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EXPERT REVIEW

Amino acid PET and MR perfusion imaging in brain tumours

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Abstract
Purpose Despite the excellent capacity of the conventional MRI to image brain tumours, problems remain in answering a number of critical diagnostic questions. To overcome these diagnostic shortcomings, PET using radiolabeled amino acids and perfusion-weighted imaging (PWI) are currently under clinical evaluation. The role of amino acid PET and PWI in different diagnostic challenges in brain tumours is controversial.
Methods Based on the literature and experience of our centres in correlative imaging with PWI and PET using *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine or 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine, the current role and shortcomings of amino acid PET and PWI in different diagnostic challenges in brain tumours are reviewed. Literature searches were performed on PubMed, and additional literature was retrieved from the reference lists of identified articles. In particular, all studies in which amino acid PET was directly compared with PWI were included.
Results PWI is more readily available, but requires substantial expertise and is more sensitive to artifacts than amino acid PET. At initial diagnosis, PWI and amino acid PET can help to define a site for biopsy but amino acid PET appears to be more powerful to define the tumor extent. Both methods are helpful to differentiate progression or recurrence from unspecific posttherapeutic changes. Assessment of therapeutic efficacy can be achieved especially with amino acid PET, while the data with PWI are sparse.
Conclusion Both PWI and amino acid PET add valuable diagnostic information to the conventional MRI in the assessment of patients with brain tumours, but further studies are necessary to explore the complementary nature of these two methods.

Keywords Amino acid PET · ^{18}F-FET · ^{18}F-FDOPA · Perfusion-weighted MRI · Relative cerebral blood volume (rCBV) · Brain tumours

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Introduction

Cerebral gliomas arising from different brain tissue types are the most prevalent primary brain tumours with an incidence of 5–6 in 100,000, apart from meningiomas [1]. Metastases in the brain originating from various peripheral tumours are even more frequent tumours with an incidence of 8−14/100.000 [2]. Histologically, gliomas are subdivided into astrocytomas, oligodendrogliomas, ependymal

tumours, and tumours of the choroids plexus. The classification of gliomas by the World Health Organization (WHO) has been updated recently, combining now molecular parameters, such as IDH mutation and 1p/19q co-deletion with histology [3].

During the diagnostic process of brain lesions, it may be crucial to differentiate brain tumours from benign lesions, such as demyelination, hematoma, abscesses, and infarctions which may appear similar on MRI. MRI is at present the standard neuroimaging modality [4] owing to its excellent soft-tissue contrast and spatial resolution. The standard MRI for diagnostic imaging in brain tumours is based on pre- and postcontrast T1-weighted images and T2-weighted images, including fluid-attenuated inversion recovery (FLAIR) images. However, there are limitations in the standard MRI with regard to differentiating tumour tissue from nonspecific changes, which is especially relevant after therapy.

With positron emission tomography (PET), different radioactively labelled tracers are injected to target various metabolic and molecular pathways. This may add important information especially in clinically challenging situations to improve diagnosis and therapy planning. Over the past decades, PET with radiolabelled amino acids has become a highly relevant diagnostic tool. Recent joint recommendations of the Response Assessment in Neuro-Oncology working group (RANO) and the European Association for Neuro-Oncology (EANO) consider amino acid PET as clinically helpful and suggest its use for managing patients with brain tumours additionally to MRI [5]. Meanwhile, advanced MRI methods, such as perfusion-weighted imaging (PWI), are being evaluated in the clinical setting and can provide complementary pathophysiological information to the standard MRI. Based on the experience of our centres in correlative imaging with PWI and PET using *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET) or 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine (FDOPA) in more than 500 brain tumour patients, this review focuses on the clinical impact of amino acid PET and PWI in adult patients during the workup of brain tumours. Literature searches were performed on PubMed using the search terms "brain tumours", "gliomas" "positron emission tomography", "magnetic resonance imaging", "Amino acids", "methionine", "FET, "FDOPA", "perfusion imaging", "PET", and "rCBV". Additional literature was retrieved from the reference lists of identified articles. Only papers in the English language published until the end of 2016 were selected for review. The references cited in the review were selected by the authors with respect to the scientific quality, with preference to more recent publications, and relevance of the papers in the field according to the personal experience of the authors. In particular, all studies were included in which amino acid PET was directly compared with PWI. These studies are summarized in Table 1. The performance of amino acid PET and PWI is discussed with respect to differential diagnosis of brain lesions, tumor delineation and biopsy guidance as well as therapy monitoring and discrimination between tumour progression or recurrence and treatment-related changes.

PET using radiolabelled amino acids

Amino acids present several advantages over ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG) and are now regarded as the tracers of choice for PET imaging of brain tumours [6]. The first radiopharmaceutical of this class to be used clinically was ^{11}C-methyl-L-methionine (MET), an isotopically labelled methionine made from $^{11}CH_3$-I alkylation of homocysteine [7]. Data on the clinical usefulness of MET in brain tumours have been collected for more than 30 years; however, due to the short half-life of ^{11}C (20 min), which limits the use of MET to centres equipped with an onsite cyclotron, the interest around fluorinated compounds has grown significantly in the recent past. The two most popular amino acid PET radiopharmaceuticals labelled with ^{18}F (109.8 min half-life) are *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET) and 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine (FDOPA). FET is a tyrosine derivative, which is synthesized with high yield by a two-step fluoroethylation of tyrosine [8]. FDOPA is an analogue of the non-proteinogenic amino acid L-DOPA, which has historically been synthesized via electrophilic substitution. However, because of isomeric impurities, low specific activity, low radiochemical yield, and precursor toxicity, this process has been later abandoned for nucleophilic substitution [9, 10]. The molecular structures of the abovementioned synthetic amino acids are shown in Fig. 1.

With the exception of MET, these radiolabelled amino acids are not incorporated into proteins [11]; nevertheless, their uptake mechanisms are highly efficient, leading to very favourable tumour-to-background ratios. The uptake of radiolabelled amino acids is based on the expression of the Na^+-independent large neutral amino acid transporters on the cell surface of tumour cells, namely, LAT1 and LAT2. This mechanism is independent from blood–brain barrier permeability; therefore, amino acid probes are able to depict non contrast-enhancing brain tumour regions, which are a clear advantage over other PET tracers, such as 3′-deoxy-3′-[^{18}F]fluorothymidine (FLT) [12] and ^{18}F-Fluorocholine (FCH) [13]. MET and FDOPA uptakes are thought to be largely due to LAT1 [14, 15], while FET is transported by both LAT1 and LAT2 [16]. A recent study showed that the retention of FET into cells is due to an asymmetric intra- and extracellular recognition of LAT1, with consequent poor efflux from the cell back to the extracellular space [17].

Table 1 Studies comparing amino acid PET and PWI

First author and year	Patient group	PET tracer	No of patients	Results
Berntsson 2013 [83]	Untreated low grade glioma	MET	24	Spatial overlap of MET hotspots and PWI max but no correlation of rCBV and MET uptake
Cicone 2015 [23]	Recurrent/progressive glioma	FDOPA	44	Higher tumor to brain contrast in FDOPA PET and larger tumor volumes than in rCBV maps, poor spatial congruence of FDOPA and rCBV
Cicone 2015 [147]	Recurrent metastasis versus radionecrosis	FDOPA	42	Better performance of FDOPA PET than rCBV in differentiating recurrent metastasis from radionecrosis
Dandois 2010 [140]	Recurrent glioma versus radionecrosis	MET	28	Equal performance of rCBV and MET PET in differentiation of tumor recurrence versus radionecrosis
D'souza 2014 [133]	Recurrent glioma versus radionecrosis	MET	29	rCBV and MET uptake equally useful to differentiate recurrence versus radionecrosis
Filss 2014 [79]	Primary and recurrent gliomas	FET	56	Higher tumor to brain contrast in FET PET and larger tumor volumes than in rCBV maps, poor spatial congruence of FET and rCBV
Henriksen 2016 [80]	Pretreated gliomas	FET	41	Higher tumor to brain contrast in FET PET and larger tumor volumes than in rCBV maps, poor spatial congruence of FET and rCBV
Kim 2010 [141]	Recurrent glioma versus radionecrosis	MET	10	Equal performance of rCBV and MET PET in differentiation of tumor recurrence versus radionecrosis
Rossi Espagnet 2016 [118]	Pretreated low grade gliomas	FDOPA	12	No correlation of rCBV and FDOPA uptake
Sadeghi 2006 [78]	Primary and recurrent gliomas	MET	18	rCBV and MET uptake strongly correlated
Sadeghi 2007 [77]	Primary and recurrent gliomas	MET	14	rCBV and MET equivalent in the assessment of tumor infiltration
Tietze 2015 [82]	Untreated gliomas	MET	13	rCBV helpful in HGG but not useful in LGG in contrast to MET PET
Göttler 2017 [81]	Untreated gliomas	FET	30	Moderate overlap of tumor volumes in FET PET and rCBV maps

No relevant differences between available radiolabelled amino acids have been shown in terms of tumor to brain contrast [18–21]. However, some differences exist with regard to tracer biodistribution in the brain and the time-activity curves of tracer uptake. FDOPA is a substrate for the enzyme aromatic amino acid decarboxylase in dopaminergic neurons [22]; this is responsible for FDOPA prominent uptake by the basal ganglia which might interfere with tumour delineation [23]. In addition, available data suggest that FET kinetics may add additional biological information, which may be helpful for glioma grading [24, 25], the differentiation of both glioma and brain metastasis recurrence from radiation-induced changes [26–28] or the prognostication of untreated gliomas [29, 30]. Although amino acid PET shows high accuracy for the detection of brain tumours [31], tracer uptake in non-neoplastic brain lesions has to be taken into account. Thus, unspecific amino acid uptake in the brain has been reported in multiple sclerosis and other inflammatory lesions, vascular malformations, ischemic lesions, hematomas, etc [32–36]. Moreover, amino acid PET may be negative in a significant proportion of low-grade gliomas [37, 38].

MRI and MR perfusion imaging

MRI is the method of choice for anatomical imaging in patients suspicious for brain tumours as well as during the course of therapy in brain tumour patients due to its excellent soft-tissue characterization, high resolution, and easy multiplanar reconstruction. The standard MRI includes pre- and postcontrast T1-weighted sequences as well as T2-weighted sequences possibly with FLAIR sequences [4, 39–41]. MRI has a high sensitivity to detect brain lesions due to its excellent soft-tissue contrast, but hyperintense signal in T2-weighted images may also be caused by peritumoural oedema. In tumours with diffuse cell infiltration, a clear demarcation of tumour from peritumoural changes may not be possible. In contrast, enhancement in T1-weighted images indicates a disruption of the blood–brain barrier (BBB) and is typical but not specific for malignant tumours. Particularly, treatment-related changes after surgery, radio-, or chemotherapy of brain tumours may also cause contrast enhancement and be challenging to differentiate from tumour recurrence [4, 42, 43].

PWI is an advanced MRI method which provides information on brain hemodynamics in addition to the

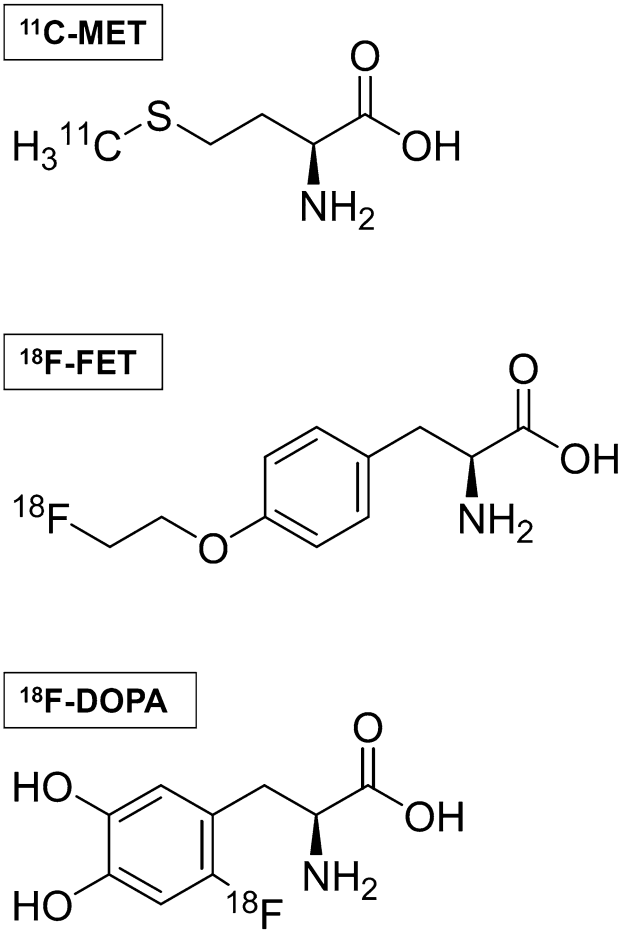

Fig. 1 Molecular structure of ^{11}C-methyl-L-methionine (MET), *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET), and 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine (FDOPA)

conventional MRI [44, 45]. Important parameters which can be determined by PWI are the relative cerebral blood volume (rCBV), relative cerebral blood flow (rCBF), and the relative mean transit time (MTT) [45–47]. PWI is usually performed with paramagnetic gadolinium as an exogenous contrast agent which causes an apparent signal increase in T1-weighted images and a signal loss in T2 or T2*-weighted images. Dynamic susceptibility contrast MRI (DSC) based on T2*weighted imaging using a 2D echo planar imaging (EPI) is the most widely used method for PWI [44, 45]. Blood–brain barrier leakage may be a source of error with DSC which can be reduced by a pre-bolus of contrast agent prior to acquisition as well as post-processing techniques for leakage correction [45, 48]. Another method, dynamic contrast-enhanced MRI (DCE) is also based on a short bolus of contrast agent and measures changes in T1-weighted images over time. DCE is less prone to artifacts, but signal changes are smaller compared with DSC which results in rather low signal-to-noise ratio in the calculated parametric maps. Therefore, DCE is infrequently used in clinical practice and not included in the standard software of most scanners [47]. Recently, however, multi-echo sequences have been proposed to correct for leakage effect for DSC [49] and to extract T_1 dynamics [50]. By combining DSC and DCE in a GRE and SE sequence (GESE) [51], further information about vasculature can be obtained [52]. Such parametric images can also be used to track therapy response in brain tumours to antiangiogenic agents [53]. Moreover, CBF can be measured by arterial spin labeling (ASL) using magnetically labelled water as endogenous tracer which avoids an exogenous contrast agent but the long acquisition time is a disadvantage [45].

Amino acid PET and MR perfusion imaging for tumour differential diagnosis

If a brain lesion of unclear origin is detected in a patient, it is of paramount clinical importance to differentiate between a neoplastic or non-neoplastic process. MRI with gadolinium-based contrast agents provides a number of imaging features, which may allow a differential diagnosis in a considerable fraction of the lesions. The imaging findings of brain tumours may include diffusely delineated tumour margins, perifocal oedema, central necrosis, presence of cystic formations, and a ring-enhancing pattern of contrast enhancement. The reliability of these signs, however, is limited. PWI can be helpful in special situations, for example, to differentiate brain abscesses from malignant gliomas or brain metastases [54].

PET using radiolabelled amino acids generally shows higher uptake in neoplastic lesions than in non-neoplastic lesions and increased amino acid uptake in benign lesions is rare. Nevertheless, false-positive uptake of MET, FET and FDOPA has been reported in infectious lesions (e.g., in brain abscesses), demyelinating lesions, ischemic stroke, in cerebral haemorrhages, and also in patients with status epilepticus or seizure clusters [34, 55]. Regarding differential diagnosis, a meta-analysis evaluated 462 patients with newly diagnosed brain lesions suspected of being brain tumours and revealed a pooled sensitivity of 82% and specificity of 76% for the correct diagnosis of primary brain tumours [56] based on a threshold of the maximum tumour/brain ratio of 2.1. A subsequent study evaluated 174 patients with newly diagnosed brain lesions and reported a high specificity (92%), but a lower sensitivity (57%) for the differentiation of neoplastic from non-neoplastic tissue [35]. Nevertheless, in that study, a maximum tumour/brain ratio of 2.5 or more yielded a very high positive predictive value for neoplastic tissue of 98%. Comparative studies between amino acid PET and PWI in this field are not yet available in the literature.

In summary, imaging findings from both the conventional MRI and PWI as well as amino acid PET may add

valuable additional information for the characterization of equivocal brain lesions, but they lack sufficient diagnostic accuracy. Therefore, a histological evaluation of these suspicious brain lesions by biopsy or resection is frequently indispensable.

Amino acid PET and MR perfusion imaging for imaging of tumour extent and biopsy guidance

The diagnostic performance of the conventional MRI to depict the true extent of cerebral gliomas and to detect the most aggressive areas in inhomogeneous gliomas is limited and especially difficult in gliomas showing no contrast enhancement. Representative tissue samples of brain tumours are vitally important for the correct histological tumour diagnosis and grading, evaluation of molecular markers (e.g., IDH mutation), prognostication, and treatment decisions. Particularly, in infiltrating brain tumours with enhancing and non-enhancing tumour portions, the correct delineation of tumour extent and the identification of the most malignant parts can be challenging and may result in under-diagnosis.

For PET, a number of studies have explored the spatial correlation of histopathological findings with amino acid uptake and provided evidence that the solid tumour mass of gliomas typically shows increased amino acid uptake and detects tumour extent more reliably than standard MRI [57–62] (Fig. 2). The improved delineation of tumor extent is one of the most important advances in brain tumor diagnostics provided by amino acid PET, but it has to be considered that a fraction of approx. 5% of all gliomas, especially low-grade gliomas, do not accumulate radiolabeled amino acids [35]. Nevertheless, amino acid PET is clearly superior to the standard MRI and the property of amino acid PET to detect tumour extent has been used in many studies for treatment planning, especially in tumor resection and radiation therapy [63–73]. In contrast, only a few studies have investigated the diagnostic value of PWI for the detection of brain tumour extent [74, 75]. Those studies observed elevated rCBV beyond the contrast-enhancing volume indicating that tumour infiltration might also be detected by PWI. A biopsy-controlled study reported that rCBV regionally correlates with both cell and microvessel density within gliomas [76]. Another biopsy-controlled study demonstrated that rCBV correlated with cell proliferation in high-grade gliomas but a correlation of rCBV with tumour cell density could not be confirmed [74]. These studies suggest that rCBV mapping allows only very limited conclusions with regard to tumor extension. While some earlier studies comparing amino acid uptake and rCBV observed similarities between MET uptake and rCBV abnormalities in gliomas [77, 78], more recent publications reported on considerably larger tumour volumes in amino acid PET than in rCBV maps and a poor spatial overlap [23, 79–82] (Figs. 3, 4; Table 1). Furthermore, rCBV mapping exhibited a lower lesion-to-brain contrast and a highly variable background noise as compared with amino acid PET [23, 79]. Another hybrid PET/MRI study reported that artifacts due to susceptibility differences between bone and air, iron accumulations, and blood degradation products hampered interpretation of the rCBV signal in the tumour area in 56% of the patients [80]. Thus, amino acid PET appears to be superior to rCBV mapping for the detection of the extent of cerebral gliomas and interpretation of rCBV maps appears to be more challenging than with amino acid PET.

Regarding biopsy guidance, parametric rCBV maps have been used to target the most malignant tumour parts, since the rCBV may indicate tumour parts with neovascularization. Some studies directly comparing local hot spots in amino acid PET and rCBV maps in gliomas reported on a spatial colocalization of local maxima [77, 83], but other studies observed considerable spatial

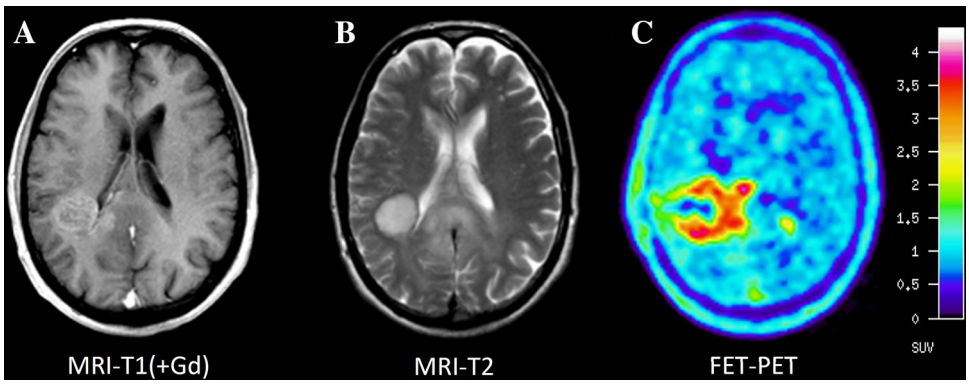

Fig. 2 Comparison of MRI and FET PET of patient with an anaplastic astrocytoma WHO grade III. Contrast-enhanced T1-weighted MRI (**A**) shows pathological contrast enhancement in the vicinity of the posterior horn of the right ventricle and corresponding signal abnormalities in the T2-weighted image (**B**). FET PET (**C**) detects metabolically active tumor tissue extending beyond the abnormalities in MRI

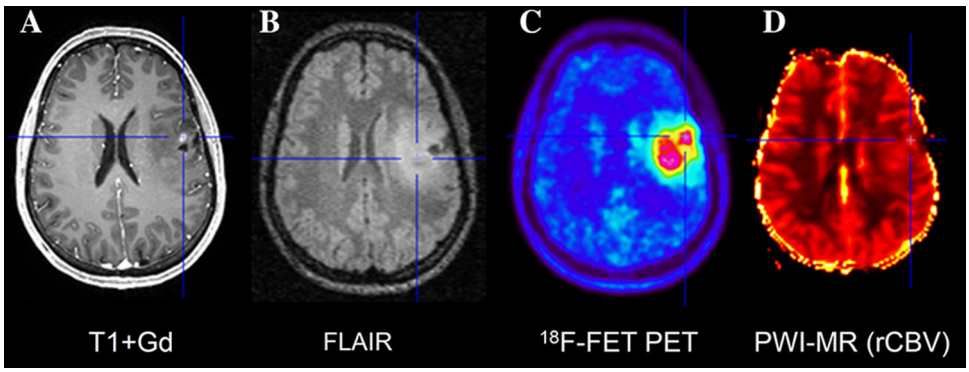

Fig. 3 Hybrid PET/MRI of patient with an astrocytoma WHO grade II. Contrast-enhanced T1-weighted MR imaging (**A**) shows a small area with contrast enhancement in the left frontal lobe while FET PET (**C**) detects a large tumor extending within the area of signal abnormality in the FLAIR image (**B**). Tumor depiction in rCBV map (**D**) is difficult because of a poor tumor to brain contrast

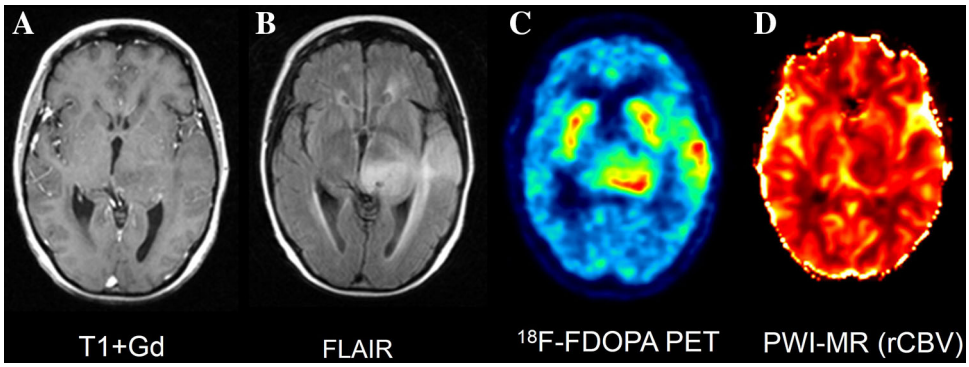

Fig. 4 Comparison between MRI and ^{18}F-DOPA PET of a patient with an astrocytoma. A non-enhancing (**A**), FLAIR positive (**B**) left temporo-thalamic lesion is seen, corresponding to ^{18}F-DOPA uptake (**C**) above the physiological radioactivity of the basal ganglia. In contrast, rCBV map (**D**) fails to show increased tumor perfusion. An anaplastic transformation was observed 3 months later, characterized by contrast enhancement and increased rCBV (images not shown)

distances of the local maxima in both methods [23, 79] (Table 1; Figs. 5, 6). It remains unclear whether the spatial position of the local maxima of amino acid uptake or rCBV in gliomas correspond to the most aggressive part of the tumour and further comparative studies are needed to investigate this aspect. Amino acid has been shown to be a very sensitive method to identify metabolic hot spots in gliomas for biopsy guidance [84–86]. In low-grade gliomas, a sensitivity of 72–79% has been reported for FET PET to identify a hot spot for biopsy guidance [35, 84]. Furthermore, the evaluation of kinetic parameters such as time-to-peak values or the curve pattern of FET uptake derived from dynamic PET scans in gliomas appears to be helpful to identify areas of malignant progression and unfavourable prognosis [29, 30, 37, 87–89]. These data highlight the potential of amino acid PET for the identification of metabolically active areas in brain tumours to target biopsies.

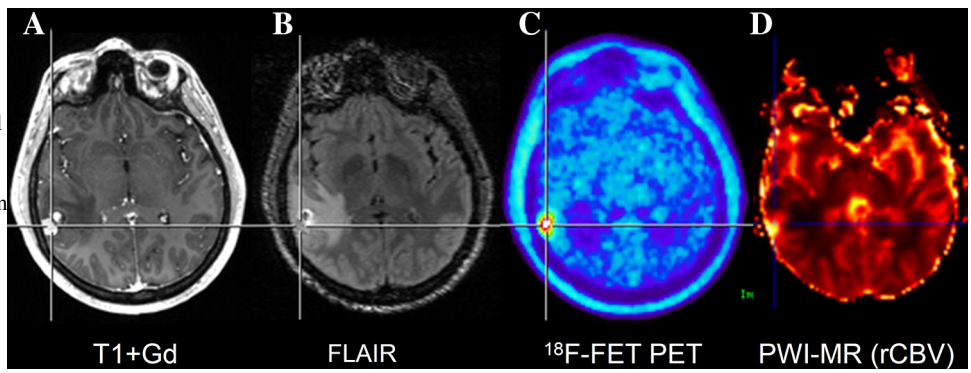

Fig. 5 Hybrid PET/MRI of patient with a glioblastoma WHO grade IV. Contrast-enhanced T1-weighted MR imaging (**A**) shows a small area with contrast enhancement in right parietal lobe and corresponding signal abnormality in the FLAIR image (**B**) which shows focal tracer uptake in FET PET (**C**) and correspondingly increased rCBV (**D**)

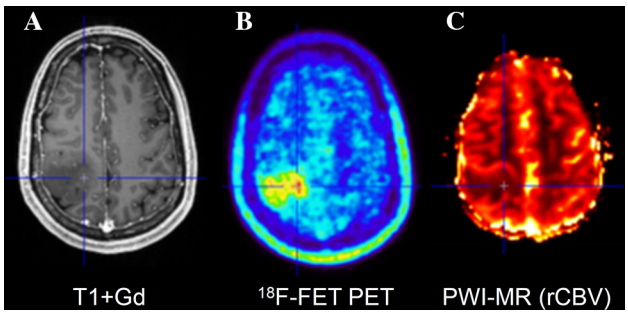

Fig. 6 Hybrid PET/MRI of a patient with an oligoastrocytoma WHO grade III. Contrast-enhanced T1-weighted MR imaging (**A**) shows a large mass in the right parietal lobe showing no contrast enhancement. FET PET (**B**) detects a local maximum in the paramedian part of the tumour which is not obvious in the rCBV map (**C**)

In summary, both amino acid PET and PWI may be helpful for biopsy guidance, but the more reliable method to delineate the glioma extent seems to be amino acid PET.

Amino acid PET and MR perfusion imaging for tumour grading and prognosis

The evaluation of brain tumor histology is the method of choice for tumour grading and decisive for treatment planning. Tissue samples, however, are sometimes not representative of the most aggressive tumor parts and varying interpretation by different neuropathologists may cause uncertainties. Therefore, an agreement of histopathology with non-invasive imaging parameters may support the clinical decision-making.

Most studies using amino acid PET in gliomas come to the conclusion that amino acid uptake does not allow a reliable prediction of tumour grade owing to highly variable amino acid uptake in gliomas of different WHO grades [90]. Glioma grading is further affected by high amino acid uptake in oligodendrogliomas despite the better prognosis of these tumours in comparison with astrocytomas of the same grade [91–94]. Therefore, static amino acid PET achieves only an accuracy of 70–80% for predicting a high-grade gliomas [31, 35, 93, 95]. Analysis of FET kinetics may slightly improve the discrimination of high-grade and low-grade glioma in both primary tumours and recurrent tumours [24, 25, 29, 88, 93, 96, 97].

The significance of PWI for tumour grading has been investigated in many studies with variable results [54, 98–101]. One study reported no difference between PWI and contrast-enhanced MRI [102]. Especially, low-grade oligodendroglioma may exhibit increased rCBV despite an excellent prognosis similar to the findings with amino acid PET [103]. A prospective study with 129 patients achieved a high accuracy in tumour grading with the conventional MRI based on the parameters contrast enhancement and necrosis (sensitivity 96%; specificity 70%) and the results did not improve when including PWI [104]. In contrast, a recent meta-analysis came to the conclusion that differentiation of low- and high-grade gliomas was improved by PWI compared with the conventional MRI [105].

While the prognostic significance of amino acid uptake ratios in gliomas remains questionable, recent studies indicate that the "biological tumour volume" (BTV) as determined by amino acid PET represents an independent prognostic factor [106–108]. In addition, amino acid PET seems to be useful to predict survival in patients with low-grade gliomas [38, 109–113]. In patients with newly diagnosed low-grade glioma, FET PET together with anatomical MR has been reported to be a significant factor to predict outcome [38]. In low-grade gliomas, particularly, FET kinetics may be useful to locate regions of malignant transformation and poor prognosis [30, 37, 87, 89, 114]. Using PWI, some studies have reported a relationship between rCBV in gliomas and overall survival [115–117]. A first study comparing FDOPA PET and rCBV in a small cohort of low-grade gliomas showed a better correlation of PET parameters with outcome than rCBV [118].

In summary, amino acid PET and PWI can support non-invasive grading and prediction of outcome in gliomas. However, the final diagnosis is based on histology of tumour tissue.

Amino acid PET and MR perfusion imaging for the diagnosis of tumour recurrence/progression

The distinction between tumour recurrence or progression and treatment-related changes represents a major challenge for the conventional MRI, since subacute and late types of treatment-induced injury, namely, pseudoprogression and radionecrosis, are characterized by an increase of contrast enhancement, indistinguishable from tumor progression [119]. Pseudoprogression usually occurs within the first 12 weeks after irradiation in 10–30% of patients with high-grade gliomas treated with concomitant temozolomide [120]. A recent study using FET PET showed an excellent overall accuracy of 96% (sensitivity, 100%; specificity, 91%) in discriminating pseudoprogression from early progression in 22 patients with glioblastoma [26]. Studies assessing pseudoprogression with perfusion-weighted MRI are more numerous though less promising, probably because rCBV is influenced by disruption of the BBB [121–125]. A recent meta-analysis yielded a pooled sensitivity of 89% and a pooled specificity of 80% for DSC perfusion-weighted imaging in this clinical setting [126]. Diagnostic accuracy of DCE perfusion-weighted images has been reported in the same range of values [127].

More data are available on the performances of amino acid PET to differentiate tumor recurrence from treatment-related changes in the later stage of the disease. Earlier experiences with FET showed the superiority of amino acid PET over the standard MRI in this setting [128]. In a large heterogeneous cohort of 124 patients with gliomas of different grades and histologies, Galldiks and coworkers found an accuracy of 93% (sensitivity = 93%, specificity = 100%) in differentiating neoplastic disease from treatment-related changes by combining static and dynamic information from FET scans [129]. In a similar-sized study of 110 patients, performances of FDOPA PET were slightly lower, with an accuracy of 82% (sensitivity = 89.6%, specificity = 72.4%) [130]. The results of these two latter studies, however, are hardly comparable because of the different methods of image analysis and of an unbalanced percentage of recurrent diseases and unspecific changes in the two patient cohorts. Another study using F-DOPA PET in a smaller population of 35 patients showed an overall accuracy of 97% in the same setting [131]. Using MET PET, Terakawa and coworkers studied a heterogeneous sample of 26 gliomas showing both sensitivity and specificity of 75% for discriminating between tumour recurrence and radiation necrosis [132]. In a later study, D'Souza and coworkers found an overall accuracy of 89.6% (sensitivity = 94.7%, specificity = 80%) in 29 patients with high-grade gliomas [133]. The same group has recently extended these results to a larger cohort of 64 tumours from various histologies, particularly emphasizing the higher accuracy of MET over FDG PET in low-grade gliomas (sensitivity = 93.3% specificity = 90%) [134].

The performances of PWI techniques (either DSC or DCE) in correct classification of late treatment-related changes were assessed by several studies, resulting in cumulated sensitivity and specificity of 90 and 88%, respectively [126, 135–138]. Of note, the presence of haemorrhage, image distortion, and susceptibility artifacts limits the applicability of DSC perfusion MR images in a non-negligible number of cases [136, 139]. In some of these non-interpretable cases, however, DCE MRI seems to overcome the limitations of DSC images [139]. Some studies have compared amino acid PET vs PWI and reported on a similar diagnostic power of PWI in this setting, but the number of patients in those studies is relatively small, so that currently, no reliable conclusion can be drawn [133, 140, 141] (Table 1).

Amino acid PET imaging has also proved to be valuable in discriminating between tumour recurrence and radionecrosis in brain metastases. Radionecrosis occurs after a median of 12 months after radiation treatment and its incidence varies depending on the local radiation dose [142, 143]. Using FET PET, the combination of static imaging with dynamic information yielded an overall accuracy ranging between 87 and 93% in two different patient cohorts with a total of 76 [28, 144] and 34 brain metastases, respectively [145]. Encouraging results were also obtained with FDOPA in 83 brain metastases using a qualitative approach for image analysis (sensitivity = 81.3%, specificity = 84.3%) [146] and in another study in 50 brain metastases using a semiquantitative approach for image analysis (sensitivity = 90%, specificity = 92.3%, accuracy = 91.3%) [147]. In addition, this latter paper reports on the only available direct comparison between amino acid PET and PWI in this setting, demonstrating better performances of amino acid PET in classifying indeterminate enlarging brain metastases after radiation treatment (37 lesions available for comparison, 91.9 vs 75.6% overall accuracy for FDOPA and DSC PWI, respectively). Recent data from the same group confirmed the superior performances of F-DOPA PET over MRI including DSC PWI techniques in assessing the evolution over time of predominantly radionecrotic brain metastases after stereotactic radiosurgery [148]. As regards MET, available data suggest moderately lower discriminating power (sensitivity = 79%, specificity = 75%) in 51 secondary lesions [132]. PWI holds promises in the setting of brain metastases as well, albeit the number of available studies and patients included is limited [149–151]. At present, a combined approach for differential diagnosis is to be encouraged, as already put in practice by single specialized centers [152, 153].

In summary, available literature shows that both amino acid PET and perfusion-weighted MRI are useful aids to the differential diagnosis between tumour progression and treatment-related changes in both gliomas and brain metastases; hence, an integrated approach is advised.

Amino acid PET and MR perfusion imaging for treatment monitoring of brain tumours

The early detection of tumour response to therapy is of great importance for the optimization of individual tumor therapy.

In the context of both chemoradiation with temozolomide and temozolomide monotherapy, the reliability of treatment monitoring using MET was shown in a cohort of 15 patients with heterogeneous tumour histologies and prior treatment history [154]. Using FET PET, Piroth et al. demonstrated that an early (7–10 days after treatment completion) >10% reduction of TBRmax from baseline was predictor of disease free survival and overall survival in a homogeneous population of 22 patients with glioblastoma, whereas no such prognostic significance could be found for changes in contrast enhancement [107, 155]. In addition, FET PET demonstrated the ability

Table 2 Contribution of MRI, amino acid PET, and PWI in brain tumour diagnosis

	MRI	PWI	Amino acid PET (MET, FET, FDOPA)
Differential diagnosis	++	–	+
Tumour extent	+	+	++
Biopsy guidance	+	++	++
Grading	++	++	+[a]
Prognosis	+	++	+
Recurrence	+	++	++
Therapy monitoring	+	+	++

It reflects the personal opinion of the authors on the basis of this literature review and their personal experience in the field

++, high diagnostic value; +, limited diagnostic value; –, not helpful

[a] Increased diagnostic value when using dynamic FET PET

to stratify responses to temozolomide several months earlier than MRI in 11 patients with progressive non-enhancing low-grade gliomas [156]. More recently, a multicenter study demonstrated that changes of tumour volume in amino acid PET were superior to MRI for evaluating responses to temozolomide in WHO grade II glioma and to predict progression-free survival [157].

Amino acid PET tracers were also tested in the response evaluation of antiangiogenic treatments. A special problem represents the so-called "pseudoresponse" during antiangiogenic treatment. Here, a fast reduction of contrast enhancement in MRI may hide the underlying growth of the non-enhancing, T2-positive, portion of the tumour. The sensitivity and reliability of the conventional MRI in this setting is limited [4]. In a cohort of 11 patients under bevacizumab treatment, a significant discrepancy between FET uptake and RANO criteria was observed in 4/11 patients suggesting that FET can detect treatment failure earlier than the conventional MRI [158]. Similar findings were subsequently reported in an independent cohort of ten patients treated with bevacizumab [159]. Using FDOPA PET, metabolically active tumour volume measured as early as 2 weeks after therapy initiation, as well as tumour volume changes during therapy, was also found to be strong predictors of survival in a larger cohort of 30 patients under bevacizumab/irinotecan [160]. In that study, there were eight (26%) discordant cases and PET outperformed MRI-based RANO criteria.

A few studies have evaluated the performances of PWI in early treatment assessment. Unfortunately, up to now, no direct comparison with amino acid PET exists. Sawlani and colleagues have retrospectively evaluated 16 patients with glioblastoma undergoing bevacizumab treatment, deriving an index of local perfusion (hyperperfusion volume, HPV) which correlated with time-to-progression [161]. The largest study available included 36 patients with high-grade gliomas who underwent perfusion-weighted sequences in addition to standard MRI before and during bevacizumab treatment [162]. In that study, an improved survival was obtained in patients with low tumour rCBV either before or during treatment. In contrast, a study evaluating the effect of cediranib, a pan-VEGF receptor tyrosine kinase inhibitor, showed that an increase in tumour perfusion was predictive for better outcome [163], according to the "vascular normalization hypothesis" [164].

In summary, amino acid PET shows convincing results concerning sensitive and specific assessment of treatment response at an early stage during chemotherapy or antiangiogenic therapy. In contrast, despite widespread availability, PWI has so far only been investigated to a small extent in this area and further investigations are needed.

Conclusion

In contrast to amino acid PET, most neuro oncological centres have access to PWI which, however, requires a great deal of experience to ensure meaningful assessment are made and therefore is not always used efficiently. Another limitation of PWI is the lack of standardization of the methods used and in data processing. Amino acid PET is as yet not available in every centre, but the method is rapidly spreading not only because of its diagnostic power but also because of its robustness and the fact that interpreting amino acid PET may be easier for clinicians involved in neuro oncology than PWI owing to the higher tumour to background contrast and more homogenous background. The two methods are based on different biochemical-physiological mechanisms but can provide diagnostic information beyond the conventional MRI depending on the clinical question.

At initial diagnosis of space occupying brain lesions, a relatively reliable differential diagnosis can be achieved by the use of the conventional MRI and PWI, and amino acid PET appears necessary in equivocal situations only. In the case of highly suspicious lesions, both methods can help to define a site for biopsy to obtain a meaningful histology.

Amino acid PET, on the other hand, appears to be more powerful to define the tumor extent (Table 2). If, after the primary therapy of the tumour, there is a suspicion of progression or recurrence, both methods are helpful to differentiate these from unspecific posttherapeutic changes. An early and sensitive assessment of therapeutic efficacy can be achieved especially with amino acid PET, while the data with PWI are sparse despite a broad availability. To further improve the diagnostics of brain tumours, it seems necessary to explore the complementary nature of these two methods in further studies. This is not only in the interest of the patients, but also of society, since the treatment costs for this disease are extremely high.

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Compliance with ethical standards

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