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*OBM Neurobiology*

Review

# Contribution of PET Imaging to Clinical Management of Gliomas

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**Academic Editor:** Antonio Meola

**Special Issue**: Tumors of the Central Nervous System

*OBM Neurobiology*
2018, volume 2, issue 3
doi:10.21926/obm.neurobiol.1803011

**Received:** July 2, 2018
**Accepted:** September 5, 2018
**Published:** September 20, 2018

**Abstract:**

Gliomas originating from glial cells comprise about 30% of all primary central nervous system tumors and 80% of malignant brain tumors. Gliomas differ in their biological activity and are categorized according to grades, from benign to malignant with high recurrence rates. For diagnosis, location and extent of the tumor is assessed by CT and MRI, but for grading, additional parameters are necessary: contrast enhanced CT and MRI reveal damage of the blood–brain barrier, perfusion-weighted MRI shows regional blood supply, and MR spectroscopy permits insight into regional metabolism. Positron emission tomography (PET) of glucose metabolism as well as amino acid and nucleoside uptake can assess tumor grade and invasive growth, indicate effects on function of tissues outside of the tumor, demonstrate treatment efficacy, detect recurrences, and yield prognostic information.

Coregistration of PET and MRI combines high-resolution morphological information with biological information. This imaging technology is optimized in hybrid MRI/PET by which morphologic, functional, metabolic, and molecular information is assessed simultaneously in the human brain.

**Keywords**
Gliomas; tumor recurrence; morphologic imaging; functional imaging; molecular imaging; PET

## 1. Introduction

Gliomas are the most frequently occurring primary tumors affecting the central nervous system (accounting for 29%), with an incidence of 20.5 per 100,000 people each year. Within this group, 54% are malignant gliomas with an incidence of 6.6 per 100,000 [1]. Survival rates are dependent on the grade of gliomas: 35.7% at 1 year and 4%–7% at 5 years for glioblastoma, 60%–80% at 1 year and 26%–46% at 5 years for astrocytomas and oligodendrogliomas of WHO grade III, and 94% at 1 year and 67% at 5 years for astrocytomas and oligodendrogliomas of WHO grade II [2]. Patients with malignant tumors have an average survival of 15–20 months despite surgical resection followed by radiotherapy and chemotherapy [3]. Imaging plays an integral and decisive role in the grading of gliomas, therapeutic management, and in the development of new treatment strategies. Furthermore, multimodal and molecular imaging may have an especially significant role in detecting and defining new targets for research [4-6].

Morphological imaging by CT and especially MRI detects the location of brain tumors and is improved by contrast enhancement, due to damage of the blood–brain barrier. MR spectroscopy may provide additional information on the tissue, including the presence or level of malignancy. Information detected by MRI is limited since brain tumor tissue may extend into tissue outside the areas affected by a blood–brain barrier disruption. After radiation therapy, a blood–brain barrier disruption may persist in non-tumorous tissue. MR spectroscopy is unreliable in certain areas, specifically close to the skull or the ventricles. Nuclear medicine procedures can detect physiological and metabolic changes in the involved brain tissue [7, 8]]. Notably, positron emission tomography (PET) can quantify tumor metabolism, proliferation rate, and invasiveness and demonstrate the effects on functional networks as well as monitor changes after therapy [9-12].

In this review, which is an update of a previously published paper [13], clinically relevant results studying glucose metabolism, amino acid uptake, and cell proliferation with PET tracers are summarized. Other tracers specifically applied for research topics [4, 14] are not discussed.

Energy for the brain is nearly exclusively supplied by glucose**.** For the measurement of the cerebral metabolic rate of glucose, 18F-labeled deoxy-d-glucose (FDG) is used, which becomes phosphorylated to FDG-phosphate and accumulates in proportion to local metabolism. Regional quantitative metabolic rates of glucose (rCMRGlc) are determined from the tissue activity measured by PET and the arterial input function [15].

Amino acid uptake in gliomas is increased due to altered overexpressed L-type amino acid carriers [16, 17]. This tracer indicates the different metabolic activities in the tumor cell. Amino acid uptake in gliomas is higher than in white matter, and also often higher than in the normal cortex. The most frequently used amino acid for tumor brain imaging with PET is (methyl-11C)-L-methionine (MET) [18, 19], but this tracer suffers from a short half-life of 11C. Amino acids labeled with 18F-fluorine as O-(2-[18F] fluoroethyl)-L-tyrosine (FET) and 3, 4-dihydroxy-6-[18F]-fluoro-L-

phenylalanine (FDOPA) showed comparable results to MET. However, since FET is not further metabolized it can only reflect transport in tissue. FDOPA is a substrate for the enzyme aromatic amino acid decarboxylase in dopaminergic neurons, which is responsible for FDOPA uptake by the basal ganglia and might therefore interfere with tumor delineation. On the other hand, MET is incorporated into proteins, used for methylation, and is needed for DNA translation.

As nucleosides are involved in cellular proliferation, they can indicate histologic grade 3'-deoxy-3'-[18F] fluorothymidine (FLT) accumulation correlates with activity of thymidine kinase-1, which is expressed during the DNA synthesis phase [20]; this makes it a suitable tracer of tumor proliferation [21]. Accumulation of FLT depends on blood-brain barrier (BBB) permeability, and high FLT uptake is found in tumors with impaired BBB; therefore, FLT is not useful in low grade gliomas with intact BBB [22-24].

PET studies during functional activation show the effect of tumors on brain tissue outside the tumor and on eloquent areas. Blood flow tracers such as 15O-water are frequently used for this purpose, but functional changes can be also recorded by FDG. Accurate anatomic localization can be achieved by coregistration and fusion with MRI [25]. However, perfusion MRI is the method used most in the clinical setting for demonstration of functional activation.

## 2. Diagnosis, Grading and Prognosis

The World Health Organization (WHO) classification of gliomas distinguishes four grades of gliomas: I and II are benign; grade III is anaplastic; and grade IV, glioblastoma multiforme, is the most malignant with the worst prognosis [26]. The WHO classification of gliomas has been updated recently [27], combining molecular parameters such as the IDH mutation and 1p/19q co-deletion with histology, which defines five subgroups. However, since nearly all imaging studies were done on the basis of the previous classification, the prior classification was used in this review for the description of imaging data. Gliomas are frequently heterogeneous [28] and therefore, histologic grading may not be representative for further prognosis/development. Anatomic imaging is still the first step in diagnosis, but it does not yield all the information on tumor pathology essential for individualized treatment. PET can supplement conventional CT and MRI information on tumor grading, necrosis, proliferative activity, and vasculature.

## 3. Glucose Metabolism

The first PET study in oncology [29] already showed increased glucose consumption in brain tumors and the effect of radiation necrosis, especially in malignant gliomas. FDG uptake levels in low-grade tumors is the same as in white matter, and uptake in high-grade tumors can be in the range of that of normal gray matter. Regions with low and high uptake can be near each other in a single tumor. This variability must be taken into account when tumors are graded. Usually, uptake ratios of tumor to white matter greater than 1.5 or of tumor to gray matter greater than 0.6 are used for distinction of benign tumors (grades I and II) from malignant tumors (grades III and IV) (Figure 1) [30]. Additionally, delayed PET after injection may help to distinguish tumors from normal gray matter [31].

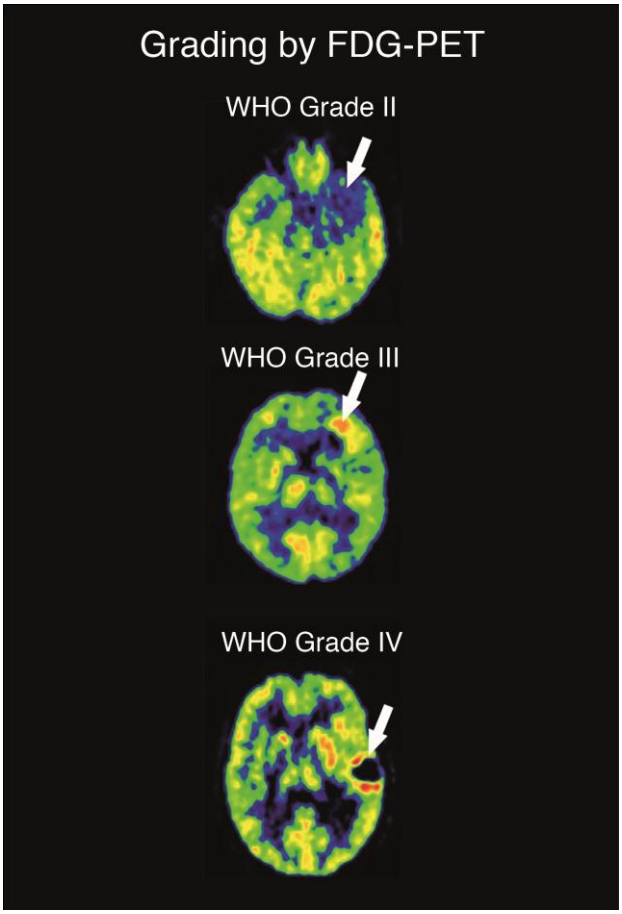


**Figure 1** Typical patterns of glucose (FDG) uptake in gliomas of different grades: Astrocytoma WHO grade 2 shows low uptake in relation to gray matter and can hardly be differentiated (a), in malignant gliomas (grade 3 (b) and grade 4 / glioblastoma (c)) glucose uptake is significantly increased and above the level of gray matter; in the glioblastome (c) a central necrosis (reduced FDG uptake) is visible.

In a primary glioma, FDG uptake correlates with histologic tumor grade [32], cell density [33], and survival [34]. Additionally, metabolism in normal brain tissue is impaired and the reduction is related to prognosis [35]. FDG-PET is therefore of value in patient management [36]. Necrotic compartments in glioblastoma often cause heterogeneous FDG uptake. In pilocytic astrocytoma with metabolically active fenestrated endothelial cells, uptake can be rather high, but prognosis is good. The similarity of FDG uptake in tumors to that in the cortex and the partial-volume averaging by PET limit the detection of small gliomas. This limitation can be overcome by coregistration with MRI. Coregistered MRI/FDG-PET can help in the selection of the most metabolically active tumor part for stereotactic biopsy [37]. Other malignant tumors in the brain, especially medulloblastomas, often show high FDG uptake [38, 39]. It should be considered that the Response Assessment in Neuro-Oncology (RANO) guidelines emphasize superiority of amino acid PET over FDG–PET [40]. Therefore, the use of FDG for brain tumor imaging has been widely abandoned in PET centers with access to radiolabeled amino acids.

## 4. Amino Acid Uptake

Uptake of MET in gliomas is 1.2 to 6.0 times above that in normal tissue and correlates to cell proliferation, Ki-67 expression, nuclear antigen expression, microvessel density, and angiogenesis [41]. MET-PET has a sensitivity of 76% and a specificity of 87% for the diagnosis of brain tumors [42]. Due to the low uptake in normal brain tissue and the accumulation despite the unimpaired blood–brain barrier, amino acid tracers are especially suited for detection of low-grade tumors (Figure 2). Even tumors not visible on FDG-PET can be detected with MET [43]. Amino acid uptake was correlated to histological tumor grade in high- and low-grade gliomas [44]. Additionally, the invasion of malignant cells into the surrounding brain could reliably be distinguished by MET-PET [45], demonstrating the importance of integrating this technique into radiation therapy planning [46]. In some gliomas, MET-PET is superior to contrast-enhanced MRI [47]. MET-PET can help determine prognosis in gliomas and is superior than FDG-PET and MRI in predicting survival in low-grade gliomas [48]. Recent reviews have summarized the value of MET-PET for imaging of gliomas [4, 49-51].

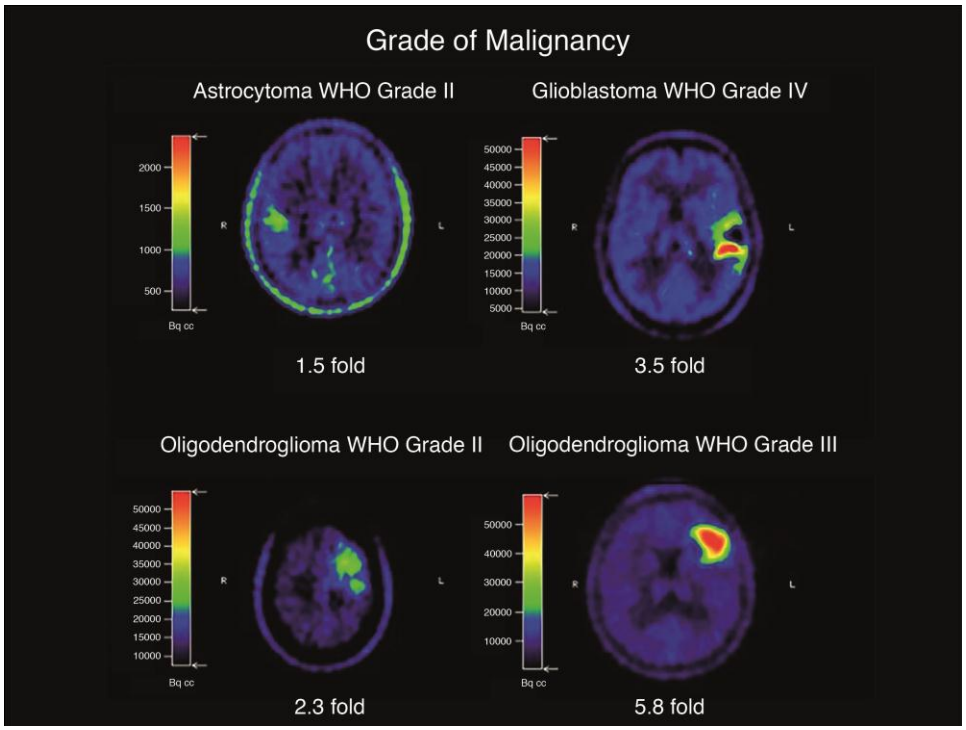


**Figure 2** (11C)-MET-PET in low and high grade gliomas: uptake of (11C)-MET is increased in relationship to grade in astrocytoma and glioblastoma as well as in oligodendrocytoma.

MET uptake differs with tumor type: in oligodendrogliomas, uptake tends to be higher than in astrocytomas of the same histological grade, although they are less aggressive [52]. In oligodendrogliomas, 11C-choline PET may be useful in evaluating the potential malignancy, but MET-PET is superior in detecting “hot lesions” [53]. MET uptake is increased in other malignant intracranial tumors, but also in benign neoplasias, such as meningiomas (for review see [38]).

The disadvantage of MET is the short half-life of 11C (20 min). Therefore, 18F-labeled aromatic amino acid analogs O-(2-[18F] fluoroethyl)-L-tyrosine (FET) and [18F]-fluoro-dihydroxy-phenylalanine (FDOPA)) with similar brain uptake as MET were introduced for tumor imaging [18, 19, 54-56]. Uptake of FET is related to grade and prognosis [57, 58]; specifically, the volume of increased FET uptake correlated to survival of patients with glioblastoma [59]. Despite significant differences between high- and low-grade gliomas, sensitivity and specificity for detection were 87% and 68%, respectively [60]. As with MET, coregistration with MRI [61] and combination with MRS [62] improves diagnostic accuracy: high FET accumulation was related to neuronal cell loss indicated by MRS [63]. The early phase of FET uptake appears to be most informative for grading [64, 65] and prognosis [66]; tracer accumulation is slow in low-grade gliomas, for which late scans provide the best contrast [67]. The FET uptake kinetic analysis independently predicted overall and progression-free survival [68]. Dynamic FET studies with inclusion of early and late scans therefore improved differentiation and grading performance [69-72]. Kinetic analysis of dynamic FET uptake parameters is of special prognostic value in diffuse low-grade gliomas [51].

FDOPA was more sensitive and specific than FDG for differentiating high- and low-grade tumors, and uptake was related to proliferation [73]. FDOPA studies have demonstrated association with tumor grade [74], progression-free survival [75], and overall survival in recurrent tumors [76, 77]. High uptake (an SUV of more than 1.75) was a predictor of progression in low-grade gliomas [78]. A direct comparison of FDOPA and FET in high-grade gliomas revealed no significant difference in patterns, but uptake ratios were 10-15% higher for FET than for FDOPA [79].

## 5. Nucleoside Uptake

Imaging of nucleoside uptake adds another dimension to the assessment of the biological activity of tumors, specifically in regards to cellular proliferation (Figure 3)[80]. The tracer FLT achieves high tumor to normal tissue ratios of grade III and IV gliomas [81], which was not observed in grade II gliomas. FLT uptake was correlated to Ki-67 expression [82]. For preoperative tumor grading, FLT -PET was superior to MRI and MRS for differentiation between grades III and IV [83]. FLT-PET was superior to MET-PET in tumor grading and assessment of proliferation in some gliomas; notably, the combination with MET-PET added significant information [84]. A direct comparison in primary and recurrent low-grade gliomas showed low FLT uptake (SUV = 1.8) but high uptake of FDOPA (SUV = 5.75) and FDG (SUV = 8.5), and tumor to normal tissue ratios of 2.3 ± 0.5 for FDOPA, 1.8 ± 0.9 for FLT, and 1.0 ± 0.6 for FDG, confirming the value of FDOPA for evaluation of low grade gliomas [85]. In high-grade gliomas, FLT-PET predicted overall survival of patients [86].

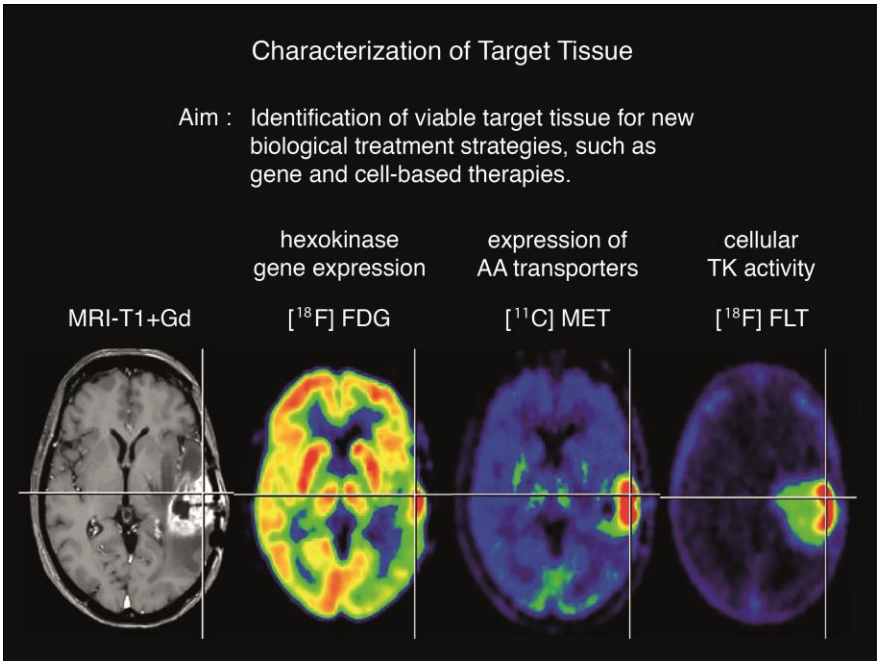


**Figure 3** Comparison of Gd-Ti-MRI, FDG-, MET- and FLT-PET in glioblastoma: disruption of blood brain barrier and peritumorous edema visible on MRI, increase of glucose turnover in tumor and reduction in surrounding tissue, increased MET-uptake in tumor core, infiltration detected by FLT-PET.

## 6. Effects on Surrounding and Remote Brain Areas

The rim of reduced metabolism in normal tissue around malignant tumors might be partly due to edema and infiltrating tumor tissues [87]. Additionally, function of the non-tumorous brain is affected: cortical centers are displaced and functional activations are reduced or occur at atypical locations, even in contralateral areas which indicate reorganization of functional networks; the knowledge of these altered networks is important for planning tailored surgery. In the motoric network, activation of secondary motor areas and of the motor cortex ipsilateral to the paretic limbs has been observed [88]. Functional MRI is the most important procedure to determine functional anatomy in patients with gliomas [6].

In patients with brain tumors in the dominant hemisphere, a considerable reorganization of the language-related network is observed [89], dependent on the speed of the development of the brain lesion: a verb generation paradigm analysis showed increased activation area beyond the primary language regions to the left frontal medial gyrus, the orbital inferior frontal gyrus, the anterior insula, and the left cerebellum (Figure 4), as well as the contralateral functional network. Successful resection of a left frontotemporal tumor improved aphasia and restored left hemisphere dominance, suggesting a reversible disinhibition by removal of the primary functional damage. The hierarchy of the functional network for recovery in an individual patient as shown in these examples should be taken into account in tailored surgery.

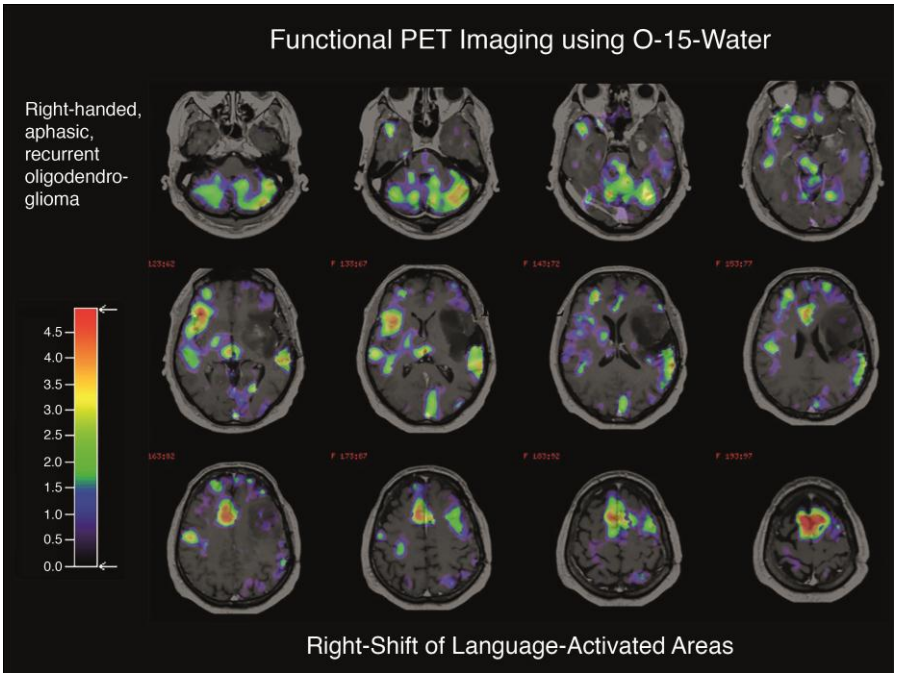


**Figure 4** Activation of H215O PET by verb generation coregistered to MRI. Primary speech centers are affected by the tumor, temporal Wernicke center and frontal Broca center are shifted and language activation pattern is shifted to the right hemisphere.

## 7. Monitoring Treatment Effects

PET studies can follow the efficiency of therapy in brain tumors [90]. Via FDG-PET, reduction of the tumor is visible after only a few weeks of radiation and chemotherapy [91], and recurrence is indicated by progressive hypermetabolic regions [92]. The early assessment of therapy efficacy by PET can help to optimize therapy of gliomas: FDG accumulation was measured before and after 14 days of temozolomide chemotherapy and tumor response after 8 weeks was analyzed [91]. Pre-treatment FDG uptake was higher in responders than non-responders, and responders showed a greater than 25% reduction of metabolic rate in tumor regions after 8 weeks [91]. FDG-PET also predicted response to temozolomide (TMZ) versus TMZ plus radiotherapy (RT) in recurrent malignant glioma [93]. Changes in tumor glucose metabolism were observed also with everolimus or rapamycin in combination with RT and TMZ [93, 94]. However, hypermetabolism is sometimes mimicked by the infiltration of macrophages, especially after radiotherapy. This disadvantage makes FDG-PET not the optimal method for the evaluation of treatment [95].

Amino acid and nucleoside tracers do not possess this disadvantage and several studies indicated that patients can benefit from treatment studies based on MET- or FET-PET [96-100]. Differentiation of recurrent tumors and necrosis is detected by MET-PET with high sensitivity and specificity (~75%), and progression was detected early (Figure. 5) [101-104]. In many patients, information supplied by MET-PET affected further treatment management [105].

The changes observed by amino acid PET [106-109] indicate deactivation of amino acid transport as an early sign of response to chemotherapy. FET-PET was more efficient (sensitivity 80%, specificity close to 100%) [110] than MRI in showing effects of multimodal treatment [111, 112] Early changes of FET uptake of > 10% after postoperative radiochemotherapy predicted a

significantly longer disease-free and overall survival in patients with glioblastomas [113]. Similar results were obtained with FET- and FDOPA-PET [114, 115]. FET-PET was also useful to assess pseudoprogression in glioblastomas [116] and could also demonstrate treatment effects in recurrent tumors [115, 117-121].

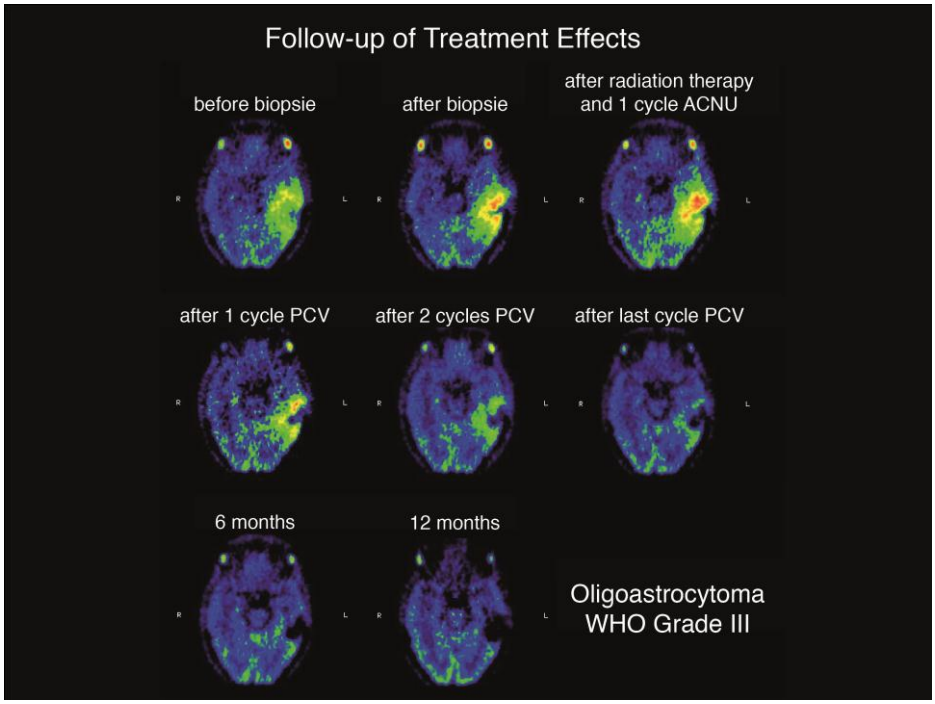


**Figure 5** Decrease of 11C-Methionin uptake in PET demonstrated response to chemotherapy with favorable prognosis.

FLT-PET was successful in the prediction of the prognosis of responders and non-responders to a combination therapy and also in predicting survival. An SUV decrease of more than 25% or less than 25% distinguished responders and non-responders, respectively [122]. Additionally, the responders survived 3 times as long as non-responders. Notably, the kinetics of FLT uptake are closely related to prognosis, early efficacy of treatment, and outcome [123-126], and can serve as early surrogate markers of longtime survival.

These results indicate that coregistration of various PET and MRI modalities are useful for evaluating new treatments, e.g. targeting proliferating cells[127], angiogenesis [114], or applying gene therapy vectors [128].

FET-PET was also useful to assess pseudoprogression in glioblastomas [116] and could also elucidate treatment effects in recurrent tumors [115, 117-120]. Antiangiogenic treatment with bevacizumab causes a rapid decrease in T1 contrast-enhancing tumor parts, which suggests radiographic response rates are related to pseudonormalization of abnormal blood-brain barrier permeability [129]; the distinction between anti-vascular and true antitumor effects by MRI criteria is difficult, therefore, the RANO criteria were developed [130]. On the other hand, transiently-increased permeability of the vasculature may be a consequence from irradiation and can be enhanced by temozolomide [131]. Pseudoprogression as well as pseudoresponses after therapy can be differentiated from actual tumor response by FET-PET [70, 132].

With FLT-PET, a distinction between responders and non-responders to a combination therapy was possible: FLT-PET at 2 and 6 weeks predicted survival better than MRI [122]. FLT uptake investigated at different time points in the course of treatment was able to differentiate between responders and non- responders by a SUV decrease of more than 25% or less than 25%, respectively, and the responders survived 3 times as long as non-responders [122]. As shown by several groups [123-126], the kinetics of FLT uptake are closely related to prognosis, early efficacy of treatment, and outcome. These therapeutic effects may be related to neovascularization by bevacizumab and/or permeability changes by chemotherapy [123, 133] and can serve as early surrogate markers of longtime survival [11]. Similar results were obtained with FDOPA-PET [134].

Multimodal imaging, including various PET and MRI modalities, will have a great impact on the development of new therapeutic strategies, such as targeting proliferating cells [127], angiogenesis [114], or applying gene therapy vectors [128].

## 8. Residual Tumors, Recurrences and Necrosis

The capacity of PET to identify tumor compartments that differ in activity is especially important for the detection of residual or recurrent tumors after resection, and for differentiation between treatment-induced changes (such as necrosis) and active proliferating tissue. After tumor resection, normal postsurgical changes do not show increased FDG uptake. Therefore, a hypermetabolic activity after surgery is highly suspect of residual tumor, and FDG-PET can be performed within a few days after surgery [92]. While normalization of glucose metabolism in the surrounding area of the resected tumor might be related to edema and increased intracranial pressure, a newly detected hypermetabolism weeks after therapy indicates a recurrent tumor and progression from low-grade to high-grade glioma [37, 92, 135, 136]. One of the most important applications of PET tracers after treatment of gliomas is the differentiation between radiation-induced changes, like necrosis, or recurrent or residual tumors after radiation therapy [29, 137]. Generally, the question, “Tumor or necrosis?” is an oversimplification as in most cases both tumor and necrotic tissue can be found next to each other in patients or may even overlap [138]. Sensitivity of FDG-PET was 75% at a specificity of 81% for the detection of recurrent tumor versus radiation necrosis [17, 139]. However, there is a specific overlap in FDG-uptake in recurrent tumor and radiation necrosis [138] (review in [140]). Stereotactic biopsy based on FDG-PET improves the detection of tumor tissue when compared to anatomical imaging alone [37]. A disadvantage of FDG-PET is that accumulation of FDG may occur from macrophages that potentially infiltrate the sites having received radiation therapy [91, 141]. Therefore, radiation necrosis may be indistinguishable from a recurrent tumor.

Necrosis and gliosis after therapy show a reduction of amino acid uptake in contrast to uptake in recurrent or residual tumor growth. Therefore, MET-PET successfully differentiates between recurrent tumor growth and radiation necrosis with the detection of a recurrent tumor at a high sensitivity and high specificity (Figure 6). Again, MET-PET is more sensitive than FDG-PET for differentiation between recurrent tumor and radiation necrosis (Figure 7) [102, 104, 142] and provided high accuracy [143], despite its limitations in tumor grading [144], and is especially effective in combination with MRI [145, 146]. Even in brain lesions that did not show increased uptake in FDG-PET, a sensitivity between 89% (tumors) and 92% (gliomas) with a specificity of 100% was obtained [43] (for detailed review see [147]). A recent systematic review and meta-analysis

[148] demonstrated that FET-PET has good sensitivity (82%) and average specificity (76%) for diagnosis of brain tumors; it allows discrimination between infection and tumoral lesions and also between tumor recurrence and radionecrosis [149]. MET-PET and FET-PET differentiated tumor tissue and treatment-related changes with a sensitivity of 91% and a specificity of 100%. In adequately equipped centers, amino acid PET is the method of choice for differentiation between necrosis and progressive disease [40]. Fusion of FDOPA-PET with MRI provides precise anatomic localization of tracer uptake [150], and FDOPA-PET better identifies large tumor volumes than perfusion-weighted MRI [151]. FDOPA-PET is also superior to FDG-PET in detection of recurrences [152] and is able to differentiate glioma recurrence from treatment-related changes.

FLT-PET had a moderately better overall accuracy for diagnosing glioma recurrence than FDG-PET [153, 154]. The FLT influx rate differentiated recurrence from radionecrosis, but the SUV did not [155]. For monitoring treatment effects and the differentiation between necrosis and recurrence, multimodal imaging is most effective [12].

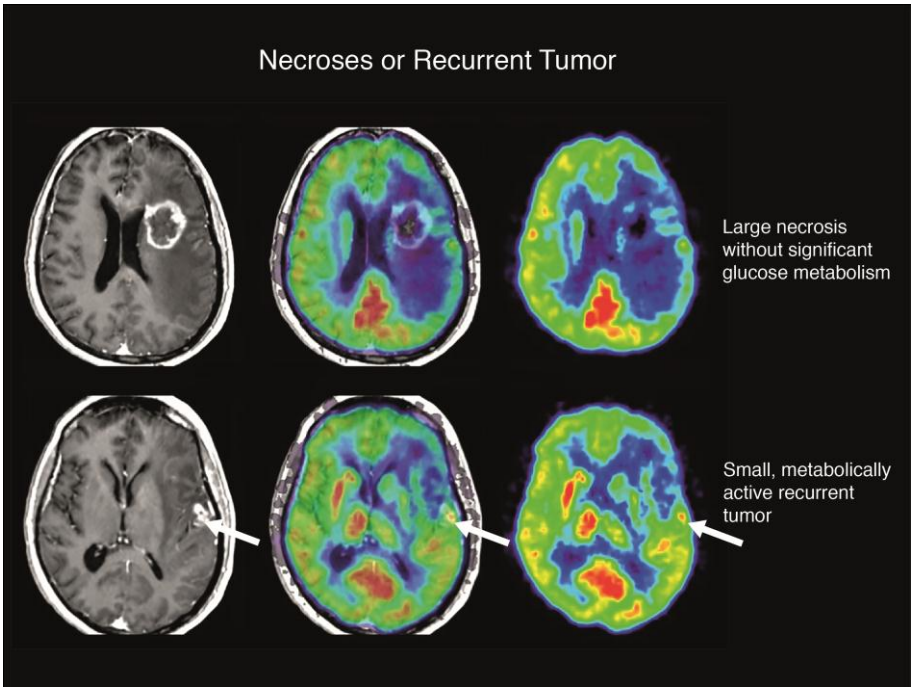


**Figure 6** Differentiation between recurrent tumor and radiation necrosis by FDG-PET.

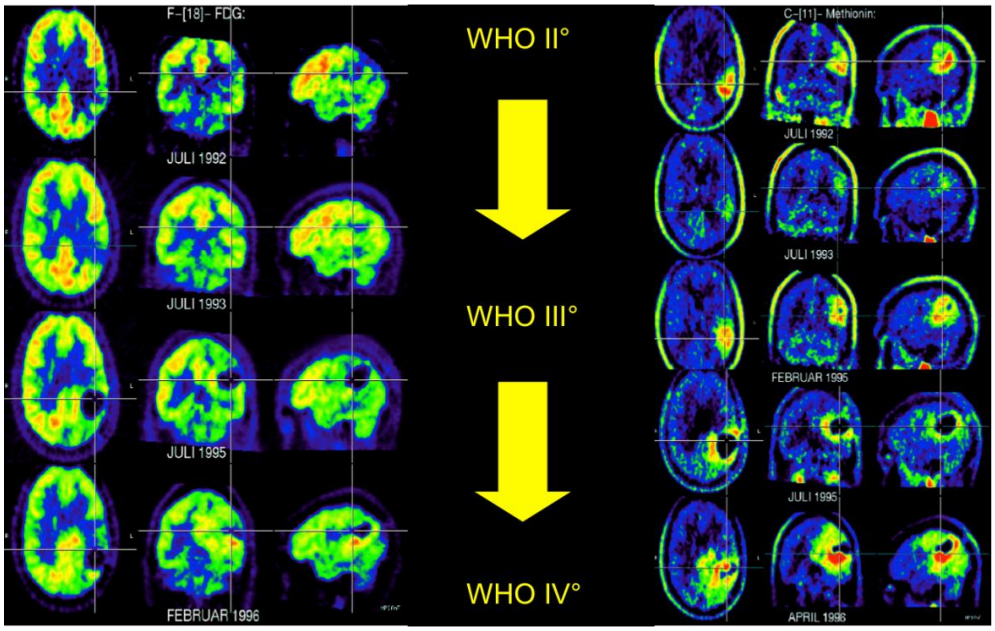


**Figure 7** Uptake of glucose (FDG) and methionin (MET) in the course of a patient with glioblastoma: After tumor resection and radiation therapy the uptake of FDG and METis initially reduced; MET-PET indicates the recurrency long before it can be proven by FDG-PET.

## 9. The Future: Hybrid PET/MRI Systems

Coregistration of PET and MRI data requires positioning the patient in different scanners, often under different conditions and at different times. Hybrid PET/MRI systems combine high-resolution MRI (including spectroscopy, functional MRI, diffusion- and perfusion-weighted imaging) with the molecular, biochemical, and functional imaging properties of PET. In contrast to PET/CT data acquisition, a hybrid PET/MRI system analyzes simultaneously due to PET detectors [156] in the MRI gantry. After the feasibility of simultaneous PET/MRI recording was shown [157], dedicated brain PET/MRI scanners tested some promising applications [158]. In the first clinical studies, the hybrid system demonstrated simultaneous high-resolution structural, functional, and molecular imaging in tumor patients [159].

BesideIn addition to the time-saving benefits and patient management advantages, hybrid MRI/PET improves the presurgical diagnosis of patients with focal epilepsy, where small lesions, hypoplasias, or heterotopies can be delineated [160, 161]. As previously stated, hybrid MRI/PET has great advantages in the differential diagnosis of brain tumors, grading of gliomas, assessment of progression, and the distinction between necrosis and recurrence of tumors [162-166]. Additionally, it is an important tool for the selection of sites for biopsies and in the evaluation of treatment effects [160, 167-176]. Adding diffusion tensor imaging/fiber tracking, fMRI, PWI, MRS, and activation-PET to multimodal imaging can enhance the assessment of a tumor on the functional networks in the brain [177-181] and show anaerobic changes as well as the effect on efferent and connecting fiber tracts and on task-related activation patterns.

**Author Contributions**

The author has completed all the work.

**Funding**

Supported by the WDH Foundation within the Max Planck Society.

**Competing Interests**

The author has declared that no competing interests exist.

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