Published in final edited form as:

Semin Nucl Med. 2012 November ; 42(6): 356–370. doi:10.1053/j.semnuclmed.2012.06.001.

Brain Tumors

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Abstract

This review addresses the specific contributions of nuclear medicine techniques, and especially positron emission tomography (PET), for diagnosis and management of brain tumors. ¹⁸F-Fluorodeoxyglucose PET has particular strengths in predicting prognosis and differentiating cerebral lymphoma from nonmalignant lesions. Amino acid tracers including ¹¹C-methionine, ¹⁸F-fluoroethyltyrosine, and ¹⁸F-L-3,4-dihydroxyphenylalanine provide high sensitivity, which is most useful for detecting recurrent or residual gliomas, including most low-grade gliomas. They also play an increasing role for planning and monitoring of therapy. ¹⁸F-fluorothymidine can only be used in tumors with absent or broken blood–brain barrier and has potential for tumor grading and monitoring of therapy. Ligands for somatostatin receptors are of particular interest in pituitary adenomas and meningiomas. Tracers to image neovascularization, hypoxia, and phospholipid synthesis are under investigation for potential clinical use. All methods provide the maximum of information when used with image registration and fusion display with contrast-enhanced magnetic resonance imaging scans. Integration of PET and magnetic resonance imaging with stereotactic neuronavigation systems allows the targeting of stereotactic biopsies to obtain a more accurate histologic diagnosis and better planning of conformal and stereotactic radiotherapy.

Brain tumors share some features and challenges for diagnosis and therapy with tumors elsewhere in the body, but they also pose specific issues that are related to the unique properties of the organ they sit in. Most of the brain is separated from the blood by the blood–brain barrier (BBB) that exerts a much more restrictive control over substances that are allowed to pass (or may even be subject to facilitate transport) than most other organs. Thus, many tracers that easily reach tumors in the body would reach brain tumors only once the tumor caused a disruption of the BBB, for instance glioblastomas; when the tumor developed from intracranial tissues that do not have a BBB, for instance meningioma (derived from the meninges); or for brain metastasis (seeding from within the blood vessels). Thus, the disruption of the BBB, which can easily be detected on contrast-enhanced magnetic resonance imaging (MRI) and computed tomography (CT), is regarded as the main diagnostic indicator for malignant gliomas, meningiomas, and brain metastases, as well as for some less frequent tumors without an intact BBB. As a consequence of the exclusion of all radiotracers that cannot pass the BBB from normal brain, there usually also is a good tumor-to-brain contrast for all tracers with these properties, which historically included ^{99m}Tc-pertechnetate and ⁶⁸Ga-diethylene triamine pentaacetic acid, and currently

also fluorothymidine (FLT) and virtually all labeled macromolecules (although low-capacity slow-specific transfer by receptors has been observed for some). However, the excellent contrast may not indicate much more than the presence of BBB damage, which can readily be seen and even quantified by contrast-enhanced MRI. Therefore, much interest and effort has been invested into the development and evaluation of brain tumor tracers that do not depend on BBB damage, such as fluorodeoxyglucose (FDG) and labeled amino acids, because they are being transferred by large-capacity specific transporters across the intact BBB.

There are brain tumors with an intact BBB, notably most low-grade gliomas (LGG), which may be missed on a contrast-enhanced CT scan but are easily detected by increased signal (as a consequence of their different tissue structure) on T₂-weighted MRI scans without contrast enhancement. Thus, in general, there is little need for nuclear imaging for detection of brain tumors, whereas MRI with and without contrast-enhancement is the standard method providing excellent sensitivity (but not necessarily specificity) for virtually all kinds of brain tumors. The role of nuclear imaging is more in the realm of biological characterization of brain tumors, especially of those aspects that are relevant for therapy planning.

It is important to grade tumors with respect to their malignancy. Although some tumor types, for example, meningiomas and neurinomas rarely become malignant, gliomas as the most frequent brain tumors exist in all 4 grades, usually classified internationally according to the World Health Organization (WHO) system.¹ Grade 1 gliomas are rare and largely limited to childhood. Grade 2 gliomas (with subtypes astrocytoma and oligodendroglioma) occur in all ages with a peak in young adults. They show little cellular atypia and proliferation, but frequently infiltrate healthy surrounding brain, and, therefore, cannot be cured by surgery or radiotherapy. They represent a significant chronic medical problem and pose large uncertainties with regard to therapeutic decisions, which need to balance the imperative of saving intact functioning brain while trying to prevent those tumors from progression. More malignant gliomas are anaplastic (grade 3) or include gross cellular atypias and necroses, which characterize glioblastoma (grade 4). MRI and CT rely on BBB damage (frequent in grade 3 and 4, absent in grade 2) and morphologic appearance (eg, presence of necrosis, vascularity) for grading. Although this is regarded as largely sufficient in untreated gliomas, it becomes unreliable in treated tumors because BBB damage and necrosis also can result from formation of reactive tissue after therapy. In that situation, imaging methods that distinguish tumor from reactive non-neoplastic tissue will contribute significantly to clinical decision making. Contrast enhancement also cannot provide proper grading in brain tumors with a constitutive lack of BBB, such as meningiomas and lymphomas. In general, functional measures related to tumor proliferation are expected to deliver more reliable information on prognosis than morphologic imaging methods.

Often, brain tumors exhibit different degrees of anaplasia in different tumor parts. Thus, surgical biopsies, especially when taken stereotactically, may miss the most malignant tumor part and therefore underestimate the tumor grade. To overcome this problem, targeting of biopsies toward the most malignant tumor part is an important clinical utility of positron emission tomography (PET) imaging, which requires integration with operation planning and stereotactic neuronavigation.

As mentioned earlier, another big problem with gliomas is their potential to infiltrate normal brain. Already normal astrocytes and oligodendrocytes can move preferentially along the preformed fiber paths in the brain, and neoplastic cells often exhibit that capacity even more. Even complete solid tumor removal (or any other local therapy) will not reach these cells, and they will likely cause tumor recurrences. There is a possibility that fractionated

radiotherapy or chemotherapy, which would selectively attack tumor cells while sparing normal brain tissue, may be successful in destroying them. Thus, the degree and extent of infiltration is potentially important information for tailoring therapy (eg, by conformal or stereotactic radiotherapy) individually. MR fluid-attenuated inversion recovery (FLAIR) sequences and diffusion tensor imaging may provide good sensitivity but lack specificity. Molecular imaging techniques providing sensitivity and specificity would be regarded as a major step forward.

There is a large variation in the response of tumors to therapy by irradiation and cytostatic drugs within tumor types and often even in different areas of the same tumor. However, with morphologic imaging, it is difficult to determine whether a tumor is responding, and only late after completion of therapy, the outcome becomes evident. Especially with chemotherapy, monitoring of therapeutic efficacy is a major goal to modify inefficient therapy before the patient's condition worsens to a degree that reduces any further therapeutic options. Thus, molecular imaging techniques are expected to provide improved outcome parameters for therapy monitoring, which also is relevant for conducting efficient clinical trials of new therapeutics.

¹⁸F-Fluorodeoxyglucose

The principle of the method by which PET using ¹⁸F-FDG permits the determination of regional cerebral metabolism was originally established by Sokoloff and colleagues as an autoradiographic technique and subsequently modified for PET.² There is a high uptake of FDG in normal gray matter, mostly reflecting the metabolic demands of neuronal activity. Therefore, standard FDG-PET studies of the brain are being conducted under resting conditions. Quantitation of FDG uptake in brain and tumors can be provided by calculation of metabolic rates of glucose, which requires measurement of blood glucose, an arterial input function or suitable surrogate, and adoption of a value for the "lumped constant" to account for differences in enzyme affinity between FDG and glucose. Thus, in clinical practice, tumor standard uptake values (SUV) or, usually more clinically relevant, activity ratios (equivalent to SUV ratios, SUVR) relative to contralateral brain (mirror region and gray or white matter [WM]) are being reported.³

The high and regionally variable FDG uptake in normal brain often makes the delineation of brain tumors difficult. Therefore, they need to be interpreted in conjunction, ideally by image fusion, with CT or MRI scans (Fig. 1). There have been studies suggesting that additional delayed imaging at 180 minutes or later after tracer injection can increase the contrast between malignant tumors with high FDG uptake and normal brain.⁴⁻⁶

Prognosis and Grading

One of the first reports describing the utility of FDG in PET in the evaluation of brain tumors and the effect of radiation (RT) necrosis of the brain was published in 1982 by Patronas et al.⁷ In this article, the authors described the problem of management of patients who have undergone previous therapy. The main issue is that therapy with RT produces RT necrosis. Once RT necrosis occurs, the associated clinical symptoms may become worse, and it becomes difficult to differentiate cerebral necrosis from recurrent viable tumor. The CT images demonstrate a mass of increasing size surrounded by edema with or without cavitation; after intravenous administration of contrast medium, enhancement of the lesion generally occurs. However, these clinical and CT findings are essentially indistinguishable from those encountered in some recurrent neoplasms. Using FDG-PET, the authors were able to establish a diagnosis of RT necrosis, later verified, in 10 of 95 patients referred for the purpose of differentiating tumor recurrence from necrosis. The critical FDG-PET feature

was focal hypometabolism in the area of necrosis, which contrasted with the hypermetabolism associated with the residual/recurrent tumor.

The distinction between recurrent tumor and cerebral necrosis after RT therapy and chemotherapy was further addressed by Di Chiro et al in 1988.⁸ They were able to distinguish areas of necrosis by corresponding hypometabolic areas of FDG uptake, as contrasted with areas of residual recurrent high-grade glioma (HGG), demonstrating hypermetabolic glucose use. Further studies of the accuracy of FDG-PET for discrimination between viable tumor and necrosis demonstrated a sensitivity range of 43%-83% with a specificity range of 40%-100% (Table 1). There was also a good discrimination between atypical cerebral tumors and infarcts.²³ The PET imaging technique can also be used in conjunction with MR spectroscopy, which shows other aspects of tumor metabolism that can help with the distinction between necrosis and tumor (Fig. 2).

Di Chiro et al²⁵ found a positive correlation between FDG uptake and degree of malignancy. In their study, FDG-PET was used to measure local cerebral glucose in 23 patients with cerebral gliomas. All 10 high-grade (III and IV) astrocytomas demonstrated a region of high activity with a glucose consumption of 7.4 ± 3.5 (standard deviation) mg/100 g per min. The 13 low-grade (I and II) gliomas had a glucose metabolic rate of 4.0 ± 1.8 mg/100 g per min, with no distinctly visible hot spot. The authors found a correlation between the rate of glycolysis and malignancy in primary cerebral tumors. Cerebral cortical glucose use was often depressed in areas adjacent to or neurally connected to the tumor site because of vasogenic edema and diaschisis. In a subsequent study,²⁶ PET was used to assess prognosis in patients with a high-grade glioma. In this study of 45 patients with grade 3 or 4 astrocytoma, the mean survival time in patients with tumors exhibiting high glucose uptake was 5 months, whereas patients with a tumor showing lower glucose uptake had a mean survival time of 19 months.

A study by Alavi et al²⁷ on the prediction of prognosis of high-grade tumors showed that patients with hypermetabolic tumors had a median survival time of 7 months compared with 33 months for those patients with hypometabolic lesions. In addition, patients with HGG with a positive PET scan had a poor prognosis compared with those HGG patients with relatively hypometabolic PET scans. The association of tumor FDG uptake with survival was confirmed in the majority of subsequent studies.^{17,26,28}

FDG in Central Nervous System (CNS) Opportunistic Infections and CNS Lymphoma

Establishing the diagnosis of a brain tumor can be difficult because many non-neoplastic neurological diseases can mimic brain neoplasms on neuroimaging or on histologic examination, including stroke, pyogenic abscess, toxoplasmosis, tuberculosis, cysticercosis, fungal infections, and sarcoidosis.²⁹

FDG-PET has shown some clinical advantage in assessing high-grade or LGG versus lymphoma or other opportunistic infections, such as histoplasmosis. Discrimination between lymphoma and toxoplasmosis is an issue most frequently arising in immunocompromised patients with acquired immunodeficiency syndrome. Most cerebral lymphomas have a high cell density and a high glucose metabolism,³⁰ usually even higher than that of malignant gliomas and cerebral metastasis.^{31,32}

The utility of FDG-PET for distinction between lymphoma with high uptake and toxoplasmosis with low uptake was described by Hoffman et al³³ and is illustrated in a study by Villringer et al.³⁴ Eleven patients with acquired immunodeficiency syndrome, 6 with toxoplasmosis, 1 with a tuberculoma, and 4 with a primary CNS lymphoma (PCNSL) were studied. The FDG uptake within the lesion was compared with the uptake in a contralateral

brain area. In all subjects with cerebral infections (toxoplasmosis, tuberculoma), the SUV ratio was significantly ($P < 0.05$) lower than the SUV ratio in patients with lymphoma (range: 0.3-0.7 vs 1.7-3.1), with no overlap of the uptake values. Their findings were confirmed in several subsequent studies.^{35,36} FDG-PET is also useful to demonstrate a response to chemotherapy in lymphoma patients very early after the initiation of therapy.

It is sometimes difficult to distinguish between PCNSL and glioblastoma multiforme (GBM). A study was undertaken to investigate whether the addition of FDG-PET and apparent diffusion coefficients to conventional MRI improves diagnostic accuracy for distinguishing between PCNSL and GBM with similar MRI findings.³¹ Conventional- and diffusion-weighted MRI and FDG-PET scans of 21 patients with histologically confirmed brain tumors exhibiting similar MRI findings (PCNSL, $n = 14$; GBM, $n = 7$) were performed. The authors found that the addition of apparent diffusion coefficient values to conventional MRI failed to improve the differentiation between PCNSL and GBM. Maximum SUV (SUV-max) was higher (16.76 ± 7.19) for PCNSL and less (8.24 ± 3.05) for GBM. The mean SUVmax of PCNSL was significantly higher than that of GBM.

Another recent study that was aimed to determine whether FDG-PET can be used to differentiate among common enhancing brain tumors such as lymphoma, HGG, and metastatic brain tumor³² evaluated 34 patients with an enhancing brain tumor on MRI, including 7 lymphomas, 9 HGG, and 18 metastatic tumors. All patients also underwent FDG-PET. For PET image analysis, regions of interest were placed over the tumor (T), contralateral cortex (C), and WM. Average and maximum pixel values were determined at each site. On the basis of these measurements, average and maximum standard uptake values (SUVavg and SUVmax) were calculated, along with activity ratios (T/Cavg, T/WMax, T/WMax, and T/Cmax), and comparisons among lesions were then made. All parameters were significantly higher for lymphoma than for other tumors ($P < 0.01$). HGG showed significantly higher SUVavg and SUVmax than metastatic tumors ($P < 0.05$). Other parameters did not differ between lesion types. SUVmax was the most accurate parameter for distinguishing lymphomas. Using an SUVmax of 15.0 as a cutoff for diagnosing CNS lymphoma, only 1 HGG was found as false positive (SUVmax: 18.8). The authors conclude that FDG-PET may be useful for differentiating common enhancing malignant brain tumors, particularly lymphoma versus HGG and metastatic tumor.

Therapy Response Assessment

FDG-PET imaging has been shown to be of value in prediction of tumor metabolic response to temozolomide (TMZ) versus TMZ plus radiotherapy in recurrent HGG.³⁷ Therefore, monitoring of therapeutic response by PET imaging is now used to provide an early assessment of therapy efficacy and aid oncologists to optimize therapeutic management of brain tumors.

Another new study in therapy response assessment in GBM using an mammalian target of rapamycin (mTOR) inhibitor was performed by Sarkaria et al.³⁸ The mTOR functions within the PI3K/Akt signaling pathway as a critical modulator of cell survival. On the basis of promising preclinical data, the safety and tolerability of therapy with the mTOR inhibitor everolimus in combination with RT and TMZ was evaluated in a phase I study. The study concluded that changes in tumor metabolism could be detected by FDG-PET in a subset of patients within days of initiating everolimus therapy.

Amino Acids (PET and Single-Photon Emission Computed Tomography)

Besides FDG, radiolabeled amino acids are the most commonly used PET tracers for brain tumors. An advantage of using radiolabeled amino acids over FDG is the relatively low

uptake of amino acids by normal brain tissue. Therefore, cerebral gliomas can be distinguished from the surrounding normal tissue with higher contrast compared with FDG. Many natural amino acids and their synthetic analogs have been labeled and explored as tumor imaging agents.³⁹ Most PET studies of cerebral gliomas have been performed with the amino acid [^{11}C]methyl-L-methionine (^{11}C -MET),⁴⁰ although the short half-life of ^{11}C (20 minutes) limits the use of this tracer to the few PET centers that are equipped with an in-house cyclotron facility. The increasing use of ^{18}F -labeled amino acids (half-life: 109 minutes), such as O-(2- ^{18}F -fluoroethyl)-L-tyrosine (^{18}F -FET) will probably replace ^{11}C -MET in the future.⁴¹ Furthermore, single-photon emission computed tomography (SPECT) has been applied using radioiodinated amino acids such as L-3[^{123}I]iodo- α -methyl tyrosine (IMT) or p-[^{123}I]iodo-L-phenylalanine.^{42,43} The results obtained with SPECT using amino acid tracers are, in general, similar to those with PET, but the poorer spatial resolution of SPECT represents a major disadvantage in clinical practice.

As it is beyond the scope of this review to consider all radiolabeled amino acids applied in brain tumors, this chapter is focused on the clinical experiences with ^{11}C -MET, ^{18}F -FET, and ^{123}I -IMT, which are at present the best validated amino acid tracers for PET and SPECT.

The increased uptake of ^{11}C -MET, ^{18}F -FET, and ^{123}I -IMT by cerebral glioma tissue appears to be caused almost entirely by increased transport via specific amino acid transporters, namely amino acid transport system L for large neutral amino acids.^{44,45} ^{11}C -MET also shows some incorporation into protein and participation in other metabolic pathways⁴⁰; however, comparative studies between ^{11}C -MET, ^{18}F -FET, and ^{123}I -IMT have shown that imaging of cerebral gliomas is similar with these amino acids.⁴⁶⁻⁴⁸ Therefore, the participation of ^{11}C -MET in other metabolic pathways than transport appears to be of minor importance, and the clinical results obtained with the different tracers can be considered together. Because large neutral amino acids also enter normal brain tissue, a disruption of the BBB, that is, enhancement of contrast media in CT or MRI scans, is not a prerequisite for intratumoral accumulation of these amino acids. Consequently, uptake of the tracers has been reported in many LGG without BBB leakage.⁴⁹⁻⁵¹ The sensitivity and specificity of PET using ^{11}C -MET and ^{18}F -FET and SPECT using ^{123}I -IMT to differentiate between gliomas and non-neoplastic lesion is in the range of 70%-90%,^{50,52,53} and the possibility of non-specific enhancement in inflammatory cells or reactive glial tissue must be borne in mind. There have been reports of perifocal ^{11}C -MET and ^{18}F -FET uptake around hematomas and areas of ischemia, as well as of rare cases of uptake in or around ring-enhancing lesions like brain abscesses and acute inflammatory demyelination.^{40,54} Therefore, the predictive value is limited, and a histologic evaluation by biopsy remains the gold standard in the majority of unknown space-occupying lesions in the brain.

Imaging of Tumor Extent Biopsy and Treatment Planning

One of the most important aspects in the initial diagnosis of gliomas is the identification of tumor extension and the metabolically most active areas of the tumor. Representative tissue samples are important for histologic tumor diagnosis, prognostication, and treatment planning. The ability of MRI to show the most rapidly proliferating portions of the usually inhomogeneous gliomas is limited, particularly when the tumor does not take up contrast medium at CT or MRI. Multiple studies in which the radiological findings were compared with the histologic findings in tissue samples obtained by biopsy or open surgery have provided evidence that radiolabeled amino acids detect the solid mass of gliomas and metabolically active tumor areas more reliably than either CT or MRI.⁵⁵⁻⁵⁹ This helps to prevent the problem of nondiagnostic biopsies from nonspecifically altered tissue and to plan surgical resection (Fig. 3). A recent study demonstrated that integrating ^{11}C -MET-PET

into the image-guided resection of HGG provided a final target contour different from that obtained with MRI alone in approximately 80% of the procedures.⁶⁰ Complete resection of the tumor area with increased amino acid uptake resulted in significantly longer survival of patients, whereas MRI enhancement on the postoperative scan did not have an impact on survival. Similarly, the amount of residual tracer uptake in ¹²³I-IMT-SPECT and ¹⁸F-FET-PET had a strong prognostic influence.^{61,62} These data indicate that resection of malignant gliomas guided by amino acid PET may increase the amount of anaplastic tissue removed and thus the patient's survival. The improved imaging of glioma tissue using amino acid PET has also attracted interest for RT treatment planning.^{63,64} A number of centers have started to integrate amino acid imaging into CT- and MRI-based radiotherapy planning, particularly when high-precision radiotherapy is to be given, in the setting of dose escalation studies, or for the reirradiation of recurrent tumors.⁶⁵⁻⁶⁹ However, improved outcome of the patients with radiotherapy planning by amino acid imaging compared with conventional therapy planning has not yet been proven.

Grading of Gliomas and Prognosis

Most studies using amino acid imaging have shown that gliomas of different WHO grades overlap in their degree of amino acid uptake; therefore, the tumor grade cannot be reliably predicted with this technique.^{40,51,58,70} However, a more reliable grading appears to be possible with ¹⁸F-FET-PET, as this tracer exhibits differences in the time activity curves of tracer uptake depending on tumor grade.⁷¹ HGG are characterized by an early peak approximately 10-15 minutes after injection followed by a decrease of ¹⁸F-FET uptake, whereas LGG typically exhibit delayed and steadily increasing tracer uptake. Using dynamic ¹⁸F-FET-PET, a differentiation of HGG and LGG has been reported in primary tumors and in recurrent tumors with an accuracy of >90%.⁷²⁻⁷⁵

The prognostic significance of increased amino acid uptake in gliomas is controversial. Some studies seem to show that lower amino acid uptake especially in astrocytic glioma is associated with a better prognosis, but there may be a high uptake in oligodendrogliomas, despite their apparently better prognosis.^{40,75,76} However, there appears to be a consensus concerning the clinical role of amino acid imaging in prognostication for patients with LGG. Significant longer survival has been reported for patients with lower ¹¹C-MET uptake in the tumors compared with those with higher uptake (cutoff of the tumor to brain ratio: 2.1).^{77,78} Furthermore, the patients had a benefit from a surgical procedure only when increased ¹¹C-MET uptake was present.⁷⁷ Using ¹⁸F-FET-PET, the combination with MR morphology has also been found to be a significant prognostic predictor for patients with newly diagnosed LGG.⁴⁹ Baseline ¹⁸F-FET uptake and a circumscribed versus a diffuse growth pattern on MRI were highly significant predictors for patients' course and outcome.

Assessment of Recurrent Tumors

A number of studies have shown that using ¹⁸F-FET-PET and ¹²³I-IMT-SPECT, recurrent tumors can be differentiated from non-neoplastic posttherapeutic changes, with a sensitivity and specificity of approximately 90% (Fig. 4 and 5).^{21,22,79-81} The sensitivity of ¹¹C-MET-PET for tumor recurrence is similar, whereas the specificity appears to be lower and has been reported to be in the range of 60%-80%.^{17,20,40} This observation may be explained by a higher affinity of ¹¹C-MET for macrophages compared with ¹⁸F-FET as demonstrated in animal experiments.^{82,83} Additional use of dynamic ¹⁸F-FET-PET allowed a differentiation of recurrences of HGG and LGG with a sensitivity and specificity of 92%.⁷⁴

Treatment Monitoring

The diagnostic value of MRI and CT concerning changes in tumor size or contrast enhancement in response to therapy is limited because the known reactive transient BBB

alterations with consecutive contrast enhancement may mimic tumor progression. This phenomenon, so-called “pseudoprogression,” is seen in 20%-47% of cases and can lead to an unnecessary overtreatment.⁸⁴ The feasibility and usefulness of ¹¹C-MET and ¹⁸F-FET-PET for therapy assessment and follow-up after surgery, chemotherapy, and radiotherapy have been demonstrated in several studies. The currently available data suggest that a reduction of amino acid uptake by a glioma is a sign of a response to treatment. Recently, a prospective study evaluated the prognostic value of early changes of ¹⁸F-FET uptake after postoperative radiochemotherapy in glioblastomas.⁸⁵ It could be demonstrated that PET responders with a decrease of the tumor/brain ratio of >10% had a significantly longer disease-free survival and overall survival (OS) than patients with stable or increasing tracer uptake after radiochemotherapy in glioblastomas. A reliable monitoring of chemotherapy could also be demonstrated with ¹¹C-MET and ¹⁸F-FET-PET in recurrent glioblastoma during standard chemotherapy with TMZ,^{86,87} as well as in some experimental therapeutic approaches, such as radioimmunotherapy, convection-enhanced delivery of paclitaxel, and chemotherapy with bevacizumab and irinotecan.⁸⁸⁻⁹⁰ The cutoff values of the tumor/brain ratio of IMT, MET, and FET uptake on the different clinical questions in the literature are summarized in Table 2.

Imaging Brain Tumors in Children

The histologic subtypes of brain tumors in children differ considerably from that in adults. Only few mainly retrospective studies have been performed in children with brain tumors. In children, the determination of tumor grade with amino acids seems to be even less reliable than in adults. A broad overlap of amino acid uptake is observed in low-grade and high-grade tumors.⁹¹ Similar to glucose metabolism, amino acid uptake may be high in low-grade tumors such as pilocytic astrocytomas and gangliogliomas; uptake may be relatively low in the highly aggressive medulloblastomas (WHO grade IV), a common diagnosis in infratentorial brain tumors.⁹² The potential of amino acids to determine the site of stereotactic biopsy or for image-guided surgical resection of infiltrative low-grade brain tumors in children has been reported.⁹³ The presence of amino acid uptake after surgery indicates residual tumor in case of ambiguous findings in early postoperative MRI.⁹⁴

3'-Deoxy-3'-[¹⁸F]-Fluoro-(L)-Thymidine (FLT)

The thymidine nucleoside analog, 3'-deoxy-3'-[¹⁸F]-FLT, was developed as a molecular imaging probe to assess cellular proliferation in vivo with PET.^{95,96} After FLT is transported into the cell, it is phosphorylated by thymidine kinase (TK-1) and trapped inside the cell.⁹⁷ TK-1 is a cytosolic enzyme that is expressed during the DNA synthesis stage of the cell cycle. The rate-limiting step in FLT accumulation is phosphorylation by TK-1, causing FLT to accumulate in proportion to TK-1 activity.⁹⁸ Compared with normal proliferating tissue, tumor cells have increased levels of TK-1, resulting in increased FLT uptake.⁹⁵ Phosphorylated FLT appears resistant to degradation, and is suitable for imaging with PET.⁹⁶

The adenosine-5'-triphosphate (ATP) level is important for FLT phosphorylation. ATP initiates a transition from a dimer to tetramer structure of TK-1, which is approximately 20-fold more effective for phosphorylation of FLT. Phosphorylated FLT reflects cell proliferation, if there are no major differences in ATP level. The actual incorporation of FLT into DNA is low; the majority of FLT is trapped inside the cytosol. Phosphorylated FLT strongly correlates with thymidine incorporation into DNA,^{95,96} as has been demonstrated in various tumor models, including 2 glioma cell lines.⁹⁹ FLT as a biomarker for cell proliferation has tremendous potential for monitoring and predicting response to therapy.

The kinetic model for ^{11}C -labeled thymidine has been published by the Seattle group.^{100,101} The half-life of ^{18}F makes the analog FLT suitable for tracer kinetic analysis. The FLT model has been described extensively by Shields,^{96,97} and studied mathematically by Muzi et al.^{102,103} An adaptation to malignant brain tumors has been published by the University of California, Los Angeles.¹⁰⁴ The Cologne group has reported on the image-derived input function.¹⁰⁵ For a discussion of “true tracers vs analogs” and the effects of ^{18}F substitution in the natural substrate, the reader is referred to the study by Krohn et al.¹⁰⁶ The fidelity with which analog tracers mimic the authentic substrate is critically evaluated for FLT in this article.

Diagnosis and Grading of Gliomas

The clinical application of FLT in brain gliomas has been reported by Chen et al.¹⁰⁷ FLT uptake in brain gliomas was compared with FDG in the same patient on consecutive days. Uptake was quantified by the SUV and the tumor-to-normal (T/N) ratio. The FLT uptake curve shows fast tumor accumulation, reaching a maximum around 5-10 minutes, and remaining high thereafter; there is a mild decrease over time.

High-grade tumors (WHO grade III and IV) are all visualized, whereas low-grade tumors have no appreciable uptake. The absolute FLT uptake is low (SUVmax: 1.3), but the contrast is higher for FLT than FDG with a T/N ratio of 3.8 versus 1.5, respectively.

A significant correlation was found between the SUV of FLT and the Ki-67 index ($r = 0.84$; $P < 0.0001$). The authors concluded that a half-hour PET scan is sufficient to image high-grade brain tumors. There is a significant correlation between FLT uptake and immunostaining with Ki-67, making FLT a surrogate marker of proliferation in HGG.

Jacobs et al.¹⁰⁸ investigated methyl- ^{11}C -l-methionine (^{11}C -MET) and FLT as markers of transport and proliferation in brain tumors. The sensitivity for tumor detection was lower for FLT than ^{11}C -MET, 78% versus 91%, respectively. T/N ratios of FLT were higher than that for ^{11}C -MET, whereas SUV for FLT was significantly lower than that for ^{11}C -MET, 1.3 versus 3.1, respectively. Kinetic modeling revealed an elevated transport and increased influx of FLT. The authors concluded that FLT is promising for characterization of primary CNS tumors, and helps differentiating LGG from HGG. PET using FLT and ^{11}C -MET as well as gadolinium-enhanced MRI yield complementary information, and permit early evaluation of treatment effects, especially in HGG.

The relationship between in vivo– derived kinetic parameters and proliferation rate was investigated by Ullrich et al.¹⁰⁹ in patients with newly diagnosed HGG. They found a significant correlation between the influx rate Ki and proliferation index Ki-67 ($r = 0.79$; $P = 0.004$). The phosphorylation rate k_3 had a significant correlation with Ki-67, whereas the transport rate K_1 did not. No significant correlation was found between SUV of FLT and Ki-67 by immunostaining. They concluded that uptake ratios alone failed, and that kinetic analysis was essential for in vivo assessment of tumor proliferation in HGG.

Tripathi et al.¹¹⁰ directly compared the performance of ^{18}F -fluorodopa (L-3,4-dihydroxyphenylalanine [FDOPA]), ^{18}F -FDG, and ^{18}F -18 FLT in evaluating primary and recurrent LGG. PET/CT was used as the imaging modality. On average, the SUVmax was 5.75 ± 4.9 for ^{18}F -FDOPA, 1.8 ± 0.9 for FLT, and 8.5 ± 4.4 for FDG (8.5 ± 4.4). This shows that FLT uptake is generally low in gliomas. The T/N ratios were 2.3 ± 0.5 for ^{18}F -FDOPA, 1.8 ± 0.9 for FLT, and 1.0 ± 0.6 for FDG. The authors concluded that ^{18}F -FDOPA is superior to FLT and FDG for LGG. FLT should not be considered for evaluation of recurrent LGG.

Finally, National Cancer Institute sponsored trial with 4 participating centers enrolled 19 patients: 15 with tumor recurrence and 4 with radionecrosis.¹¹¹ The safety and preliminary efficacy of FLT as a biomarker of proliferation was the primary purpose of this trial. FLT influx rate K_i and phosphorylation rate k_3 was able to separate recurrence from radionecrosis, whereas SUV was not. They concluded that influx rate is necessary for distinguishing recurrence from radionecrosis because visual or uptake analysis could not. Thus, dynamic PET imaging is needed to estimate the influx rate.

From the published evidence, it appears that FLT functions as an in vivo biomarker of cellular proliferation, particularly for HGG. Low-grade tumors tend to have insufficient uptake to reach a sensitivity for detection that is clinically useful. Quantitative analysis provides some improvement, but amino acid tracers perform better than FLT for detecting gliomas across grades. Tumor-to-background or tumor-to-normal uptake ratios are better for FLT than FDG, which is the radiopharmaceutical that suffers from the high uptake in normal gray matter. Malignant grade and proliferation activity of primary brain tumors can be evaluated by FLT, but benign lesions that disrupt the BBB cannot be distinguished from malignant tumors.¹¹²

Therapy Monitoring

Several investigators have reported promising results for therapy monitoring and disease management with FLT (Fig. 6). In the 2005 study by Chen et al,¹⁰⁷ the radiopharmaceuticals FDG and FLT were evaluated in patients with malignant brain tumors. For HGG, FLT turned out to be a prognostic marker for patient survival and, in this respect, FLT was superior to FDG.

In a pilot study reported in the Journal of Clinical Oncology, Chen et al¹¹³ underscored the difficulty in assessing the early effects of therapy, as no reliable predictors have been established. In their prospective study, 19 patients were enrolled with recurrent malignant gliomas, who were treated with bevacizumab and irinotecan. FLT uptake was investigated at different time-points. An SUV decrease of 25% was defined as a metabolic response. The results were 50-50; there were 9 responders and 10 nonresponders. Responders survived 3 times as long as nonresponders (10.8 vs 3.4 months). PET using FLT was a better predictor of OS than MRI. Chen et al¹⁰⁷ concluded that FLT, as an in vivo imaging biomarker, is predictive of OS during treatment of recurrent gliomas.

In an extension of this pilot study, it was found that changes in FLT uptake are important in determining metabolic response, not the absolute value. Schiepers et al¹⁰⁴ demonstrated that kinetic modeling applied early during therapy, provided parameters that accurately classified patients in 3 survival groups: group 1, <6 months; group 2, from 6 to 12 months; and group 3, >1 year. There was excellent correlation between influx rate K_i and SUV75% (comprising all voxels in the tumor between 75% and 100% of the maximum). An early drop in SUV during treatment that remains stable thereafter is a predictor of long-term survival. An SUV returning to baseline levels after the initial drop is a predictor of short-term survival.

In that study, the kinetics of FLT in malignant brain tumors were compared with clinical outcome. The analysis was completely image based and virtually operator independent using iterative reconstruction, factor analysis, masking with isocontours, and compartmental modeling. The enrolled patients could be subdivided into 2 categories based on pathology and clinical follow-up: lesions that were tumor predominant versus lesions that were treatment-change predominant. These 2 categories revealed different kinetics. Although diffusion across the BBB was quite similar, phosphorylation rate k_3 and phosphorylated fraction $k_3/(k_2 + k_3)$ were significantly different ($P < 0.001$). Other investigators have reported similar results,^{96,103,114} demonstrating that transport into cells is rapid and

primarily determined by perfusion and BBB damage, whereas the phosphorylation reaction (k_3) is the rate-limiting step, determining FLT retention in tissue.¹⁰² These FLT results are similar to those obtained with ^{11}C -thymidine in malignant brain tumors.¹⁰¹

In an attempt to determine whether changes in FLT kinetics, taken early after the start of therapy, could predict progression-free survival and OS, Wardak et al¹¹⁵ studied patients with recurrent malignant glioma undergoing treatment with bevacizumab and irinotecan. They established kinetic parameter changes that, when incorporated into a linear discriminant function, could accurately differentiate short-term from long-term survivors. As expected, this set of parameter changes contains more predictive information than FLT uptake changes alone. Kinetic modeling provides such a set in a straightforward manner. Biological and functional information about the patient's tumor should be collected fully to determine (or individualize) treatment regimen and predict response to therapy correctly.

Wardak et al¹¹⁵ showed that discriminant analysis using 4 well-defined variables, was able to stratify clinical outcome in recurrent brain tumor. Patients were classified into their OS group with 100% accuracy. Relative changes in FLT kinetic parameters were of paramount importance to group classification, and not their absolute values.

How do we put the aforementioned observations and evidence gathered during treatment into perspective? A biological explanation for an adequate treatment response would speculate along (1) normalization of the neovascularization by bevacizumab and (2) permeability changes by chemotherapy. A responder to antivasculature endothelial growth factor therapy such as bevacizumab is expected to show a significant decrease in tumor distribution volume by inhibiting growth of new vessels.^{115,116} Transient normalization of tumor vasculature enhances delivery of cytotoxic agents, increasing the effectiveness of therapy. TK-1 is upregulated in response to DNA damage from genotoxic insults. Chemotherapy agents such as irinotecan are known to induce DNA breaks, causing TK-1 upregulation and increased phosphorylation of FLT. Permeability changes directly influence access of nutrients, oxygen, and toxins to the tumor and tissues. Aggressive tumors have a "more porous BBB" than low-grade tumors, allowing fast entrance into tumor cells. This explains the high transport rate (K_1) at baseline in HGG. Restoration of the permeability to "normal" is expected to decrease the transport rate, which was observed by investigators.^{103,108,109,115} Self-evidently, it is assumed that transport rate changes, as measured by FLT, are similar to those of the therapeutic agents.

The discriminant analysis of Wardak et al¹¹⁵ used 3 time-points, and can be performed within the first 6 weeks of treatment, which is usually many months before the final outcome is known. This offers another surrogate end point for trials. Kinetic modeling extracts molecular and biochemical information inherent to the tumor, which can be used to reliably distinguish patients who will respond favorably to therapy (long-term survivors) from those who will not (short-term survivors). In this way, discriminant analysis appears a powerful tool for evaluating the efficacy of a therapeutic regimen. Discriminant analysis can be expanded to a comprehensive statistical model that uses relative changes in FLT kinetics as input, and a continuous variable (numerical estimate of OS) as output, instead of a categorical variable (short- vs long-term survivor). Multimodality imaging parameters and tumor biology parameters can be incorporated into this statistical model, promising a great future for modeling prediction and prognosis in neuro-oncology.

Other Radiopharmaceuticals

Several other single- and coincidence-photon– emitting radiopharmaceuticals have been used for diagnosing, grading, and monitoring brain tumors.

Vascularization, Hypoxia, and Ion Transport

The use of perfusion agents for diagnosis of brain tumors is based on early experience with ^{99m}Tc -hexametazime (Hm-PAO) and ^{99m}Tc -ethylcysteinate dimer (ECD), but impact has been limited by variability of results and poor relation to tumor grade.¹¹⁷ Recently, the issue of tumor vascularization and perfusion has found renewed interest by promising results of antiangiogenic drugs in glioblastoma and the advent of functional MRI techniques to measure blood volume and perfusion.¹¹⁸

The classic example of a suitable and effective radiopharmaceutical for brain tumor imaging was 201 TL thallous chloride. In a series of 90 patients¹¹⁹ studied with SPECT, the sensitivity for supratentorial brain tumors was 72% and the specificity was 81%. Findings have been confirmed in subsequent studies,¹²⁰ but limited tracer availability and low spatial resolution have prevented more extensive clinical use.

The experience with ^{99m}Tc sestamibi was reported by Le Jeune et al¹²¹ in a study of 81 patients suspected of having recurrent glioma who underwent 201 SPECT studies, which were evaluated retrospectively. The sensitivity for detection of tumor recurrence was 90%, the specificity was 91.5%, and the accuracy was 90.5%, but the difference between low-grade and high-grade tumors was not significant. An overview on related agents has been provided by Alexiou et al.¹²²

Malignant gliomas, in particular, glioblastoma often include hypoxic tissue, which is believed to contribute to RT resistance. Imaging of hypoxic tissue can be provided by ^{18}F -fluoromisonidazole¹²³ and related tracers.^{124,125} Several recent studies indicate that this may provide a clinically useful tool for detection of hypoxia¹²⁶ and diagnosis of glioblastoma,¹²⁷ while quantitation of hypoxia¹²⁸ and the relation of tracer uptake with BBB damage and contrast enhancement needs further investigation.^{129,130}

Hypoxia is also among the factors that drive neovascularization in tumors, which can be imaged with tracers binding to integrins, such as RGD peptides,¹³¹ which may also hold a potential for radioimmunotherapy.¹³²

Membrane and Receptor Agents

Choline is a marker of phospholipid synthesis, which is required for the production of phosphatidyl choline, a component of the cell membrane. The uptake of ^{11}C -choline by glioblastoma cells was reported to be 3-4 times higher than normal brain, whereas uptake in LGG appears to be low, comparable with non-neoplastic lesions.^{133,134} Compared with ^{11}C -METHionine uptake appears to be less influenced by glioma subtype (astrocytoma vs oligodendroglioma).¹³⁵ In a large clinical series, diagnostic performance appeared to be superior to FDG.¹³⁶ The tracer also appears to be useful for imaging of brain metastasis,¹³⁷ where T/N ratios were, on average, higher for ^{11}C -choline (6.6) compared with ^{11}C -METHionine (1.5). Thus, further thorough clinical evaluation of ^{11}C -choline and its analog ^{18}F -fluorocholine,¹³⁸ especially in malignant gliomas and in comparison with MR spectroscopy of choline.¹³⁹

Agents binding to somatostatin receptors, such as ^{68}Ga -(DOTA(0)-Phe(1)-Tyr(3))octreotid-DOTATOC, are useful to image pituitary adenomas (which are not covered in this review) and meningiomas.^{140,141} Their potential for planning of radiotherapy in patients who cannot be cured by surgical resection has been demonstrated.¹⁴²

Summary and Perspectives

A broad range of tracers has been evaluated for clinical use in the diagnosis of brain tumors with PET or SPECT. The most widely available tracer, FDG, is a predictor of prognosis and is particularly useful for distinction of brain lymphoma from nonmalignant lesions. Image fusion with structural images (usually contrast-enhanced MRI) is increasingly becoming a standard technique. It is of particular value when reading FDG scans, which otherwise often provide little contrast between tumor and the inhomogeneous background from normal brain tissue. Amino acid tracers, including ^{11}C -METHionine, ^{18}F -FET, and ^{18}F -FDOPA, provide better sensitivity and distinction from normal tissue for gliomas, including most low-grade tumors. They appear to be particularly useful for detection of recurrent tumors, but their availability is limited as yet and they provide a less clear distinction between low-grade and high-grade tumors than FDG.

Although FDG and most amino acids are transported across the intact BBB by transporter enzymes, the uptake of most other tracers in brain tumors depends on the disruption of the BBB, similar to contrast enhancement on CT and MRI. Thus, they often provide a superior contrast between malignant lesions with BBB disruption and normal brain, but will not depict low-grade lesions lacking BBB disruption. Recently, the use of ^{18}F -FLT has been investigated among this type of tracers because its uptake also reflects tumor proliferation rates, which are of particular interest in the monitoring of chemo- and radiotherapy.

The distinction between RT-induced necrosis and recurrent tumor is a persistent challenge in the management of brain tumors. All tracers—FDG, amino acids, and FLT—have demonstrated potential to assist with this distinction, but the results from various studies show considerable variation in sensitivity and specificity. Thus, larger systematic and controlled clinical studies in comparison with state-of-the-art magnetic resonance techniques are required for definitive assessment.

Further research using PET and SPECT tracers is also being conducted in the areas of vascular proliferation, hypoxia, membrane synthesis, and receptor binding. PET imaging techniques are also increasingly being used to improve the accuracy of histologic diagnosis by targeted biopsies and for RT therapy planning. It is expected that individualized patient management based on advanced PET and SPECT techniques will ultimately lead to better therapeutic outcomes in patients with gliomas and other malignant brain tumors, which still carry a rather dismal prognosis.

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Figure 1.

Left: Positron emission tomography (PET) scan with abnormality involving the right frontal lobe. Middle: Contrast magnetic resonance imaging (MRI) scan shows enhancement in the right frontal lobe. Right: There is a focal area of increased fluorodeoxyglucose (FDG) uptake involving the right frontal lobe consistent with a high-grade transformation and recurrence of tumor in the right frontal lobe 8 years after initial diagnosis and therapy. (Color version of figure is available online.)

Figure 2.

Anaplastic astrocytoma, World Health Organization (WHO) grade III. (A) Multiple voxel spectra coregistered with postcontrast T1-weighted MRI. (B) Map of Cho/Cr demonstrates a focus of signal intensity in the right frontal lobe. Magnetic resonance spectroscopic imaging (MRSI) signal intensity is presented on a rainbow color scale where blue green is normal background and bright red corresponds to greatly elevated signal intensity. (C) Spectral analysis of the voxel demonstrating maximal Cho/Cr ratio. (D) T1-weighted MRI (postcontrast) demonstrating enhancing lesion in the right frontal lobe. (E) FDG-PET scan shows a focus of increased tracer activity greater than white matter in the right frontal lobe. (F) FDG-PET image coregistered with postcontrast T1-weighted MRI Reprinted with permission from Imani et al.²⁴

Figure 3. Oligoastrocytoma, WHO grade II: T1-weighted MRI after application of Gd-DTPA (A) shows no contrast enhancement. T2-weighted MRI scan (B) shows widespread abnormalities. (C) O-(2-¹⁸F-fluoroethyl)-L-tyrosine (¹⁸FFET-PET) identifies metabolically active areas within the tumor and indicates an optimal site for biopsy.

Figure 4. Inhomogeneous anaplastic astrocytoma, WHO grade III: T1-weighted MRI after application of Gd-DTPA (A) shows no contrast enhancement. T2-weighted MRI scan (B) shows widespread abnormalities. (C) ^{18}F -FET-PET identifies a hot spot in the posterior part that cannot be identified on MRI. Biopsy in this area yielded an anaplastic astrocytoma, WHO grade III.

Figure 5. Glioblastoma (WHO grade IV) pretreated by surgery and radiochemotherapy. T1-weighted MRI after application of Gd-DTPA (A) and T2-weighted MRI (B) are ambiguous. (C) ^{18}F -FET PET identifies pathologic tracer accumulation, which was confirmed as tumor recurrence. (Color version of figure is available online.)

Figure 6.

Composite images of frames summed between 50 and 60 minutes. The patient was a 37-year-old woman with a glioblastoma multiforme in the left insular and temporal opercular regions, who was treated with irinotecan and bevacizumab in 2-week cycles. Representative transaxial slices of the tumor are shown. All images are scaled to the same maximum concentration in Bq/mL. The initial ^{18}F -FLT uptake is high at baseline (left), drops after 2 weeks of therapy (middle), and remains similar after 6 weeks (right); the respective standardized uptake values (SUV75%) were 1.154, 1.075, and 1.076. Progression-free survival and overall survival were found to be 304 days and 460 days, respectively. (Color version of figure is available online.)

Table 1

Discrimination Between Tumor and Necrosis

Tracer	n	Sensitivity	Specificity	Lesion Type	Reference
FDG	47	75% (21/28)	81% (13/16)	Malignant tumor	9
FDG	15	43% (6/14)	100% (1/1)	Glioma	10
FDG	84	73%	56%	Malignant tumor	11
FDG	38	88% (15/17)	81% (17/21)	Glioma	12
FDG	21	81% (13/16)	40% (2/5)	Tumor	13
FDG	9	80% (4/5)	100% (4/4)	Tumor ^a	14
FDG	21	64% (9/14)	71% (5/7)	Metastases ^a	15
FDG	54	83% (5/6)	96% (46/48)	Metastases	16
FDG	30	95%	50%	Glioma	17
FDG ^b	32	95%	96%	Metastases	6
MET	30	75%	70%	Glioma	17
MET	12	100% (5/5)	86% (6/7)	Glioma ^a	18
MET	56	79%	75%	Metastases ^a	19
MET	32	75%	75%	Glioma ^a	19
MET	11	100% (6/6)	60% (3/5)	Glioma ^a	20
FET	53	100% (42/42)	100% (11/11)	Glioma	21
IMT	31	78% (18/23)	100% (8/8)	Glioma	22

FDG, fluorodeoxyglucose; PET, positron emission tomography; MET, methyl-L-methionine; FET, O-(2-¹⁸F-fluoroethyl)-L-tyrosine; IMT, L-3-[¹²³I]iodo-α-methyl tyrosine.

^aWith histopathological verification in all tumor cases.

^bDual-phase FDG-PET.

Table 2

Quantitative Thresholds for Imaging Gliomas With Amino Acid Tracers

Tracer	Clinical Question	Cutoff	Method	Reference
IMT	Glioma vs non-neoplastic lesion	1.78	Tumor/brain ratio ^a	52
	Recurrent glioma vs radionecrosis	1.8	Tumor/brain ratio ^a	22
MET	Glioma vs non-neoplastic lesion	1.47	Mean tumor/brain ratio	50
	Glioma vs peritumoral tissue	1.3	Mean tumor/brain ratio	56
	Recurrent glioma vs radionecrosis	2.2	Maximum tumor/brain ratio	17
FET	Glioma vs peritumoral tissue	1.6	Mean tumor/brain ratio	58
	Recurrent glioma vs radionecrosis	2.0	Maximum tumor/brain ratio	21
	Therapy assessment	Decrease >10%	Maximum tumor/brain ratio	85

^a 90% isocontours of tumor maximum $\approx T_{\max}/B$.