

Review

Hybrid PET/MRI in Neuro-oncology: Current Status and Perspectives

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Running title: Hybrid PET/MRI in brain tumors

Short summary: Advanced MRI methods and PET using radiolabeled amino acids provide valuable information in addition to conventional MR imaging for brain tumor diagnostics. The advent of hybrid PET/MRI allowed a convergence of the methods but up to date simultaneous imaging has reached little relevance in clinical neuro-oncology. A key factor for the benefit of PET/MRI in neuro-oncology is a multimodal approach that provides decisive improvements in the diagnostics of brain tumors compared with a single modality. This systematic review focuses on studies that were able to demonstrate the additive value of amino acid PET and advanced MRI in the diagnosis of brain tumors.

Abstract: Advanced MRI methods and PET using radiolabeled amino acids provide valuable information in addition to conventional MR imaging for brain tumor diagnostics. These methods are particularly helpful in challenging situations such as the differentiation of malignant processes from benign lesions, the identification of non-enhancing glioma subregions, the differentiation of tumor progression from treatment-related changes, and the early assessment of response to anticancer therapy. The debate over which of the methods is preferable in which situation is ongoing and has been addressed in numerous studies. Currently, most radiology and nuclear medicine departments perform these examinations independently of each other leading to multiple examinations for the patient. The advent of hybrid PET/MRI allowed a convergence of the methods but to date simultaneous imaging has reached little relevance in clinical neuro-oncology. This is partly due to the limited availability of hybrid PET/MRI scanners, but is also due to the fact that PET is a second-line examination in brain tumors. PET is only required in equivocal situations, and spatial co-registration of PET examinations of the brain to previous MRI is possible without disadvantage. A key factor for the benefit of PET/MRI in neuro-oncology is a multimodal approach that provides decisive improvements in the diagnostics of brain tumors compared with a single modality. This systematic review focuses on studies that were able to demonstrate the additive value of amino acid PET and 'advanced' MRI in the diagnosis of brain tumors. Available studies suggest that the combination of amino acid PET and advanced MRI improves grading and the histomolecular characterization of newly diagnosed tumors. However, data concerning the delineation of tumor extent and biopsy guidance are of limited value. A clear additive diagnostic value of amino acid PET and advanced MRI can be achieved regarding the differentiation of tumor recurrence from treatment-related changes. Here, PET-guided evaluation of advanced MR methods seems to be helpful. In summary,

there is growing evidence that a multimodal approach can achieve decisive improvements in the diagnostics of brain tumors, for which hybrid PET/MRI offers optimal conditions.

Keywords: brain tumor diagnosis; PET; radiolabeled amino acids; O-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET); Hybrid PET/MRI; multimodal imaging

1. Introduction

Currently, the diagnosis of brain tumors is primarily based on contrast-enhanced MRI. Structural imaging using T1- and T2-weighted sequences provides high-resolution imaging of brain tumors and allows a differential diagnosis in a large fraction of lesions [1]. Differentiating tumor tissue from non-specific tissue changes, however, can be difficult, especially in cases of gliomas with diffusely infiltrating tumor growth, lack of contrast enhancement, and reactive tissue changes after surgery, radiotherapy, alkylating chemotherapy, or other experimental therapy approaches. In this situation, PET using radiolabeled amino acids can provide important additional diagnostic information [2]. The Response Assessment in Neuro-Oncology (RANO) Working Group has recommended the use of amino acid PET, in addition to MRI, in all stages of brain tumor management [3-8]. O-(2-[^{18}F]fluoroethyl)-L-tyrosine (^{18}F -FET) was developed in our institution in the 1990s in order to provide a fluorine-18 labeled amino acid PET tracer with a longer half-life (110 min), which provides logistical advantages compared with shorter-lived carbon-11 labeled amino acids (half-life 20 min) such as [^{11}C]-methyl-L-methionine [9-11]. Since 2000, we have focused on preclinical and clinical brain tumor imaging with ^{18}F -FET, which has become one of the most frequently used amino acid tracers in the field [12, 13]. Meanwhile, the interest of neuro-oncologists, neurosurgeons and radiation oncologists in ^{18}F -FET PET has increased considerably leading to 600 - 700 ^{18}F -FET PET investigations per year in our department alone [12, 14].

The introduction of PET/CT in the early 2000's constitutes a milestone in nuclear medicine as it provides precise anatomical localization of abnormal tracer uptake in whole-body PET imaging. This has significantly improved diagnostic accuracy, and meanwhile, PET/CT systems have replaced stand-alone PET scanners [15, 16]. However, for brain imaging, the introduction of PET/CT was less important, because the rigid structure of the skull allows an efficient spatial co-registration of separately acquired PET, CT and MRI data [17].

Since around 2010, hybrid PET/MRI has become commercially available, representing another important development in the field. Although, like PET/CT, PET/MRI does not provide an essential advantage for the co-registration of images of brain tumor patients, the benefits relate more to an improved workflow, reduced examination time and, especially in pediatric patients, avoidance of radiation exposure from the CT scanner and the repeated use of general anesthesia [18]. Early reviews have highlighted the potential of simultaneous PET/MRI for the combination of various physiological parameters, MR-based motion, and partial volume correction, and optimized generation of arterial input function for metabolic modeling [19]. So far, however, these features have not had a major impact on clinical brain tumor diagnostics, and a recent paper has emphasized the equality of hybrid and sequential PET/MRI [20].

Our laboratory has been equipped with a dedicated BrainPET-hybrid PET/MRI system since 2008, in addition to an existing conventional PET system [21]. However, the hybrid scanner has only been used for approximately 25% of the ^{18}F -FET PET investigations undertaken at our institute. In our experience, the more frequent use of hybrid PET/MRI is limited due to the fact that nearly all brain tumor patients have already received conventional MR imaging before referral for ^{18}F -FET PET. Amino acid PET or advanced MRI are usually second-line investigations in patients with equivocal findings in conventional MRI (see flow chart in Figure 1). Most of the patients referred for ^{18}F -FET PET already have recent contrast-enhanced MRI scans and a second injection of contrast

medium for perfusion-weighted MRI (PWI) must be carefully weighed against clinical necessity. Moreover, our team perceives hybrid PET/MRI as more time-consuming than a PET or PET/CT scan due to checking for magnetic materials, sedation for claustrophobia or refusal of additional MRI because of noise. Despite this, hybrid PET/MRI may be particularly useful when a second line examination with both amino acid PET and advanced MRI is intended and an additive diagnostic value can be expected.

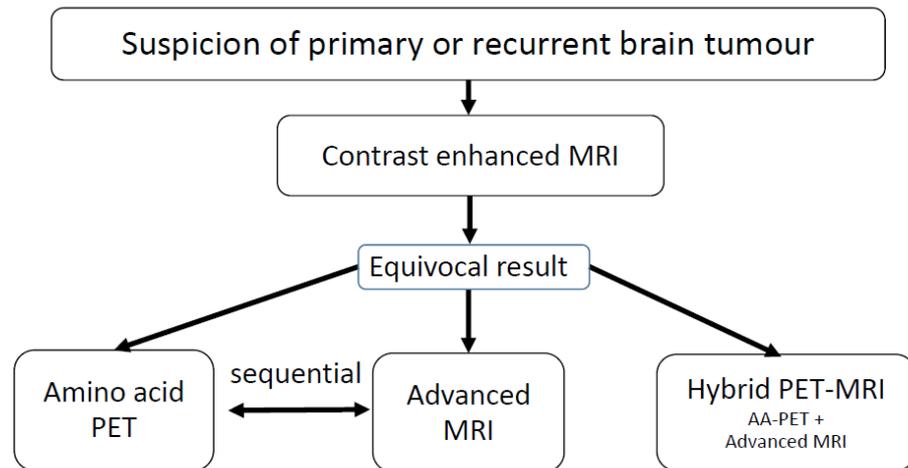


Figure 1. Workflow in brain tumor imaging: When there is suspicion of a primary or recurrent brain tumor, the first step is conventional, contrast enhanced MRI. If the findings are equivocal, further diagnostics using amino acid PET or advanced MRI procedures are considered. At this point, hybrid PET/MRI may be advantageous, if a combination of these methods can achieve higher accuracy compared with a single modality.

Several reviews have discussed the technical aspects and the potential of hybrid PET/MRI in neuro-oncology and it is not the intention of this review to repeat these aspects [18, 22-24]. Instead, this review focuses on our own studies comparing ^{18}F -FET PET with advanced MR methods and studies from the literature that were able to demonstrate an additive value of amino acid PET and advanced MRI in the diagnosis of brain tumors.

The following chapters first provide a short overview of PET and advanced MR methods in brain tumor diagnostics. Thereafter, we give a review of studies evaluating the additive or complementary value of these methods providing a special perspective for the use of hybrid PET/MRI in neuro-oncological diagnostics.

2. Search Strategy

A PubMed search of the published literature with the combination of the search terms “glioblastoma”, “brain tumors”, “high-grade glioma”, “positron emission tomography”, “magnetic resonance imaging”, “magnetic resonance spectroscopy”, “perfusion-weighted imaging”, “diffusion-weighted imaging”, “chemical exchange saturation transfer”, “kurtosis”, “DKI”, “PET”, “amino acid PET”, “MRI”, “advanced MRI”, “MRS”, “PWI”, “DWI”, “CEST”, and “hybrid PET/MR” before and inclusive of October 2022 was performed. Additional literature was retrieved from the reference lists of all identified articles. Furthermore, articles identified through searches of the authors’ files were included. Only publications in English were considered.

3. PET Tracers for Brain Tumor Imaging

Today, radiolabeled amino acids are the preferred PET tracers in neuro-oncology [1]. Amino acid PET is helpful regarding differential diagnosis, classification and the prognostication of newly diagnosed brain tumors, delineation of brain tumor extent for treatment planning, assessment of treatment response, and the differentiation of tumor recurrence or progression from treatment-related changes [1]. The most widely used amino

acid tracers are [^{11}C]-methyl-L-methionine (MET), ^{18}F -FET, and 3,4-dihydroxy-6- ^{18}F -fluoro-L-phenylalanine (^{18}F -FDOPA) as described in previous publications from the RANO Group [3, 4]. Furthermore, the synthetic amino acid analog anti-1-amino-3- ^{18}F -fluorocyclobutane-1-carboxylic acid (FACBC or Fluciclovine) has gained clinical interest for brain tumor imaging in recent years [25-27]. The uptake of these tracers in brain tumors is primarily dependent on the increased expression and functionality of large neutral amino acid transporters of the L-type (LAT, subtypes LAT1 and LAT2) [1]. In contrast to radiolabeled amino acids, the most widely used PET tracer 2- ^{18}F -fluorodeoxyglucose (^{18}F -FDG) has a limited use in brain tumors because of the high glucose metabolism in normal brain tissue. The proliferation tracer ^{18}F -3'-deoxy-3'-fluorothymidine accumulates in cerebral gliomas in relation to the grade of malignancy and prognosis [28, 29], but uptake is usually restricted to contrast enhancing tumor parts on MRI and tumor volume is smaller than that observed with amino acid tracers [30]. [^{11}C]-choline or ^{18}F -fluoro-choline are markers of cell membrane phospholipids in brain tumors, but tracer uptake is also restricted to tumor parts with disruption of the blood-brain barrier (BBB) [31]. A correlation of tracer uptake with grade of malignancy has been reported [32, 33], but the role of choline tracers in the primary diagnosis of brain tumors is limited, as the accumulation is not tumor-specific [34-36].

Many studies have explored brain tumor imaging with the hypoxia tracer ^{18}F -floromisonidazole (^{18}F -FMISO) [37, 38] and several review articles have summarized the present knowledge on this tracer [39-41]. There is widespread agreement that increased ^{18}F -FMISO uptake correlates with tumor grade and prognosis [37, 42], but the most challenging indication for ^{18}F -FMISO PET, i.e. the effectiveness of radiotherapeutic dose escalation in hypoxic areas in gliomas still remains unanswered [40, 43].

Another important approach for brain tumor imaging is the use of ligands for the mitochondrial translocator protein (TSPO) such as [^{11}C]-PK11195, ^{18}F -GE-180 and ^{18}F -DPA-714 [44]. TSPO is overexpressed in activated microglia and macrophages but also in glioma cells [45]. PET imaging of gliomas using TSPO ligands depict tumors with high contrast compared with normal brain [46], but discrimination between tumor mass and brain tissue appears to be critical at the tumor rim where glia-associated microglia/macrophages may also show high tracer binding [47-49]. TSPO ligands accumulate in brain areas with intact BBB, but differences exist in the visualization of tumor extent compared with amino acid PET [50].

In addition to the tracers mentioned, a large number of other ligands are currently under development, and it is beyond the scope of this article to provide a complete overview. In this regard, reference is made to corresponding review articles [24, 39, 51]. Overall, none of those tracers has reached a clinical status comparable to that of radiolabeled amino acids. Therefore, this review focuses on the combination of amino acid PET and advanced MRI techniques.

4. Advanced MRI Methods in Neuro-oncology

Advanced MRI methods can provide functional, physiologic and molecular information beyond conventional MRI, which may be helpful in equivocal findings [52]. A detailed description of these methods is beyond the scope of this article and therefore only a brief overview of the most important methods from this area is given. PWI either by dynamic susceptibility contrast (DSC) MRI, dynamic contrast-enhanced (DCE) MRI or arterial spin labelling (ASL) MRI provides several surrogate markers of tissue perfusion such as relative cerebral blood flow (rCBF), the relative cerebral blood volume (rCBV), and other perfusion metrics [1, 53, 54]. In particular, rCBV mapping is a valuable supplement to conventional MRI in the differentiation of tumor progression or recurrence from treatment-related changes [55].

Proton MR spectroscopy (MRS) enables the non-invasive measurement of the signals of selected metabolites *in vivo*. Important metabolites for the characterization of brain tumors are the neuronal marker N-acetyl-aspartate (NAA) and choline-containing com-

pounds as cell membrane markers (Cho). MR spectroscopic imaging (MRSI) provides parameter maps, which visualize heterogeneous distributions of different metabolites, or ratios thereof, in larger volumes of the brain [56]. Diffusion-weighted imaging (DWI) is based upon the random Brownian motion of water molecules within a voxel of tissue, which can be quantified for example by the apparent diffusion coefficient (ADC) [57]. In brain tumors, the ADC is inversely correlated with cell density, probably due to reduced water mobility from dense cellular packing. Diffusion kurtosis imaging (DKI) is an advanced neuroimaging modality that is an extension of diffusion tensor imaging by estimating the kurtosis (skewed distribution) of water diffusion based on a probability distribution function [58]. Another approach uses a combination of magnetization transfer contrast and spectroscopic techniques based on the chemical exchange saturation transfer (CEST) effect [59, 60]. The CEST effect from amides allows the imaging of amide proton transfer (APT), which appears to be related to the tumor extent of cerebral gliomas.

Another promising field for the investigation of brain tumors is sodium imaging by single-quantum and multiple-quantum ^{23}Na MRI and spectroscopy [61]. Cell membrane depolarization that precedes cell division in proliferative neoplastic tissue leads to an increase in the intracellular sodium concentration and a concomitant rise in the total sodium concentration in the tumor tissue [62]. Initial investigations have addressed treatment monitoring and analysis of IDH mutation status of gliomas [63, 64].

5. Hybrid PET/MRI in Animal Research

Hybrid PET/MRI has been successfully used in preclinical neuroimaging to correlate changes in neuronal activity using fMRI and changes in receptor expression and neurotransmitter binding [65-68]. In addition, several studies have used combined PET and MRI in animal brain tumor models to explore novel PET tracers and advanced MR methods for brain tumor diagnosis, but the investigations have used mainly sequential PET/MRI [69-73].

Previous review articles have made suggestions as to the expectation that simultaneous hybrid PET/MRI will be used for the modeling of physiological and biochemical processes, because during the simultaneous acquisition one can be sure the prevailing physiological conditions such as blood flow, perfusion, pertain to both the PET and MRI measurements [74]. However, there has been little implementation in experimental brain tumor research to date. Nevertheless, hybrid PET/MRI offers decisive logistical advantages in animal imaging, as the standard sequential execution of PET and MRI considerably prolongs examination times or leads to examinations on different days, requiring renewed vascular puncture and anesthesia. Thus, hybrid PET/MRI provides considerable advantages in terms of animal welfare and reducing the number of animal experiments. Due to the lack of an animal hybrid PET/MRI scanner in our department, we have successfully worked with a fixed animal bed, which allows rapid sequential PET/MRI without re-anesthesia [74, 75].

6. Hybrid PET/MRI in Newly Diagnosed Brain Tumors

In brain lesions suspicious for neoplasms, conventional MRI is frequently inconclusive and additional imaging methods can be helpful. This concerns differential diagnosis, the definition of an optimal biopsy site, and the detection of tumor infiltration, especially in tumors without contrast enhancement in MRI. Furthermore, the non-invasive classification of tumors and the assessment of molecular features and prognostication can be valuable, if neuropathological assessment is not possible. Pyka et al. investigated the additive value of static and dynamic ^{18}F -FET PET in a series of 67 patients with newly diagnosed gliomas [76]. Static ^{18}F -FET PET allowed the differentiation of low-grade and high-grade gliomas with an area under the curve (AUC) in receiver operating characteristics analysis (ROC) of 0.86 and MRS using the Cho/NAA with an AUC of 0.66. The combination of ^{18}F -FET PET and MRS achieved an AUC of 0.97. Furthermore, the multimodal approach was able to differentiate glioblastoma from non-glioblastoma with an AUC of 0.97. Song et al.

reported that the combination of ^{18}F -FET PET and DSC-PWI increased the diagnostic accuracy to differentiate gliomas with and without IDH mutation (AUC 0.90) compared with the single modalities (^{18}F -FET PET and rCBV, each AUC 0.80) [77]. Haubold et al. explored the non-invasive characterization of cerebral gliomas utilizing multi parametric ^{18}F -FET PET/MRI and MR fingerprinting in a series of 42 patients with suspected primary brain tumor [78]. For the differentiation of low-grade and high-grade gliomas, the combination with ^{18}F -FET PET yielded the highest AUC value (0.85), but most parameters (i.e., 1p19q co-deletion, ATRX, IDH-status, MGMT promotor methylation, WHO subtype) could be best estimated with MR parameters alone. The potential of amino acid PET for the assessment of the tumor extent of gliomas has been documented by several biopsy-controlled studies [79-84]. Most studies have compared tumor extent in amino acid PET with conventional MRI, but initial studies also considered advanced MRI methods for comparison [85-87]. One study compared preoperative imaging with ^{11}C -MET PET and PWI in oligodendrogliomas with histological sections after en bloc resection of the tumors [85]. ^{11}C -MET accumulation correlated well with cell density and reliably reflected the extent of the tumor tissue, while CBV mapping did not correlate with neuropathological markers for tumor cells such as IDH1-mutated protein and Ki67 (proliferating cells), which were used to delineate the tumor. That study confirmed the observation of other studies that rCBV is not suitable for tumor delineation [88-91]. In another prospective, biopsy-controlled study the detection of tumor extent using ^{18}F -FET PET was compared with different advanced MR methods [86]. One hundred and seventy-four tissue samples were taken from 20 patients and the contribution of ^{18}F -FET PET, PWI, DWI, APT-CEST and MRSI to delineate the tumor tissue was analyzed by multiple logistic regression. It was found that the combination of ^{18}F -FET PET and ADC mapping best reflected tumor extent. The contribution of MRSI could not be evaluated due to multiple artifacts in this series of patients. Another study compared tumor spread with ^{18}F -FET PET, APT-CEST, and PWI of newly diagnosed gliomas [87]. Tumor extent seemed to be comparable with both APT CEST and ^{18}F -FET PET and correlated well with cell density. In a study using ultra-high field MRI at 7T, APT CEST predicted tumor extent using ^{18}F -FET PET as a reference with an AUC of 0.81 and MRS with an AUC of 0.89 [92]. The combination of APT-CEST and MRS predicted ^{18}F -FET uptake with an AUC of 0.95. The authors concluded that the combination of APT-CEST and MRS might serve as an alternative to amino acid PET to delineate glioma infiltration. An overview of studies demonstrating an additive value of amino acid PET and advanced MR-methods in newly diagnosed cerebral gliomas is given in Table 1.

Table 1. Studies demonstrating an additive value of amino acid PET and advanced MR-methods in newly diagnosed cerebral gliomas .

Reference	Year	PET Tracer	MR-methods	Tumor type	No of subjects	Remarks	Main Result
Verburg et al. [86]	2020	^{18}F -FET	PWI, DWI, MRS	Newly diagnosed gliomas	20	Tumor infiltration, Verification of tumor extent by biopsies	Best result for combined ^{18}F -FET + ADC in depicting enhancing gliomas
Haubold et al. [78]	2020	^{18}F -FET	DWI, ADC, SWI	Phenotyping of newly diagnosed gliomas	42	Radiomics, multiparametric MRI and ^{18}F -FET PET parameters	Best differentiation of high-grade and low-grade glioma by combination of ^{18}F -FET PET, T1ce and SWI
Song et al. [77]	2021	^{18}F -FET	PWI	Phenotyping of newly diagnosed gliomas	52	Retrospective evaluation after surgery	Improved differentiation of IDH status by combination of ^{18}F -FET PET and PWI
Pyka et al. [76]	2022	^{18}F -FET	MRSI	Newly diagnosed gliomas	67	Characterization of intracranial gliomas	Improved differentiation of high-grade from low-grade glioma and of glioblastoma from non-glioblastoma

Summarizing, there is some evidence that combined amino acid PET and advanced MRI is helpful in improving the non-invasive characterization of suspected gliomas. Concerning tumor delineation, amino acid PET appears to be the most reliable method to identify metabolically active tumor tissue and so far, there is little evidence that combination with advanced MR methods leads to superior results.

7. Hybrid PET/MRI in Patients with Recurrent Gliomas

Most studies investigating multimodal PET/MRI to differentiate brain tumor progression or recurrence from treatment-related changes have compared PWI with amino acid PET. While some older publications reported the superiority or equivalence of rCBV mapping compared with amino acid PET [93-95], more recent publications consistently observed the superiority of amino acid PET [96-98]. Recently, we analyzed the additive value of ^{18}F -FET PET and perfusion-weighted MRI in a group of 104 patients with suspected glioma recurrence [99]. Eighty-three patients had tumor progression and 21 patients had treatment-related changes. The combination of ^{18}F -FET PET and PWI did not increase the diagnostic power, but a rCBVmax > 2.85 reached a positive predictive value of 100 % so that 44 patients could be correctly classified using rCBVmax alone. In the remaining patients, ^{18}F -FET PET still achieved an accuracy of 78%, so that 87% of the patients could be correctly diagnosed in total. These results support the sequential use of PWI and amino acid PET, particularly when a more economical use of the diagnostic methods has priority. In contrast, one study using ^{11}C -MET PET reported on an additive value of amino acid PET and DSC-PWI [100]. While both, the maximum tumor-to-brain ratio (TBR_{max}) of ^{11}C -MET uptake and mean rCBV achieved an AUC of 0.85, the combination of the parameters yielded an AUC of 0.95 in the differentiation tumor recurrence from radiation injury. Furthermore, a number of studies have reported the additive value of amino acid PET and MRI when including advanced MRI methods other than rCBV in patients with suspected tumor recurrence. Jena et al. achieved the highest accuracy (97%) in differentiating recurrent tumor from radiation necrosis when combining the TBR_{max} of ^{18}F -FET uptake and MRS using the Cho/Cr ratio [101]. An identical accuracy of 97 % was achieved by Sogani et al. with a combination of ^{18}F -FET PET, MRS, PWI and DWI [102], and a hybrid PET/MRI study achieved an accuracy of 95 % using ^{18}F -FDOPA as the amino acid tracer [103]. Another hybrid PET/MRI study compared dynamic ^{18}F -FET PET, PWI, and DWI in 47 patients with suspected glioma recurrence [104]. Static ^{18}F -FET PET alone achieved an AUC of 0.86 for differentiating recurrent tumor and treatment-related changes, which could be increased to an AUC of 0.89 when combined with PWI and DWI. Lohmeier et al. reported the highest AUC by using a combination of static ^{18}F -FET PET and ADC (0.90) versus ^{18}F -FET PET (0.81) or ADC alone (0.82) [105]. These results could not be confirmed by Werner et al., who reported the highest accuracy using static and dynamic ^{18}F -FET PET parameters (93%), which could not be further improved by ADC mapping [106].

A recent study applied a machine learning approach to a multiparametric data set of 66 patients with suspected tumor recurrence including ^{18}F -FET PET, DSC-PWI and APT-CEST [107]. The classification accuracy of the Random Forest classifier was 0.86 and therefore significantly above the no-information rate of 0.77 compared to an accuracy of 0.82 for MRI, 0.81 for ^{18}F -FET PET, and 0.81 for expert consensus. These results emphasize that the use of artificial intelligence in conjunction with multiparametric imaging can be expected to yield further improvements in diagnostic accuracy. Rather encouraging results could be observed by our group with the combination of ^{18}F -FET PET and DKI in patients with recurrent glioma [108]. In this study, ^{18}F -FET PET guided evaluation of kurtosis achieved an AUC of 0.87 (MK-C90), ^{18}F -FET uptake an AUC of 0.77 (TBR_{max}), and the combination of the two methods achieved an AUC of 0.97 to differentiate recurrent tumor from treatment-related changes (Figure 2 and Figure 3). These data were confirmed by a recent study including 87 patients with suspected recurrent glioblastoma using ^{11}C -MET [109]. In that study, combined ^{11}C -MET PET and DKI achieved an AUC of 0.95 to differentiate glioblastoma recurrence from radiation injury compared with an AUC of 0.89 for PET or 0.85 for DKI alone.

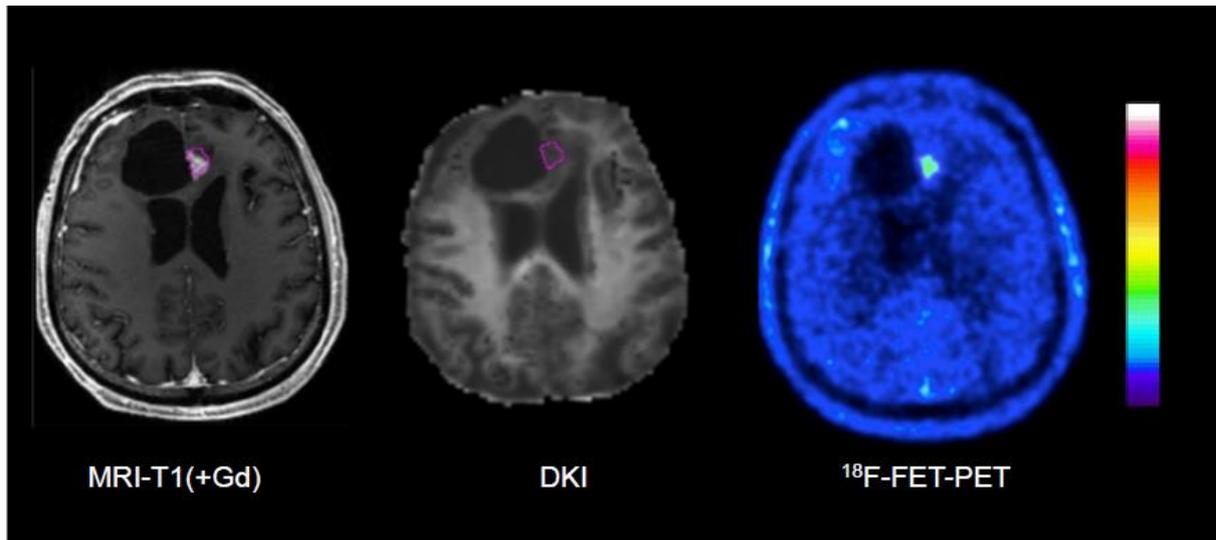


Figure 2. Example of an ^{18}F -FET PET guided evaluation of diffusion kurtosis imaging (DKI) in a patient with treatment-related changes. Please note that the region of interest (pink line) generated on the PET scan (right) is larger than the area of contrast enhancement in T1-weighted MRI (left).

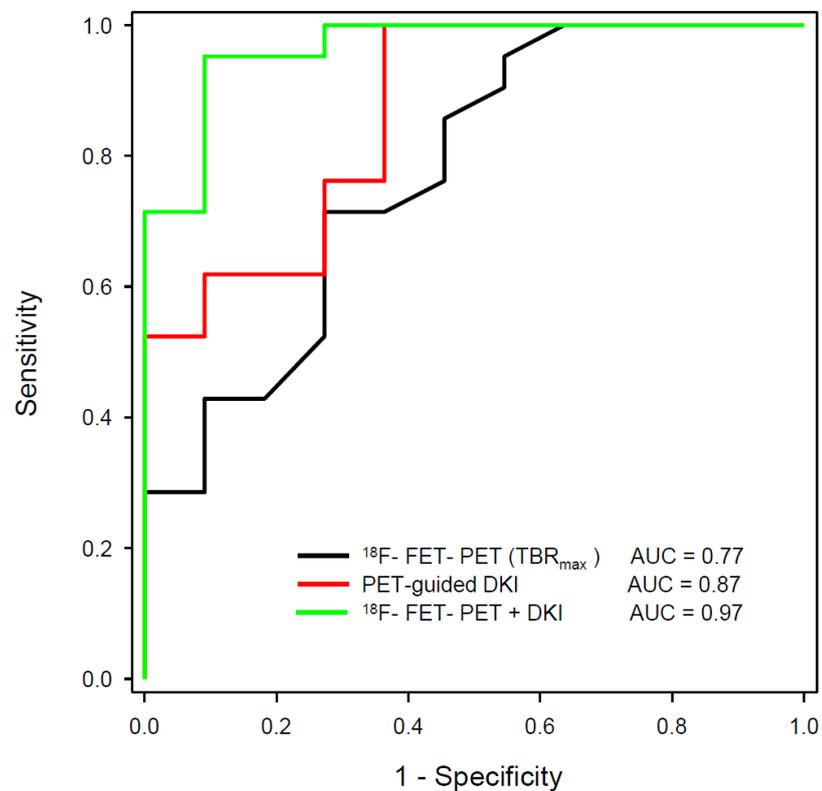


Figure 3. ROC analysis for differentiation between the tumor progression and treatment-related changes in gliomas using hybrid PET/MRI with ^{18}F -FET PET and diffusion kurtosis imaging (DKI) from a previous publication of our group [108]. The largest area under curve (AUC) could be achieved by the combination of ^{18}F -FET PET and ^{18}F -FET PET guided DKI (green line).

Little data exist concerning the additive value of amino acid PET and advanced MR methods in terms of response assessment. A recent study reported that the simultaneous evaluation of ^{18}F -FET PET and ADC metrics using PET/MRI allows the early and reliable identification of treatment response and predict overall survival in recurrent glioblastoma

patients treated with regorafenib [110]. A key aspect in this study is the fact that the authors use pathological ^{18}F -FET uptake to define the region of interest (ROI) on the ADC maps. The authors emphasize that radiological recommendations do not provide a strategy for identifying the ROI on the DWI-ADC images or how to define the threshold for pathological ADC values. Thus, a PET guided evaluation strategy for advanced MRI methods is another important aspect for the use of PET/MRI and also played a decisive role in the combined use of ^{18}F -FET PET and DKI mentioned above [108]. An overview of studies demonstrating an additive value of amino acid PET and advanced MR-methods in recurrent cerebral gliomas is given in Table 2.

Table 2. Studies demonstrating and additive value of amino acid PET and advanced MR-methods in recurrent brain tumors.

Reference	Year	PET Tracer	MR-methods	Tumor type	No of subjects	Remarks	Main Result
Jena et al. [101]	2016	^{18}F -FET	PWI, DWI, MRSI	Tumor recurrence in pre-treated gliomas	26	Verification by surgery (9) and clinical follow-up (17)	Best AUC by combination of ^{18}F -FET PET, rCBV and MRS (0.94) versus ^{18}F -FET PET (0.89), ADC (0.74), PWI (0.85), MRS (0.89)
Sogani et al. [102]	2017	^{18}F -FET	PWI, DWI, MRSI	Tumor recurrence in pre-treated gliomas	32	Verification by surgery (12) and clinical follow-up (20)	Best accuracy by combination of ^{18}F -FET PET, ADC, rCBV and MRS (97%)
Pyka et al. [104]	2018	^{18}F -FET	PWI, DWI	Tumor recurrence in pre-treated gliomas	47(63 lesions)	Verification by surgery (23) and clinical follow-up (40)	Improved accuracy by combination of ^{18}F -FET PET, ADC and rCBV (AUC 0.89)
Lohmeier et al. [105]	2019	^{18}F -FET	DWI-ADC	Recurrent high and low grade gliomas	42	Verification by surgery (36) and clinical follow-up (6)	Best AUC by combination of static ^{18}F -FET PET and ADC (90%) versus ^{18}F -FET PET (0.81) or ADC alone (0.82)
Qiao et al. [100]	2019	^{11}C -MET	PWI-DSC	Recurrent high and low grade gliomas	42	Verification by surgery (32) and clinical follow-up (10)	Best AUC by combination of ^{11}C -MET PET and rCBV (0.95) versus ^{11}C -MET PET (0.85) or rCBV alone (0.85)
Paprottka et al. [107]	2021	^{18}F -FET	APT-CEST, PWI	Tumor recurrence in pre-treated gliomas	66 (74 lesions)	Verification by surgery (46) and clinical follow-up (31), ADC evaluation guided by ^{18}F -FET PET	Best accuracy by combination of ^{18}F -FET PET, APT-CEST and PWI (0.85) versus ^{18}F -FET PET alone (0.81)
D'Amore et al. [108]	2021	^{18}F -FET	DWI, DKI	Tumor recurrence in pre-treated gliomas	32	Verification by surgery (12) and clinical follow-up (20), DKI evaluation guided by ^{18}F -FET PET	Best AUC by combination of static ^{18}F -FET PET and DKI (0.97) versus ^{18}F -FET PET (0.77) or DKI alone (0.87)
Jena et al. [103]	2021	^{18}F -FDOPA	PWI, DWI, MRS	Tumor recurrence in pre-treated gliomas	26	Verification by surgery (4) and clinical follow-up (22)	Best AUC by combination of ^{18}F -FDOPA PET, rCBV, ADC and MRS (0.94) versus ^{18}F -FDOPA-PET (0.81), ADC (0.42), rCBV (0.50) and MRS (0.77) alone
Lombardi et al. [110]	2021	^{18}F -FET	DWI	Monitoring of regorafenib therapy in recurrent glioblastoma	16	Verification by clinical follow-up, ADC evaluation guided by ^{18}F -FET PET	^{18}F -FET guided ADC promising for therapy monitoring, better than RANO
Dang et al. [109]	2022	^{11}C -MET	DWI, DKI	Tumor recurrence in pre-treated gliomas	86	Verification by surgery (23) and clinical follow-up (20)	Best AUC by combination of ^{11}C -MET PET and DKI (0.95).

8. Hybrid PET/MRI in Pediatric Brain Tumors

The use of hybrid PET/MRI appears particularly advantageous in pediatric patients in order to reduce examination time, to avoid radiation exposure from the CT scanner and prevent repeated general anesthesia in separate measurements [111, 112]. Furthermore, the fusion of separately acquired PET and MRI data may cause more problems in children than in adults owing to the fact that pediatric tumors are frequently located in the cerebellum and medulla or by high extra cerebral ^{18}F -FET uptake in the cranial bone marrow [18]. On the other hand, the logistics of anesthesia in the hybrid scanner are challenging, especially in younger children and attenuation correction in children causes problems [18] as MR based attenuation methods often are built upon reference data sets acquired in adult subjects [113, 114]. Several studies have demonstrated the additional value of amino acid PET in pediatric brain tumors compared with conventional MRI [7, 115-117]. It was reported that amino acid PET changed patient management in up to two thirds of children and adolescent with brain tumors [112, 118]. First data on the complementary value of amino acid PET and advanced MRI methods in pediatric brain tumors are available. In a comparative study between ^{18}F -FDOPA PET and ^1H -MRS in 27 children with untreated brain tumors, PET was superior in tumor grading and prognostication while ^1H -MRS was better in differentiating tumor from non-neoplastic lesions [116]. Another study in 26 children with diffuse astrocytic gliomas yielded the highest diagnostic performance in predicting tumor progression when combining ^{18}F -DOPA PET, ADC, and arterial spin labeling data [119]. Thus, there is initial evidence of an additional value of amino acid PET and advanced MRI methods in the assessment of childhood brain tumors.

9. Conclusions

In principle, all applications of combined amino acid PET and advanced MRI in brain tumors mentioned in this review do not require simultaneous acquisition and can be performed sequentially. Hybrid PET/MRI is preferable to reduce examination time, and particularly in children to reduce radiation burden and repeated anesthesia. There is increasing evidence that the combination of amino acid PET and advanced MRI improves grading and molecular characterization in newly diagnosed tumors, while data concerning the delineation of tumor extent and biopsy guidance are limited. Convincing and clinically relevant additive diagnostic value is achieved by combining amino acid PET with different advanced MR methods regarding the differentiation of tumor progression or recurrence versus treatment-related changes. In this context, the value of PET-guided evaluation of advanced MR methods should be emphasized, as defining the region of interest in these methods can be difficult.

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