Update on amino acid PET of brain tumors

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Purpose of review

To give an update on the emerging role of PET using radiolabelled amino acids in the diagnostic workup and management of patients with cerebral gliomas and brain metastases.

Recent findings

Numerous studies have demonstrated the potential of PET using radiolabelled amino acids for differential diagnosis of brain tumors, delineation of tumor extent for treatment planning and biopsy guidance, differentiation between tumor progression and recurrence versus treatment-related changes, and for monitoring of therapy. The Response Assessment in Neuro-Oncology (RANO) working group — an international effort to develop new standardised response criteria for clinical trials in brain tumors — has recently recommended the use of amino acid PET imaging for brain tumor management in addition to MRI at every stage of disease. With the introduction of F-18 labelled amino acids, a broader clinical application has become possible, but is still hampered by the lack of regulatory approval and of reimbursement in many countries.

Summary

PET using radiolabelled amino acids is a rapidly evolving method that can significantly enhance the diagnostic value of MRI in brain tumors. Current developments suggest that this imaging technique will become an indispensable tool in neuro-oncological centers in the near future.

Key Words

PET, gliomas, brain metastases, radiolabelled amino acids, [^{11}C-methyl]-L-methionine (MET), O-(2-[^{18}F]-fluoroethyl)-L-tyrosine (FET) and 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine (FDOPA), pseudoprogression, recurrence

Key points

- Amino acid PET provides significant information for differential diagnosis and delineation of cerebral gliomas in addition to MRI
- Amino acid PET shows high accuracy for diagnosis of progressive or recurrent tumor in cerebral gliomas and brain metastases and for monitoring of therapy
- Amino acid PET is robust and attractive for clinicians because of easy scan reading

Introduction

Cerebral gliomas are, besides meningiomas, the most common primary brain tumors in adults with an incidence of 5-6 in 100,000 [1]. Even more frequent are brain metastases with an incidence of 8 – 14 / 100,000 [2]. In 2016, the classification of gliomas by the World Health Organization (WHO) was expanded to include not only histological but also molecular parameters [3]. The most common and also most fatal primary brain tumors are glioblastomas, corresponding to the WHO grade IV. Despite aggressive multimodal treatment strategies (resection, radiation therapy, chemotherapy), the median survival of patients with gliomas is limited and varies from 1.5 years for glioblastoma to 2 to 3 years for a WHO grade III glioma and 5 to more than 10 years for a WHO grade II glioma [4]. Based on the WHO 2007 classification Gliomas of WHO grade III and IV are often reported together as high-grade gliomas (HGG), while grade II (together with grade I, which is very rare in adults) are low-grade gliomas (LGG). Contrast enhanced MRI is the method of first choice for brain tumor diagnosis due to its superior soft-tissue resolution and great availability. Conventional MRI includes T1- and T2-weighted sequences, but the capacity of standard imaging to differentiate tumor tissue from nonspecific tissue changes may be limited, especially after therapy. In recent years, PET using radiolabelled amino acids has developed as an important diagnostic tool. The benefits of amino acid PET over MRI for glioma imaging are manifold including a better differentiation of equivocal lesions detected with MRI, improved targeting of surgery and radiotherapy to the true extent of the tumor, differentiation between tumor progression and treatment-related changes and early identification of tumor responses to therapy. The Response Assessment in Neuro-Oncology (RANO) working group has recently recommended the use of amino acid PET imaging for brain tumor management in addition to conventional MRI at every stage of disease [5]. This work provides an overview of the clinical significance of amino acid PET in various diagnostic problems of glioma and brain metastasis, current developments and comparisons with advanced MR methods.

Radiolabelled Amino Acids for PET

In oncological diagnostics, 2-^{18}F-fluorodeoxyglucose (FDG), is the most widely used PET tracer but in the brain the detection of tumor tissue is considerably hindered by the high glucose metabolism in healthy tissue [6]. In contrast, the uptake of radiolabelled amino acids is low in normal brain tissue and brain tumors can be depicted with a high tumor-to-background contrast. The longest-established amino acid tracer amino acid tracer for PET is [^{11}C-methyl]-L-methionine (MET), which, however, is restricted to a few neurooncology centres because the short half-life of carbon-11 (20 min) requires an onsite cyclotron. Therefore, amino acids labelled with fluorine-18 (half-life of 109.8 min) such as O-(2-[^{18}F]-fluoroethyl)-L-tyrosine (FET) [7], 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine (FDOPA) [8], L-[3-^{18}F]-α-methyl tyrosine (FMT) [9], and anti-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid (FACBC, fluciclovine) [10] are increasingly gaining acceptance owing to logistical advantages compared with C-11 labelled amino acids. FDOPA is approved in some European Countries for clinical use, fluciclovine has orphan drug status for brain gliomas at the US FDA [11] and FET is approved for clinical use in brain tumor imaging in Switzerland [12]. In Europe, MET has been replaced in many neurooncology centres by the more convenient FET, and high clinical interest in this method has led to >10,000 FET PET scans being performed in some centres [13].

A key feature of these amino acid tracers is their ability to pass the intact BBB which allows the depiction of the tumor mass beyond contrast enhancement in MRI [14] and to differentiate tumor progression from non-specific, treatment-related changes[15]. Animal experiments have shown that changes of BBB permeability after administration of dexamethasone or antiangiogenic treatment with bevacizumab do not affect FET uptake in brain tumors [16, 17]. Furthermore, high uptake of amino acids has been reported in many low-grade gliomas without BBB leakage [18, 19].

According to previous findings, the transport of these amino acids occurs predominantly via the transport system L for large neutral amino acids namely the subtypes LAT1 and LAT2 although other transport systems may play a role [20-23]. The visualization of brain tumors with MET, FET and FDOPA is very similar [24-26] but in contrast to MET and FDOPA, FET shows a tumor-type specific tracer kinetics, which can be helpful in differential diagnosis [27-29, 26, 30]. When using FDOPA, an increased uptake in the striatum has to be considered, as the molecule is a precursor of dopamine, which may cause problems in the delineation of gliomas affecting the striatum [31, 32]. A recent study comparing

MET and FACBC observed higher tumor-to-brain ratios and improved tumor delineation with FACBC which may be advantageous [33].

The following chapters provide an overview of the significance of amino acid PET in various diagnostic challenges. The clinical data are based exclusively on the PET tracers MET, FET and FDOPA, for which extensive clinical experience is available.

Differential diagnosis of brain tumors

The differential diagnosis of space-occupying or diffuse lesions in the brain includes primary and secondary (metastatic) brain tumors, haemorrhage, infarction, infections (e.g., abscess), virus encephalitis, and inflammatory pathologies such as multiple sclerosis. The history and clinical symptoms of the patient as well as the morphological pattern of the lesion on MRI already provide important information on the cause of the disease. An increased amino acid accumulation has a high predictive value for a brain tumor [34-36], however, it must be taken into account that increased amino acid accumulation may also occur in non-neoplastic processes mentioned above, although this is much less common [37, 35, 38-41]. Furthermore, low amino acid uptake does not exclude a brain tumor because approximately one-third of low-grade glioma exhibit only low amino acid uptake [42, 18, 43]. Nevertheless, a meta-analysis on the diagnostic value of MET PET yielded a pooled sensitivity and specificity of 91 % and 86 % (n = 416) for differential diagnosis of unknown brain lesions while the performance of FDG PET was only moderate with a sensitivity and specificity of 71 % and 77 %, respectively (n = 857) [44]. Concerning FET PET, a meta-analysis of 13 studies including a total of 462 patients yielded a pooled sensitivity of 82% and specificity of 76% for the diagnosis of primary brain tumors [36]. A more recent study on FET PET including 174 patients reported on a high specificity (92%) but a lower sensitivity (57%) for the differentiation of neoplastic tissue from non-neoplastic tissue [34]. Nevertheless, in the latter study a maximum tumor/brain ratio of more than 2.5 yielded a very high positive predictive value for neoplastic tissue (98%). Thus, amino acid PET may be helpful in the assessment of equivocal brain lesions and this investigation is frequently used for this purpose in centres where amino acid PET is available.

Imaging of tumor spread

A number of biopsy-controlled studies have demonstrated that amino acid PET is able to detect the metabolically active mass of gliomas more reliably than conventional MRI [45-48]. Tumor extent of gliomas is often greater than contrast enhancement in MRI but smaller than signal abnormalities in

T2-weighted MRI which may be helpful in planning radiotherapy (Fig. 1) [49-51]. Furthermore, amino acid PET is under investigation to determine the extent of the residual tumor after resection [52-54]. First comparisons of amino acid PET with advanced MR methods, e.g., perfusion-weighted MRI (PWI) showed considerably larger tumor volumes in amino acid PET than in maps of the cerebral blood volume, a poor spatial congruence of both parameters and considerable differences in the locations of local hot spots [55, 31, 56]. Another study observed larger tumor volumes of cerebral gliomas using MR spectroscopic imaging (MRSI) based on elevated Cho/NAA compared with increased FET uptake and considerable variability in the overlap of these volumes [57]. Thus, amino acid uptake and increased CBV or Cho/NAA ratio appear to represent different properties of glioma metabolism and the clinical relevance of these findings needs to be explored in future studies. Amino acid PET is also used for the identification of the metabolically most active areas of the tumor for biopsy guidance since representative tissue samples are vitally important for histological tumor diagnosis (Fig 1). Compared with FDG PET, amino acid PET using MET and FET have been shown to be considerably more sensitive than FDG PET for biopsy guidance [6, 58, 59]. Using FET PET, a sensitivity of 72 – 79 % has been reported when identifying a local maximum for biopsy guidance in gliomas [6, 34]. Furthermore, kinetic analyses of FET uptake in gliomas appear to be helpful in the identification of areas of malignant transformation and poor prognosis [60-64, 19].

In our experience, the estimation of tumor extent and the identification of metabolically active changes for the biopsy guidance are important clinical issues, for which amino acid PET is frequently used in clinical practice.

Tumor grading and prognosis

The validity of PET studies using radiolabelled amino acid on the grading of cerebral gliomas is limited by the fact that most of them are based on the previous WHO classification of 2007[65] which is no longer valid. The actual classification includes molecular markers such as the isocitrate dehydrogenase (IDH) mutational status and presence or absence of a 1p/19q co-deletion [3]. Based on the previous WHO classification, the accuracy of static amino acid PET to differentiate between LGG and HGG is moderate and ranges between 70 - 80% [66, 34]. These results are similar to those of FDG PET [67] and perfusion-weighted MRI [68]. The evaluation of FET kinetics may achieve an accuracy of up to 90% [27, 63, 62, 69, 28, 29, 70] but relatively high uptake of amino acids in oligodendrogliomas with good prognosis limits the utility of amino acid PET for brain tumor grading on individual basis [71, 28]. Recent studies have focussed on the relationship of amino acid uptake with molecular markers [72-76]. Significant correlations were observed which, however, are not sufficient to allow a non-invasive

prediction of the molecular parameters derived by PET imaging parameters alone. One study, however, identified prognostically relevant information of FET PET beyond molecular markers [73]. Another approach is to measure uptake heterogeneity of amino acids using textural features analyses of tracer distribution which shows potential to improve tumor grading and prognostication [77].

The prognostic value of amino acid uptake ratios is controversial but some studies have reported that the pretherapeutic "biological tumor volume" (BTV) in amino acid PET is an independent prognostic factor[78-80]. Furthermore, amino acid PET appears to be helpful to predict survival in the subgroup of patients with LGG [42, 81, 18]. Especially kinetic analyses of FET uptake in LGG may be helpful to identify areas of malignant transformation and poor prognosis [60, 43, 64, 61, 19]

In summary, amino acid PET can assist in the non-invasive grading and prognostication of gliomas, but the method is currently of lower importance in the clinical decision-making process in this area.

The diagnosis of tumor recurrence or progression

The differentiation of early tumor progression and pseudoprogression predominantly within the first 12 weeks after chemoradiation of HGG with temozolomide [82] and between recurrent tumor and radionecrosis upwards of 6 months after treatment is difficult with standard MRI, because pathological contrast enhancement is equivocal [83]. Amino acid PET, especially FET PET has been shown to differentiate progressive gliomas from pseudoprogression with high accuracy (Fig. 2) [84, 85]. Concerning the differentiation of recurrent tumor versus radionecrosis or other treatment related changes, several studies have reported an accuracy of more than 90 % for FET or FDOPA PET [15, 86, 87]. For MET PET, a recent meta-analyses including 891 patients reported on a pooled sensitivity and specificity of 88 % and 85 % in the differential diagnosis of glioma recurrence [88].

Similar results have been reported for the differentiation of local recurrent brain metastasis from radiation-induced changes. In this differential diagnosis MET PET achieved a sensitivity of 90% and a specificity of 75% [89], FET PET an accuracy of about 90 % [90, 91] AND FDOPA PET an accuracy of 76 – 90 % [92, 93]. In the latter study, FDOPA PET performed better than perfusion-weighted MRI. Furthermore, a pilot study demonstrated that FET PET is helpful to identify pseudoprogression after immunotherapy using checkpoint inhibitors in patients with melanoma metastases [94].

In summary, the diagnosis of tumor recurrence in gliomas and brain metastases is a major problem in the management of glioma and brain metastasis, and in our experience, this is the most common indication for the use of the amino acid PET.

Treatment monitoring

The assessment of radiological response of gliomas in conventional MRI is limited by the difficulty in distinguishing vital tumor tissue and unspecific treatment effects and amino acid PET has been used successfully for this purpose (Fig. 3) [95]. Glioblastoma patients with a decrease of FET uptake of more than 10% after postoperative radiochemotherapy had a significantly longer disease-free survival and overall survival than patients with stable or increasing tracer uptake [96, 79]. A reliable monitoring of temozolomide chemotherapy could also be demonstrated with MET in patients with recurrent HGG [97, 98] and also in some experimental therapeutic approaches such as radioimmunotherapy or convection-enhanced delivery of paclitaxel [99, 100]. Furthermore, it has been shown that amino acid PET using FET and FDOPA is useful to assess treatment failure of antiangiogenic treatment with bevacizumab earlier than MRI based on RANO criteria, to overcome the problem of pseudoresponse in MRI [101-103]. In summary, amino acid PET appears to be a sensitive marker of treatment response which is a frequent indication for the use of this method.

Conclusions

Amino acid PET is a valuable diagnostic tool in addition to MRI in the assessment of patients with brain tumors and brain metastases. At primary diagnosis, amino acid PET helps in equivocal situations, in defining an optimal biopsy and in determining the extent of gliomas. The most frequent indication of amino acid PET is to exclude pseudoprogression or radionecrosis in gliomas and brain tumors. Furthermore, it helps to detect treatment response at an early stage and to overcome the problem of pseudoresponse during antiangiogenic therapy. Amino acid PET appears to be attractive to clinicians because the method is robust, image interpretation is simple and the metabolically active brain tumor tissue is visualized with a high tumor-to-background contrast. These features suggest that the method will continue to expand in clinical routine.

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Conflicts of interest

Karl-Josef Langen has received honoraria from company ABX-CRO, Dresden, Germany, as consultant for blinded image evaluation in a clinical trial.

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Figures

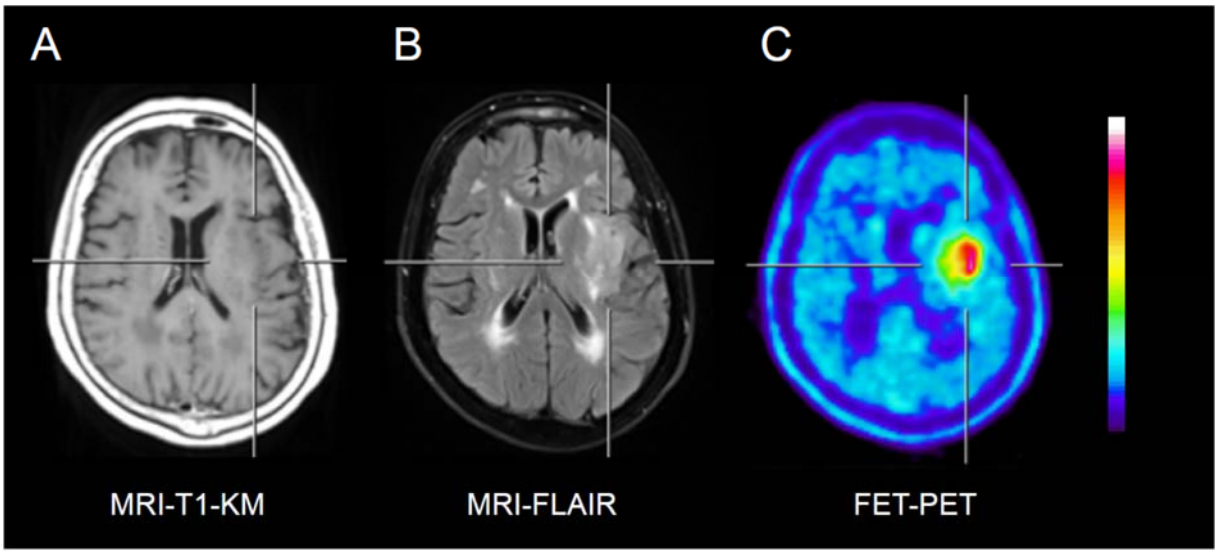

Figure 1: Patient with an anaplastic astrocytoma WHO Grade III. The true extent of the tumor and the metabollicaly most active tumor parts for biopsy guidance are difficult to identify in the contrast-enhanced T1-weighted (A) and in T2-weighted MRI (B) but clearly depicted in FET- PET (C).
Institute of Neuroscience and Medicine, Forschungszentrum Jülich, Germany.

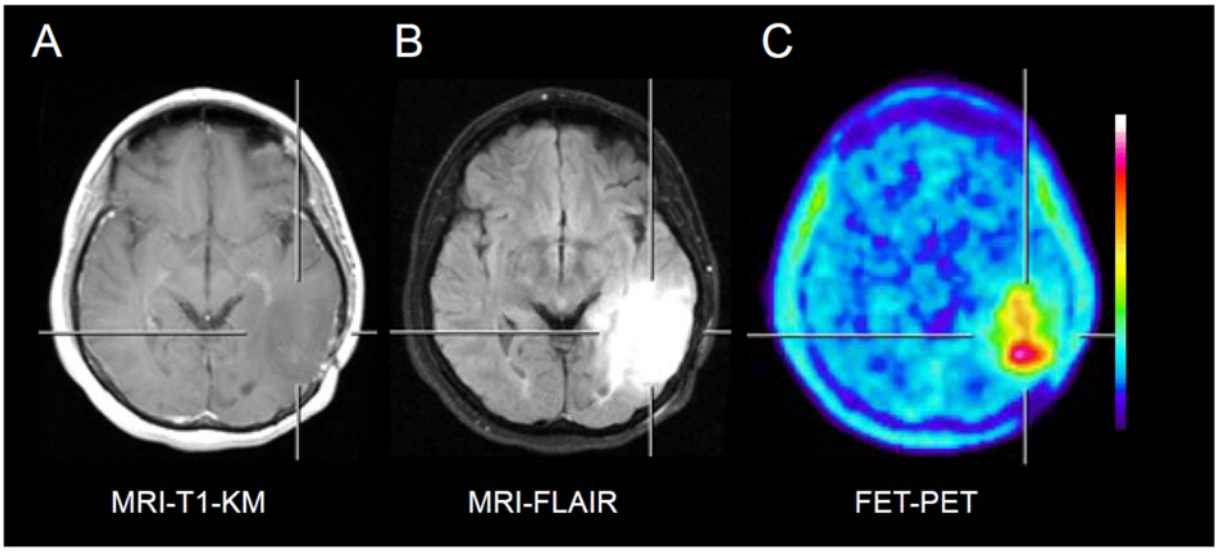

Figure 2: Patient with suspicion of tumor recurrence of an anaplastic astrocytoma WHO Grade III after resection and radiochemotherapy. Contrast-enhanced T1-weighted MRI (A) shows no clear contrast enhancement and the FLAIR (B) large area of signal abnormality which is difficult to differentiate from treatment related changes. In contrast, FET-PET (C) clearly depicts recurrent tumor tissue. Institute of Neuroscience and Medicine, Forschungszentrum Jülich, Germany.

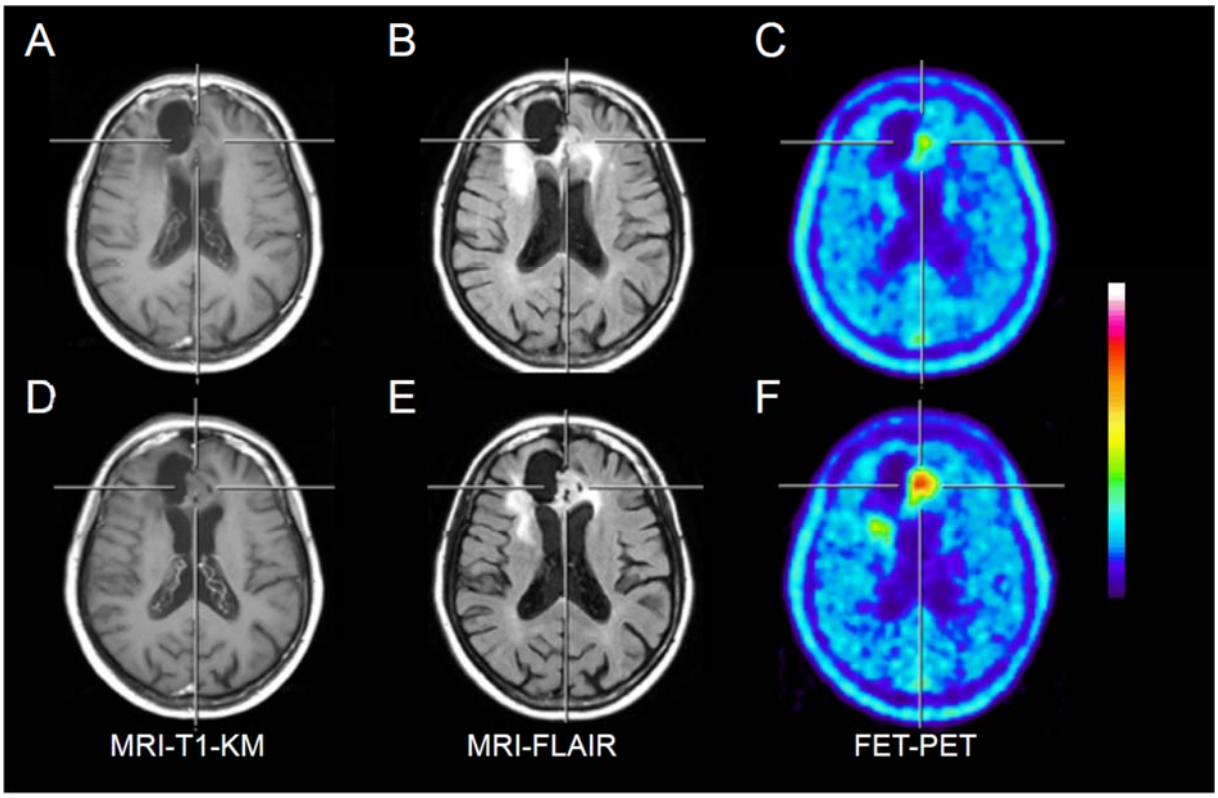

Figure 3: Patient with an oligodendroglioma WHO grade II after surgery and repeated chemotherapy with temozolomide (upper row). One year later (lower row) contrast enhanced T1-weighted MRI (D) shows no contrast enhancement and the FLAIR image (E) minor changes which are difficult to differentiate from treatment-related changes. FET-PET (F) findings are consistent with recurrent tumor. Institute of Neuroscience and Medicine, Forschungszentrum Jülich, Germany.