Neuro-Oncology

Neuro-Oncology 18(9), 1199–1208, 2016
doi:10.1093/neuonc/now058
Advance Access date 21 April 2016

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 (^{18}F-FDG) and amino acid tracers (^{11}C-MET, ^{18}F-FET, and ^{18}F-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

Received 15 January 2016; accepted 14 March 2016

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—^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}F-FDG)—and amino acid transport ([^{11}C-methyl]-methionine (^{11}C-MET), O-(2-[^{18}F]-fluoroethyl)-L-tyrosine (^{18}F-FET) and 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine (^{18}F-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 EANM (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

^{18}F-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 (SUV_{max}) were significantly higher in primary CNS lymphomas than in glioblastoma.[7,8] However, corticosteroid medication may reduce uptake.

The differential diagnosis by ^{18}F-FDG PET between WHO grades III/IV gliomas and brain metastases is limited, since considerable overlap of SUV_{max} exists between these tumor types.[7] ^{18}F-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 neurosarcoidosis[9] due to increased ^{18}F-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 ^{18}F-FET uptake does not exclude a glioma, as approximately one-third of WHO grade II gliomas and most dysembryoplastic neuroepithelial tumors (WHO grade I) are ^{18}F-FET negative.[14] However, among WHO grades III and IV gliomas, the vast majority (>95%) show increased uptake,[11,12,15] with a resultant high sensitivity for the detection of these tumors. A recent meta-analysis revealed that for brain tumor diagnosis, ^{18}F-FET PET performed much better than ^{18}F-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 ^{18}F-FDG PET in differentiating between glioma and nonneoplastic tissue.

Tumor Grading

The value of ^{18}F-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 oligodendroglial tumors.[20,21] However, WHO grades III and IV gliomas generally have higher ^{18}F-FDG values than WHO grade II gliomas, which often appear as a hypometabolic lesion, particularly when compared with the uptake in the cortex.[16]

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 ^{18}F-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 ^{18}F-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

Table 1. Diagnostic performance of different amino acid tracers compared with conventional and advanced MRI

Clinical Problem	MET	FET	FDOPA
Differentiation of glioma from nonneoplastic lesions	Numerous studies,[19] higher diagnostic accuracy than MRI alone	Higher diagnostic accuracy than MRI alone[11,12,18]	Not available for the initial diagnosis
Glioma grading (including detection of anaplastic foci)	Higher diagnostic accuracy than MRI, but still limited accuracy due to high overlap between WHO grades[19,96]	Higher diagnostic accuracy than MRI, in particular for *dynamic* PET[14,26,93] High accuracy by combination of dynamic FET-PET and diffusion MRI[97]	No studies available comparing directly PET with MRI; in the pure PET studies, conflicting results reporting high[38,98] and low[28,99] performance
Delineation of glioma extent	Metabolically active tumor larger than contrast enhancement in LGG and HGG at diagnosis and recurrence[100,101] Delineates metabolically active tumor in non-enhancing anaplastic glioma[32,102]	In newly diagnosed glioblastoma, metabolically active tumor larger than CE pre- and postoperatively[46,103] In WHO grades II/IV gliomas metabolically active tumor larger than rCBV[104]	In glioma, metabolically active tumor larger than rCBV,[105] ADC,[106] and contrast enhancement[34,36]
Differentiation of glioma recurrence from treatment-induced changes (eg, pseudoprogression, radionecrosis)	Higher diagnostic accuracy than MRI[66]	Higher diagnostic accuracy than MRI[74,81,107]	Higher diagnostic accuracy than MRI[17,37,79,108]
Assessment of treatment response (including pseudoresponse)	Superior to MRI; metabolic response to TMZ predictive for survival[70]	Superior to MRI; metabolic responses to TMZ,[83] RT,[69,71] and BEV[76,78] occurred earlier and/or were associated with improved survival	Superior to MRI; metabolic response to BEV[77] occurred earlier and was predictive of improved survival
Assessment of prognosis in gliomas	In contrast to pretreatment CE volumes, metabolically active tumor volumes are prognostic in HGG[86,95]	Metabolically active tumor volume is prognostic in WHO grade IV glioma.[46] Higher prognostic value of time-activity curves in *dynamic* PET than MRI within WHO grade II and WHO grades III/IV glioma.[15,91,92] FET uptake in combination with specific MRI findings is prognostic[94] for WHO grade II glioma	Superior to MRI in WHO grade II glioma; maximum uptake is an independent predictor of progression[109]

Abbreviations: LGG, low-grade glioma; HGG, high-grade glioma; CE, contrast enhancement; rCBV, relative cerebral blood volume; ADC, apparent diffusion coefficient; TMZ, temozolomide; RT, radiotherapy; BEV, bevacizumab.

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

Clinical Problem	MET	FET	FDOPA
Differentiation of neoplastic from nonneoplastic lesions	Stereotactic biopsy[110] Hot-spot guided resection[111]	Stereotactic biopsy and hot-spot guided resection[11]	n.a.
Differentiation between WHO grades II and WHO grades III/IV glioma	In a subset of patients stereotactic biopsy[112]	Stereotactic biopsy[14,22,25]	In a subset of patients stereotactic biopsy and hot-spot guided resection[38]
Delineation of glioma extent	Stereotactic biopsy[39,43,113,114] Hot-spot guided resection[101,115]	Stereotactic biopsy[41,116] Stereotactic biopsy and hot-spot guided resection[117]	In a subset of patients hot-spot guided resection[36]
Differentiation of glioma recurrence from treatment-induced changes (eg, radionecrosis)	Stereotactic biopsy[118]	Stereotactic biopsy[119] Stereotactic biopsy and hot-spot guided resection[81,120]	In a subset of patients stereotactic biopsy[17,108]
Detection of malignant tumor parts in MRI findings suggestive for WHO grade II glioma	Stereotactic biopsy and hot-spot guided resection[96]	Stereotactic biopsy[26] Stereotactic biopsy and hot-spot guided resection[93]	n.a.
Assessment of prognosis in untreated gliomas	Histological confirmation of glioma only[95] (local comparison not necessary)	Histological confirmation of glioma only[15,91] (local comparison not necessary)	Histological confirmation of glioma only[109] (local comparison not necessary)

Abbreviation: n.a., not available.

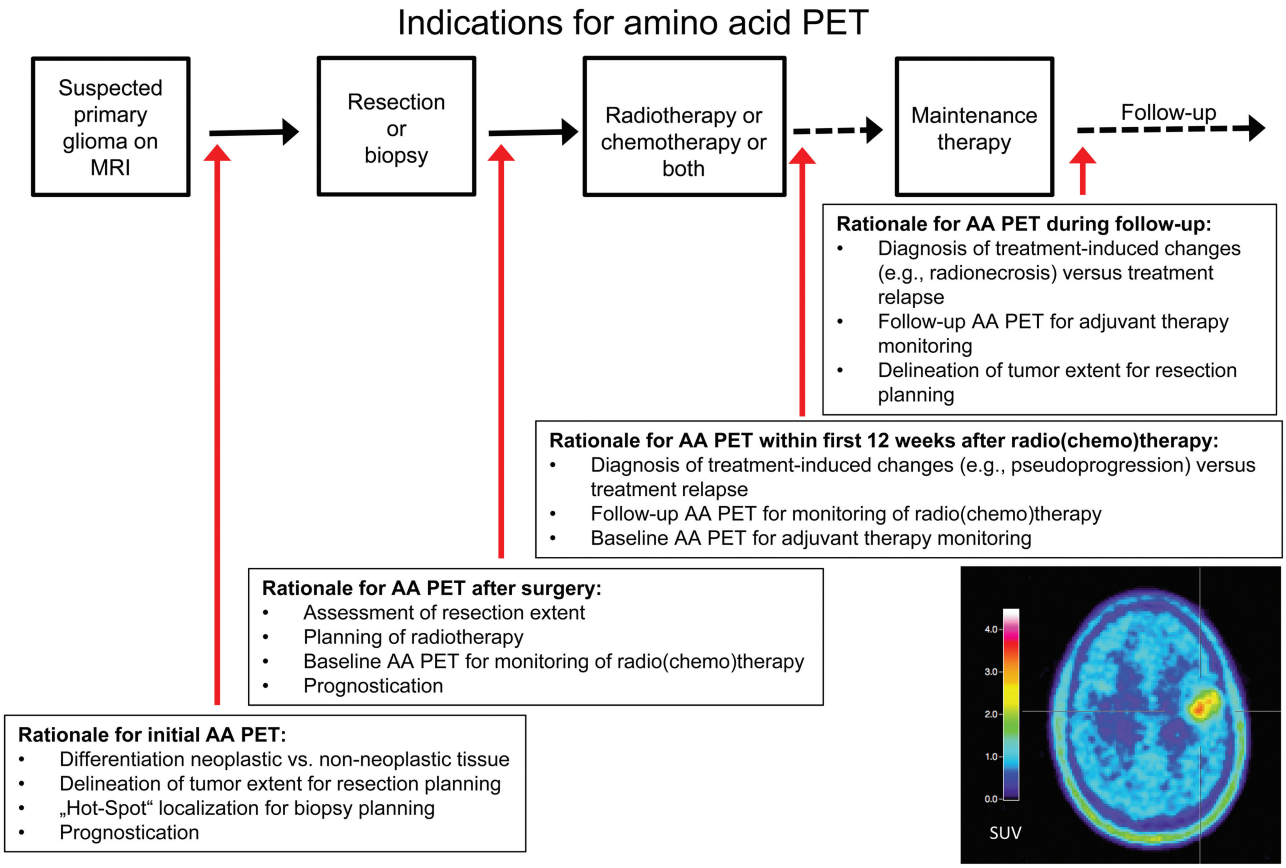

Fig. 1. Overview of indications for amino acid PET.

are similar.[33] 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.[34–37] In addition, amino acid PET identifies tumor extent within nonspecific regions of T2/FLAIR signal abnormality.[34,36]

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.[17,38–41]

- ^{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.[26,42] 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,[26,34,43] 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.[44,45,46]

- 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.[47] 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.[48,49] 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.[48]

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.[50–52] 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.[53,54] 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.[53–56]

- 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.[4] The extent of contrast enhancement on MRI is usually considered an indicator of treatment response (eg, Macdonald criteria, RANO criteria),[5,57] although its reliability in distinguishing tumor tissue from treatment effects, which can include blood–brain barrier breakdown, is limited.[58] 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."[59,60] In addition, since the introduction of anti-angiogenic agents such as bevacizumab, the phenomenon of pseudoresponse complicates the assessment of treatment response using standard MRI alone.[59,61]

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.[62–64] ^{18}F-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.[65,66,67,68] However, there are several limitations: most studies were retrospective, jointly assessed gliomas of all WHO grades, used differing treatments, had varying assessment strategies, and utilized varying ^{18}F-FDG thresholds of tumor to normal brain for image interpretation.

The feasibility and usefulness of **amino acid** PET such as ^{11}C-MET, ^{18}F-FET, or ^{18}F-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.[69–73] Amino acid PET using ^{18}F-FET may facilitate the diagnosis of pseudoprogression in glioblastoma patients within the first 12 weeks following completion of chemoradiotherapy.[74]

Furthermore, several studies suggest that treatment response and outcome in bevacizumab therapy can be assessed by amino acid PET using ^{18}F-FET and ^{18}F-FDOPA better than by MRI.[75–78]

Amino acid PET is useful for the differentiation between treatment-related changes and true progression with high sensitivity and specificity.[37,79,80] A combination of static and dynamic ^{18}F-FET PET parameters identified correctly progressive or recurrent glioma with higher accuracy (93%) than conventional MRI.[81]

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.[82,83] As these tumors are usually negative on **^{18}FDG PET**, the latter is not suitable for response evaluation.

- Analysis of ^{18}F-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 **^{18}F-FDG** uptake in gliomas has been suggested by several studies.[84–87] Additionally, pretreatment ^{18}F-FDG PET has been reported to correlate with survival in patients with newly diagnosed glioblastoma[88] or recurrent high-grade gliomas receiving bevacizumab.[89]

The prognostic value of **amino acid** PET has been increasingly explored.[15,90–92] At diagnosis, *dynamic* ^{18}F-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.[91,93] Similarly *dynamic* ^{18}F-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.[15]

To date, the association of glioma ^{18}F-FET uptake with survival has remained controversial. Some groups have reported a better outcome of patients with absent or only low tumoral amino acid uptake.[86,90,94] In contrast, a larger study of ^{18}F-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.[15]

A prospective multicenter trial investigating the role of pretreatment ^{18}F-FET PET in newly diagnosed glioblastoma found biological tumor volume prior to chemoradiotherapy to be highly prognostic for outcome.[46] This is in accordance with results of previous studies investigating amino acid PET in malignant glioma prior to therapy.[69,95]

- Uptake of ^{18}F-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 ^{18}F-FET uptake provides prognostic information within all grades of glioma prior to treatment.

Current Limitations

While ^{18}F-FDG is used at all PET sites, only a few centers offer amino acid PET so far. However, due to the ^{18}F labeling of FET and FDOPA, the radiotracer can be delivered in the same way as ^{18}F-FDG, facilitating the availability of amino acid PET. Only for ^{11}C-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 ^{18}F-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.

Funding

This work has not been funded.

Conflict of interests statement. M.W. has received research grants from Acceleron, Actelion, Alpinia Institute, Bayer, Isarna, MSD, Merck & Co, Novocure, PIQUR, and Roche and honoraria for lectures or advisory board participation or consulting from Celldex, Immunocellular

Therapeutics, Isarna, Magforce, MSD, Merck & Co, Northwest Biotherapeutics, Novocure, Pfizer, Roche, and Teva. M.M.K. has received research funding from EpicentRx, Inc. C.I.F. has received personal fees from Bayer and GE Healthcare, advisory board fees from Bayer, Endocyte, and GE Healthcare, grants from GE Healthcare, Pierre Fabre, and Siemens Healthcare. W.P. is consultant for Celldex Therapeutics, Imaging Endpoints, LLC, and Tocagen. J.A. has received financial research support from Siemens and Avid-Lilly and honoraria as a speaker or advisory board member from Bayer, Advanced Accelerator Applications, Lilly, Piramal, and General Electric. M.A.V. is an officer with intellectual property, equity, and royalty interests at Infuseon Therapeutics, is a member of DSMB Neuralstem, and is a consultant for Pharmaco-Kinesis. B.M.E. is a consultant for MedQIA, LLC and is a consultant for and has received grants from or participated on the advisory board of Siemens Healthcare, Roche/Genentech, Agios Pharmaceuticals, Bristol-Meyers Squibb, and Merck. J.C.T. is a consultant/advisory board member for Merck Serono, Roche, and Celldex. He received speakers bureau honoraria from Merck Serono, Roche, Brainlab, and Siemens. N.L.A., B.S., N.G., R.S., I.L., and M.C. report no conflicts of interest.

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