planning using amino acid PET appears feasible, with preliminary evidence of potential benefit.

**Follow-up: Treatment Response, Progression, Pseudoprogression, and Radionecrosis**

To date, standard, structural MRI is the most important diagnostic tool for assessing treatment effects in patients with gliomas. The extent of contrast enhancement on MRI is usually considered an indicator of treatment response (eg, Macdonald criteria, RANO criteria), although its reliability in distinguishing tumor tissue from treatment effects, which can include blood–brain barrier breakdown, is limited. For example, transient blood–brain barrier alteration with contrast enhancement—such as after radiotherapy with or without concomitant temozolomide—can mimic tumor progression and is termed “pseudoprogression.” In addition, since the introduction of anti-angiogenic agents such as bevacinuzumab, the phenomenon of pseudoprogression complicates the assessment of treatment response using standard MRI alone.

**WHO grades III/IV glioma**

Few [18]F-FDG PET studies have measured the glucose metabolic rate following either radiotherapy, chemotherapy, or both: decrease of [18]F-FDG uptake correlates with treatment
response. 18F-FDG PET has been found to be of only moderate additional value to MRI for differentiation between malignant glioma recurrence and radionecrosis, especially due to low specificity. However, there are several limitations: most studies were retrospective, jointly assessed gliomas of all WHO grades, used differing treatments, had varying response assessment strategies, and utilized varying 18F-FDG thresholds of tumor to normal brain for image interpretation.

The feasibility and usefulness of amino acid PET such as 11C-MET, 18F-FET, or 18F-FDOPA PET for treatment assessment after chemoradiotherapy, stereotactic brachytherapy, chemotherapy, and other experimental approaches have been demonstrated in several studies, primarily in WHO grades III/IV gliomas. Current amino acid PET data suggest that a reduction of amino acid uptake and/or a decrease of the metabolically active tumor volume is a sign of treatment response associated with long-term outcome. Amino acid PET using 18F-FET may facilitate the diagnosis of pseudoprogression in glioblastoma patients within the first 12 weeks following completion of chemoradiotherapy.

Furthermore, several studies suggest that treatment response and outcome in bevacizumab therapy can be assessed by amino acid PET using 18F-FET and 18F-FDOPA better than by MRI. Amino acid PET is useful for the differentiation between treatment-related changes and true progression with high sensitivity and specificity. A combination of static and dynamic 18F-FET PET parameters identified correctly progressive or recurrent glioma with higher accuracy (93%) than conventional MRI.

WHO grade II glioma

In contrast to patients with WHO grades III/IV gliomas, the experience with amino acid PET for monitoring after treatment in patients with WHO grade II gliomas is limited, with only a few studies available in the literature. As these tumors are usually negative on 18FDG PET, the latter is not suitable for response evaluation.

- Analysis of 18F-FDG uptake does not reliably distinguish between recurrence and radionecrosis.
- A decrease in amino acid uptake and/or volume is associated with treatment response across gliomas of WHO grades III/IV.
- Amino acid PET improves the assessment of pseudoprogression, radionecrosis, and pseudoresponse.

Prognostication

The prognostic value of 18F-FDG uptake in gliomas has been suggested by several studies. Additionally, pretreatment 18F-FDG PET has been reported to correlate with survival in patients with newly diagnosed glioblastoma or recurrent high-grade gliomas receiving bevacizumab.

The prognostic value of amino acid PET has been increasingly explored. At diagnosis, dynamic 18F-FET PET identified highly aggressive astrocytomas within the same WHO grade— for instance, WHO grade II gliomas with decreasing time-activity curves manifested earlier tumor progression, malignant transformation, as well as shorter survival. Similarly dynamic 18F-FET PET identified anaplastic astrocytomas with a very early decrease of time-activity curves—and consequently short time-to-peak—as having a comparably poor outcome.

To date, the association of glioma 18F-FET uptake with survival has remained controversial. Some groups have reported a better outcome of patients with absent or only low tumor amino acid uptake. In contrast, a larger study of 18F-FET-negative glioma patients did not reveal an association with improved outcome, as neither time to transformation, which was proven upon histological evaluation, nor overall survival differed from that of FET-positive glioma patients.

A prospective multicenter trial investigating the role of pretreatment 18F-FET PET in newly diagnosed glioblastoma found biological tumor volume prior to chemoradiotherapy to be highly prognostic for outcome. This is in accordance with results of previous studies investigating amino acid PET in malignant glioma prior to therapy.

- Uptake of 18F-FDG and amino acid tracer is associated with outcome in WHO grades III/IV glioma both in a pretreatment setting and following therapy.
- Biological tumor volume in amino acid PET is associated with survival following therapy in glioblastoma.
- Dynamic analysis of 18F-FET uptake provides prognostic information within all grades of glioma prior to treatment.

Current Limitations

While 18F-FDG is used at all PET sites, only a few centers offer amino acid PET so far. However, due to the 18F labeling of FET and FDOPA, the radiotracer can be delivered in the same way as 18F-FDG, facilitating the availability of amino acid PET. Only for 11C-MET is an on-site cyclotron required. The major obstacle for the widespread use of amino acid PET in glioma patients is to date the limited reimbursement by health insurance companies/institutions, despite the fact that current data clearly favor amino acid over 18F-FDG PET.

Across all tracers, numerous studies differed in terms of methodology, which limits comparability of data and might eventually jeopardize acceptance in the clinical setting. However, this guideline collected convincing support that PET imaging is of additional value beyond MRI in glioma management.

Outlook Perspective

Future clinical studies should consider the use of amino acid PET as an imaging modality for gliomas complementary to MRI. Standardized technical guidelines for PET imaging procedures and recommendations by the EANM/EANO/RANO group will be published separately.

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