Molecular imaging of gliomas with PET: Opportunities and limitations

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Neuroimaging enables the noninvasive evaluation of glioma and is considered to be one of the key factors for individualized therapy and patient management, since accurate diagnosis and demarcation of viable tumor tissue is required for treatment planning as well as assessment of treatment response. Conventional imaging techniques like MRI and CT reveal morphological information but are of limited value for the assessment of more specific and reproducible information about biology and activity of the tumor. Molecular imaging with PET is increasingly implemented in neuro-oncology, since it provides additional metabolic information of the tumor, both for patient management as well as for evaluation of newly developed therapeutics. Different molecular processes have been proposed to be useful, like glucose consumption, expression of amino acid transporters, proliferation rate, membrane biosynthesis, and hypoxia. Thus, PET might help neuro-oncologists gain further insights into tumor biology by “true molecular imaging” as well as understand treatment-related phenomena.

This review describes the method of PET acquisition as well as the tracers used to image biological processes in gliomas. Furthermore, it considers the clinical impact of PET on the use of currently available radiotracers, which were shown to be potentially valuable for discrimination between neoplastic and nonneoplastic tissue, as well as on tumor grading, determination of treatment response, and providing an outlook toward further developments.

Keywords: glioma, molecular imaging, PET.

Advances in neurosurgical techniques, radiotherapy planning, and novel chemotherapeutics for glioma treatment go hand in hand with an increasing demand for noninvasive, quantitative imaging techniques. Whereas structural imaging such as conventional MRI provides information on the size and localization of tumors and delineates secondary phenomena such as mass effect, edema, hemorrhage, necrosis, and signs of increased intracranial pressure, PET is expected to characterize the tumor on a metabolic and molecular level; these new imaging data might improve noninvasive tumor evaluation, promote the development and application of tailored treatment concepts, and facilitate prognostic assessment before and after treatment. Since its advent in 1970, PET has gained an additional value in evaluation of patients with gliomas, which represent the most frequent primary brain tumors, being most difficult to treat. Depending on the radiotracer used, various molecular processes can be visualized; the vast majority of these agents are related to increased intratumoral cell proliferation. However, the increasing variety of radiotracers implemented for glioma evaluation and the lack of standardized analysis as well as mostly retrospective reports based on single-institution low case numbers constrain the potential informative value of PET-based investigations. This review attempts to give an overview of the radiotracers currently utilized in view of their applicability for diagnostic purposes, treatment planning, and therapy monitoring, as well as to provide an outlook for the future development of PET imaging in glioma.

Molecular Imaging with PET

Principles of PET

PET imaging allows highly sensitive measurements (in the picomolar range) of biochemically active molecules labeled with short-lived positron-emitting radionuclides (radiotracers). Positrons emitted from the nucleus of radioisotopes subsequently annihilate on contact with electrons after traveling a short distance within the tissue (mean range, 0.2 up to 1.5 mm, depending on...
the mean energy of the positron). Each annihilation results in a pair of 511 keV photons traveling in opposite directions that can be counted by detector units, which commonly are arranged in a ring surrounding the subject. When 2 opposing detectors simultaneously register a pair of photons (time window, 15–20 ns), the annihilation event is counted and assigned to a line of response joining the 2 relevant detectors. Accordingly, a PET scan consists, in essence, of the acquisition of a large number of lines of response, which are used to reconstruct 3D images by means of standard tomographic techniques that also include scatter correction, random correction, and the effects of attenuation in order to obtain an accurate quantification. The physics of coincidence detection enable high spatial resolution and high sensitivity, which are necessary to perform dynamic data acquisition. The spatial resolution currently is about 1.5 mm at its best.

Basically, different positron-emitting isotopes can potentially be used, which are produced in a cyclotron (e.g., carbon-11 [11C], nitrogen-13 [13N], oxygen-15 [15O], fluorine-18 [18F]) or with a generator (e.g., gallium-68 [68Ga]). While isotopes with very short half-lives (15O: 2 min; 13N: 10 min; 11C: 20 min) permit multiple studies in a single setting, their use is restricted to centers with an adjacent cyclotron unit, and they therefore can hardly be implemented for clinical practice. The use of 18F (half-life, 110 min) enables more complicated and time-consuming labeling processes and permits the commercial distribution of radiotracers by PET radiopharmacies at offsite locations.

Useful radiotracers should have unaltered biological properties when compared with the unlabeled molecule, should not be easily dissociable from the radionuclide, and should ideally come with low unspecific uptake in the background or blood in order to obtain higher-contrast images. Several hundred million cells in relatively close proximity must accumulate the radiotracer to visualize them against the background.

Radiotracers are typically injected intravenously. The tracer uptake into targeted structures within the brain depends on different parameters, like regional perfusion, individual pharmacokinetic and pharmacodynamic properties, and permeability of the blood-brain barrier.

**PET Data Acquisition and Analysis**

Different strategies are necessary for PET data acquisition (simple static scan for the assessment of the tracer uptake in steady-state versus dynamic image acquisition in order to obtain the molecular information as a function of time), leading to more sophisticated PET data analysis. Ideally, this analysis should be performed after co-registration with high-contrast anatomical images (e.g., MRI) in order to combine the functional and morphological information, a procedure that can be done easily also in clinical practice.

Assessment of the maximal or mean standardized uptake value (SUV) is the most widely used procedure for a semiquantitative measurement of the radioactivity in the target. It can be calculated as a ratio of tissue radioactivity concentration at time t (C(t)) and injected dose (D) at the time of injection divided by patient’s body weight. This can be performed voxelwise as well as by means of regions or volumes of interest. Additionally, these values have to be corrected for the unspecific uptake in the background.

Dynamic PET data acquisition obtains time activity courses to get additional information about uptake, metabolism, and wash out of the tracer. This procedure is necessary for radiotracers with more complex pharmacokinetic properties that do not reach steady state after uptake into the cells or by irreversible binding to a target structure. Time activity courses are assessed in predefined regions (e.g., in the tumor) or by each pixel of the image sequence. They can be used to extract quantitative parameters through their mathematical description by means of kinetic or compartmental models, which in some cases do necessitate blood samples for the correction of tracer metabolites. However, the latter can hardly be performed in clinical routine.

**Available PET Radiopharmaceuticals for Glioma Imaging**

For imaging of gliomas, several radiotracers have been suggested as useful for different purposes, like diagnosis, grading, assessment of recurrence, and treatment planning and monitoring. In the following, the most important or promising approaches are presented.

**Glucose metabolism**—The glucose analogue 2-[18F] fluoro-2-deoxy-D-glucose ([18F]FDG) is the most frequently used radiotracer for PET to measure the local metabolic rate of glucose that represents a common pathway of neurochemical activity in the brain. Intravenously injected [18F]FDG is rapidly cleared from vascular to interstitial space and is afterward actively transported through cellular membranes into the cells by glucose transporter proteins (GLUTs). According to the first step of the glycolysis, [18F]FDG is phosphorylated by the enzyme hexokinase to [18F]FDG-6-phosphate, which cannot further act as a surrogate for the glycolytic pathway. This results in metabolic trapping in the cells. Due to the pharmacokinetic properties (high early uptake and trapping in the cell within the first 10 minutes and quite fast blood clearance and renal elimination) steady-state images can be obtained 30 min postinjection (p.i.). The physiological brain glucose metabolism and consequently the [18F]FDG brain uptake is very high, because glucose provides approximately 95% of the required ATP and is also tightly connected to neuronal activity.

[18F]FDG PET was proposed to be useful for imaging gliomas because of an increased glucose metabolism in high-grade glioma as well as a positive correlation between the glycolysis rate and malignancy. The increased uptake was suggested to be related to changes in transport rate via modulation of GLUTs. However, the diagnostic accuracy of [18F]FDG PET is
hampered by the high physiologic glucose metabolism in different brain areas, such as the cerebral cortex, the basal ganglia, and the thalamus, which significantly limits the sensitivity for detection as well as the specificity for delineation of adjacent glioma tissue. The demarcation of glioma is most notably impeded in low-grade gliomas, which show mostly only modest uptake, similar to that of white matter and decreased uptake when compared with gray matter.\(^2\)\(^5\) Low contrast to background can also be found in some high-grade gliomas, where \(^{[18F]}\)FDG uptake was found to be similar to or less than in the cerebral cortex.\(^10\) Finally, \(^{[18F]}\)FDG is known to accumulate in macrophages and inflammatory tissue, making distinction between glioma and acute or chronic inflammatory process often difficult.

**Amino acid transport and protein synthesis**—Radiolabeled amino acids were introduced in 1982 as suitable PET tracers in brain tumors.\(^11\) The use of amino acids is based upon an increased amino acid utilization, which is known to play a key role in cell proliferation, as well as extracellular matrix growth production in glioma.\(^12\) Amino acid transport as well as protein synthesis were both demonstrated to be enhanced in most gliomas and can potentially be used as targets for imaging.\(^13\) For this purpose, a variety of radiolabeled amino acids, like \([^{11C}]\)methionine (\([^{11C}]\)MET),\(^14\) and aromatic amino acid analogues, like \([^{18F}]\)fluorotyrosine (\([^{18F}]\)TYR),\(^15\) \([^{18F}]\)fluoroethyltyrosine (\([^{18F}]\)FET),\(^16,17\) \([^{18F}]\)fluoromethyltyrosine (\([^{18F}]\)FMT),\(^13\) and \([^{18F}]\)fluorodopa (\([^{18F}]\)DOPA),\(^18\) were proposed. Comparable uptake in cerebral gliomas, at least for the most widely used radiotracers like \([^{11C}]\)MET and \([^{18F}]\)FET,\(^19,20\) has been shown. The artificial analogues of the amino acids, in contrast to the acids themselves, are not incorporated into proteins.\(^21\) Active amino acid transport in tumor cells is supposed to be one of the rate-limiting factors of amino acid imaging\(^22\) and has been shown to be upregulated in the cell membranes of tumor cells, especially when their growth conditions become adverse, regardless of the phase of the cell cycle.\(^23\) However, possible bias may be caused by unspecified increase of amino acid uptake due to damage of the blood-brain barrier in glioma.\(^24\) High-contrast images can be acquired due to high amino acid uptake in both low- and high-grade glioma and low uptake in normal brain tissue. Using the conventional uptake ratio-based approach (e.g., SUV\(_{\text{max}}\)/background, where SUV = standard uptake value) does not provide a reliable grading on an individual level, because of quite high interindividual variability in amino acid uptake in gliomas, which can be attributed mainly to differences in amino acid transport characteristics.\(^14,25\) However, recently published data have shown that the use of dynamic analysis of \([^{18F}]\)FET uptake (zero to 40–50 min) to obtain the time course of the radioactivity does allow a differentiation between low- and high-grade gliomas with high diagnostic power because of different FET kinetic uptake behavior.\(^26\) Plotting analysis of uptake activity over time shows a slight increase in low-grade gliomas, whereas high-grade tumors present with an early peak followed by a decrease (Fig. 1).

**Proliferation rate**—Increased cell proliferation and DNA replication is a characteristic of malignant transformation. Therefore, the assessment of cellular proliferation was suggested to be useful for therapy guidance as well as for early evaluation of treatment response, because a decrease in cellular proliferation precedes morphological changes.\(^27\) In order to image the proliferation rate by means of PET, radiolabeled nucleosides like the thymidine analogue \([^{18F}]\)fluorothymidine (\([^{18F}]\)FLT)\(^28\) have been developed and validated. Thymidine is rapidly transported into the cells by means of a nucleoside transporter and can be phosphorylated by the enzyme thymidine kinase (TK)-1 to thymidine nucleotides, which are among the molecular building blocks of DNA but not of RNA.\(^28\) TK-1 is highly expressed during DNA synthesis of proliferating cells\(^29\) and leads to intracellular trapping of the radiotracer.\(^29\) Therefore, the retention of \([^{18F}]\)FLT within the cell provides a measure of cellular TK-1 activity.\(^28\) \([^{18F}]\)FLT was thought to be a helpful predictor of tumor progression and useful for the monitoring of treatment response.\(^30,31\) In gliomas, elevated \([^{18F}]\)FET uptake was associated with increased expression of antigen Ki-67, an index of mitotic activity.\(^30\) In addition, the use of \([^{18F}]\)FLT was suggested to be beneficial because it accumulates at lower levels in most of the brain regions due to a lack of significant neuronal cell division.\(^2\) However, the value of this tracer in gliomas needs further evaluation in prospective studies.

**Membrane biosynthesis**—Choline is a precursor for the biosynthesis of phosphatidylcholine and other phospholipids, which are major components of cell membrane.\(^32\) Because cell proliferation can be associated with increased metabolism of cell membrane components, choline was proposed to be useful for imaging in oncology. Radiolabeled choline was previously demonstrated to be rapidly cleared from blood within a few minutes and to show increased uptake in different tumor entities.\(^33\) In brain tumors, the choline analogue \([^{18F}]\)fluorocholine was considered to distinguish high-grade gliomas, metastases, and benign lesions on the basis of the measured uptake. In addition, increased peritumoral \([^{18F}]\)fluorocholine uptake was suggested as a discriminating characteristic of high-grade gliomas.\(^34\) However, \([^{11C}]\)choline uptake was reported to be extremely high in the choroid plexus, the venous sinuses, and the pituitary gland, which limits its use for the demarcation of tumor border in the vicinity of these structures. Therefore, amino acid tracers were supposed to be superior for the evaluation of tumor extension, even if radiolabeled choline was suggested to be useful in evaluating the potential malignancy of oligodendrogial tumors.

**Oxygen metabolism**—Tumor hypoxia results from rapid tumor growth and concomitant insufficient blood supply that comes along with significantly
lower oxygen concentrations in parts of the tumor compared with normal tissue. Hypoxia may drive the peripheral growth of a tumor and is associated with tumor progression and resistance to radiotherapy. The nitroimidazole derivatives $[^{18}\text{F}]$fluoromisonidazole ($[^{18}\text{F}]$FMISO) and $[^{18}\text{F}]$FAZA have been shown to be suitable markers for hypoxia, since their metabolites are trapped exclusively in hypoxic cells. After diffusion into all cells, the nitroimidazole derivatives are reduced, reoxidized, and finally slowly cleared from tissue in normal cells but not in hypoxic cells, where these substances are further reduced and finally retained.

$[^{18}\text{F}]$FMISO uptake was observed in high-grade but not in low-grade gliomas, and a significant relationship was found between $[^{18}\text{F}]$FMISO uptake and expression of vascular endothelial growth factor receptor–1 and antigen Ki-67. Generally, increased $[^{18}\text{F}]$FMISO uptake is found in the periphery but not in the center of a glioblastoma, since only viable cells are able to accumulate the tracer, and enrichment in necrotic tissue is low. On the basis of the biological links between hypoxia and the aggressiveness of disease, including tumor-induced neoangiogenesis, it is instructive to compare images of hypoxia with MRI scans to reveal aspects of new vasculature and invasion. However, only limited data investigating the role of hypoxia markers for glioma in clinical settings are available at present. Despite the encouraging preliminary results, suboptimal imaging properties (low target-to-background ratio as well as slow uptake in malignant tissue) have limited the use of $[^{18}\text{F}]$FMISO in routine clinical practice so far.

**Perfusion**—Pathological angiogenesis is a hallmark of malignant gliomas, as it is one of the most prominent mechanisms driving tumor development and progression. Several efforts in this area of research are leading to the development of antiangiogenic molecules for cancer treatment. The ability to measure blood flow noninvasively may be of importance in monitoring glioma therapies. Suitable perfusion tracer should come with high extraction from the blood and high diffusion into the tissue that is proportional to delivery and should not participate significantly in metabolic processes. However, reliable quantification of perfusion requires arterial blood samples and is performed mostly with very short-lived $^{15}$O-labeled water, which definitely restrains its use for research purposes only.

**Clinical Applications**

**Grading and Differential Diagnosis**

Management and prognosis of gliomas highly depend on histological grading. The value of conventional MRI may be limited to differentiation between low-grade gliomas and benign nonneoplastic lesions or to detection of high-grade gliomas without obvious MR-morphological signs of malignancy. Currently, evaluation based on PET imaging of glioma-suspicious lesions is conducted by means of mainly 4 radiotracers: the glucose analogue $[^{18}\text{F}]$FDG and the radiolabeled amino acids $[^{11}\text{C}]$MET, $[^{18}\text{F}]$FET, and $[^{18}\text{F}]$DOPA.

The first and the most widely used radiotracer for brain tumors is $[^{18}\text{F}]$FDG. $[^{18}\text{F}]$FDG uptake was
shown to be correlated with tumor cell density, the grading and malignancy of glioma, and survival prognosis. However, the sensitivity of [18F]FDG PET was found to be limited in primary diagnosis of glioma, because only 3% to 6% of patients with low-grade gliomas and 21% to 47% of patients with high-grade gliomas presented with increased tracer uptake. To overcome the slight contrast between glioma and normal grey matter tissue, delayed scanning intervals up to 7 h p.i. have been proposed. However, this procedure is hardly applicable in a clinical setting.

For the past few years, PET using radiolabeled amino acids has gained increasing importance in the diagnostic workup of glioma, since it overcomes the limitations of [18F]FDG by showing a much higher tumor/nontumor contrast. [11C]MET PET was shown to permit a better delineation in gliomas that were iso-/hypometabolic on [18F]FDG PET and to provide a sufficiently high sensitivity in differentiation between nonneoplastic lesions and low-grade gliomas (up to 79% positive predictive value). Thus, increased amino acid uptake can be found in 72% to 76% of low-grade and 95% to 100% of high-grade gliomas for both [11C]MET and [18F]FET (Fig. 2). A recently developed dynamic analysis of [18F]FET uptake enables the differentiation between low- and high-grade gliomas with high diagnostic power (sensitivity, 94%; specificity, 100%). In addition, recently published data show that [18F]DOPA PET was able to differentiate between low- and high-grade gliomas and that the tracer uptake correlated with tumor proliferation in newly diagnosed gliomas but not in previously treated recurrent tumors. Preliminary data also suggest that dynamic analysis of [18F]FET PET might enable the differentiation between highly vascularized low- and high-grade oligodendrogliomas, which display both increased amino acid uptake and increased [18F]FDG uptake, independent of World Health Organization (WHO) grading. This has to be confirmed in ongoing studies. Furthermore, the combination of static uptake evaluation together with the proposed dynamic approach can be implemented for identification of anaplastic foci within a heterogeneous glioma. Thus, for noninvasive grading of primary gliomas, the standard method should be supplemented by the dynamic approach. A similar kinetic analysis has been attempted for [11C]MET; however, the uptake characteristics of this tracer do not allow differentiation between low- and high-grade gliomas on an individual patient basis.

Because differential diagnosis of newly diagnosed masses with ring enhancement on MRI includes neoplastic (e.g., gliomas, brain tumors, metastases) as well as nonneoplastic entities such as abscesses, parasitic lesions, demyelinating and reactive lesions, infarction, and resolving hematoma, a noninvasive per therapeutic identification is highly desirable. PET with [18F]FDG was previously shown to be of limited value to reliably predict whether a lesion was malignant, due mainly to unspecific tracer uptake related to a higher metabolic rate and increased density of inflammatory cells, as well as the very heterogeneous uptake in cerebral metastases. Furthermore, relatively benign tumors, including pilocytic astrocytoma and ganglioglioma, often present with increased [18F]FDG uptake that is caused by presence of metabolically active endothelial cells. Even if considered to be more specific, currently available data show false positive findings in benign or inflammatory processes (mainly in abscesses but also in demyelinating lesions) for choline (5/110; 4.6%) as well as amino acid PET (up to one-third of newly diagnosed solitary intracerebral lesions showing ring enhancement on contrast-enhanced MRI). In addition, from our own experience cerebral metastases are associated mostly with increased amino acid uptake that does not allow the differentiation of gliomas.

In conclusion, the use of [18F]FDG PET is of questionable value for initial diagnosis, especially when amino acid tracers are available, but it might provide some helpful information—for instance, for the differentiation of low-grade gliomas (low [18F]FDG uptake) from inflammatory lesions (slightly increased [18F]FDG uptake). In addition, due to its limited accuracy for differential diagnosis, PET cannot be considered to be a sufficient alternative to histological diagnosis provided by means of biopsy or resection.

**Tumor Extension and Treatment Planning**

**PET guidance for biopsy planning in low- and high-grade gliomas**—Biopsy is performed to obtain a diagnosis in de novo cases when the tumor is located in an eloquent brain region and resection cannot be performed without compromising normal function, or when the patient’s general condition or refusal to undergo surgery does not allow an open resection. In addition, it constitutes a safe and reliable method to disclose tumor recurrence or progression following previous multimodal treatment, as well as malignant transformation of a glioma previously classified as low grade. Most widespread, the procedure for stereotactic biopsy involves contrast-enhanced morphological (MRI) imaging.

Although contrast enhancement, among other criteria, has been shown to be the strongest predictor of malignancy, up to 10% of all high-grade gliomas and approximately one-third of anaplastic astrocytomas do not present with contrast enhancement on gadolinium T1 images. Conversely, low-grade gliomas can sometimes demonstrate peritumoral edema as well as contrast enhancement and, therefore, be mistaken for high-grade gliomas. Thus, target selection for stereotactic biopsy based on MRI/CT guidance alone has been regarded with controversy, since the degree of malignancy might be underestimated, especially in gliomas with a rather “benign” appearance on MRI. Taking into consideration the often encountered inter- and intratumoral heterogeneity, PET might be a valuable additional tool for exposure of the most malignant areas of the tumor, ensuring correct evaluation of the biopsy site.
Despite its limited validity in low-grade glioma, $[^{18}\text{F}]$FDG, being the most widely applied radiotracer, was shown to be superior for stereotactic biopsy target selection compared with CT or MRI alone. However, its additional value for biopsy guidance in lesions already highly suggestive on MRI of a high-grade glioma remains limited.

In a prospective study combining amino acid PET ($[^{18}\text{F}]$FET) and MRI, the use of both modalities was shown to enhance the accuracy significantly (sensitivity 93%; specificity 94%) compared with MRI alone (sensitivity 96%; specificity 53%) and to be more accurate in identifying active tumors than $[^{18}\text{F}]$FDG PET, indicating that amino acid PET is better suited for biopsy target selection than $[^{18}\text{F}]$FDG, especially in low-grade gliomas. As nonenhancing lesions tend to exhibit malignant histopathological features within a presumed WHO II glioma, the diagnostic and prognostic assessment most notably depends on the sampling location.

Recently, $[^{18}\text{F}]$FET PET was demonstrated to reliably detect anaplastic foci and to be able to differentiate between grade II and grade III histopathology within one and the same lesion (sensitivity 92%; specificity 82%) when the dynamic analysis was applied (Fig. 3).

While there is growing evidence for the implementation of PET for biopsy planning in low-grade gliomas, the necessity of PET guidance in high-grade gliomas is arguable. Due to their metabolic and vascular properties based on increased proliferation, high-grade gliomas generally effectuate high uptake values of all well-established radiotracers. Therefore, $[^{18}\text{F}]$FDG, $[^{11}\text{C}]$MET, and $[^{18}\text{F}]$FET, as well as $[^{18}\text{F}]$FLT, which can identify regions of tumor with increased proliferation rate, could be implemented for combined PET/MR guidance in a high-grade glioma.

**PET guidance for surgery planning**—Due to its ability to reveal the most malignant areas within a gliomatous...
tumor, PET might potentially help to plan the resection and to guide the surgeon. Especially in heterogeneous gliomas consisting of high- and low-grade components, resection including the most malignant parts of the tumor should be aimed for, in order to ensure a correct histological evaluation. However, only 2 studies have investigated the value of a PET-guided resection so far. The multimodal navigation system including amino acid PET was suggested to be more useful than the conventional navigation system in determining the resection area by providing a clearer discrimination of tumor boundary, which resulted in decreased remnant tumor mass and was associated with improved postsurgical survival. In addition, preoperative [18F]FET uptake highly correlates with the degree of intraoperative 5-aminolevulinic acid fluorescence in glioma. However, the significance of this finding remains limited as far as patient selection for surgical treatment is concerned. Further investigations are necessary to evaluate the relationship of a PET-guided extent of resection with patients’ outcomes, as well as procedure-related morbidity compared with MRI-based resection.

PET guidance for radiation therapy planning—Stereotactic radiotherapy, radiosurgery, intensity-modulated radiotherapy, and 3D planning of brachytherapy enable a highly precise delivery of radiation in glioma. Even if the target volume definition is currently based on CT and MRI techniques, additional information from molecular imaging techniques to visualize biological pathways is expected to have a major impact on radiation oncology. As a consequence, the concept of biological target volume (BTV) was proposed in addition to the concepts of gross tumor volume (GTV), clinical tumor volume (CTV), and planning target volume (PTV). In high-grade gliomas, early recurrence after local treatment is a common feature, and relapse occurs in terms of continuous growth within 2–3 cm from the margin of the original lesion in approximately 80% of cases.

Recent studies claim the usefulness of PET-based BTV for radiation therapy planning. In high-grade gliomas, amino acid–based assessment of BTV was supposed to be more accurate than morphological GTV, which in several cases was shown to differ substantially in size. The inadequate coverage of BTV by morphological GTV was linked with increased risk of noncentral failures, and therefore amino acid–based BTV was suggested to be useful for identifying areas for conformal boost. In addition, a nonrandomized study dealing with patients with recurrent high-grade gliomas showed that treatment planning based on radiolabeled amino acids combined with CT/MRI was also associated with improved survival in comparison with treatment planning using CT/MRI alone (median survival time, 9 months vs. 5 months). Therefore, in order to spare normal tissue, reduce toxicity, and decrease the likelihood of geographical misses in target volume definition, biological treatment planning seems to be very promising. However, this has to be validated in prospective studies in order to assess both the impact of amino acid PET for target volume definition and the importance of biological tumor tissue definition for patients’ overall survival. In contrast to amino acid PET, the use of [18F]FDG PET does not appear to have a major additional impact for the delineation of target volume, as the area of increased [18F]FDG uptake has been shown to correlate closely with contrast enhancement in MRI.

Assessment of tumor hypoxia prior to radiotherapy is also expected to be beneficial, as it would provide a rational means of demarcating radio-resistant hypoxic zones within the treatment volumes in glioma and therefore could lead to an adaptation of individual treatment strategies by increasing the dose deposition in hypoxic areas and minimizing the doses in well-oxygenated areas or by using radiosensitizing drugs in well-selected patients. However, to the best of our knowledge, no clinical study assessing the hypoxia-marker uptake and treatment response to radiotherapy has yet been published.

Value of PET for Follow-up of Glioma

The use of multimodal individual therapy strategies, including surgery, radiotherapy, and chemotherapy, as well as therapies involving antiangiogenic substances...
and other biologically targeted therapies, necessitates an accurate and early assessment of treatment response, particularly in high-grade glioma, in order to optimize patient care and treatment. Current standard therapeutic regimen in high-grade glioma, notably glioblastoma multiforme, involves a combination of radio- and chemotherapy with temozolomide followed by adjuvant temozolomide monotherapy according to the protocol of the European Organisation for Research and Treatment of Cancer.83

Assessment of treatment response is very challenging, because posttherapeutic changes reflected by contrast enhancement or changes in tumor size obtained with conventional MRI and CT techniques are of limited value61 and often fail to detect early treatment response, as they occur with a delay of weeks up to months.84,85 In addition, posttreatment MRIs often show contrast-enhancing lesions that can be associated either with tumor relapse or with treatment-induced changes. These changes, which are attributed mostly to radiation-induced damage of neural and vascular tissue, can be classified as pseudoprogression (early radiographic changes, reversible) or radiation necrosis (subacute radiographic changes, irreversible). In contrast to genuine tumor recurrence, these treatment-related alterations can be asymptomatic, especially in case of a pseudoprogression, usually fail to progress, and are associated with prolonged survival.86 As a consequence of temozolomide treatment, the incidence of pseudoprogression has increased, mainly in glioblastoma with a methylated O(6)-methylguanine-DNA methyltransferase status. As the discrimination between contrast enhancement related to tumor recurrence and treatment-related effects is quite challenging, the accuracy of MRI-based predictions of patient’s disease status remains limited.87 Although the recently introduced criteria of the Response Assessment in Neuro-oncology for assessment of treatment response by MRI address pseudoprogression or pseudoresponse phenomena, proposing a reevaluation of diagnosis by a subsequent MRI scan after a time period of 4 weeks,88 the additional evaluation by means of magnetic resonance spectroscopy (MRS) and PET prior to imaging or as a supplementary imaging modality has been suggested as a valuable tool for subsequent therapy monitoring and adjustment.

With regard to standard therapy regimens in glioma, [18F]FDG PET was able to predict response to temozolomide but not to temozolomide plus radiotherapy,89 probably due to energy-dependent apoptosis of tumor cells, rapid infiltration of tumor by inflammatory cells after radiotherapy,90 or alterations in the blood-brain and blood-tumor barriers.91 Currently available data on [18F]FDG PET are quite inconsistent and show limited accuracy for the differentiation of recurrence from radiation necrosis, with sensitivities between 40% and 90% and specificities between 40% and 80%, respectively,8,92–94 which could lead to an inappropriate treatment in up to one-third of patients.

In contrast, radiolabeled amino acid tracers are not taken up by glycolytic inflammatory cells and therefore have been suggested to be more appropriate for discrimination between recurrence or progression versus unspecific therapy-related changes.95 However, the experience for treatment monitoring is still comparably...
limited. Higher diagnostic power was confirmed in different studies with \[^{11}C\]MET (sensitivity, 75\%-90\%; specificity, 75\%-92\%)\(^{96-98}\) as well as with \[^{18}F\]FET (positive predictive value, 84\%; sensitivity, 82\%; specificity, 100\%).\(^{99,100}\) Slightly increasing and homogeneous uptake around the tumor cavity pointed to benign therapy-related changes, whereas locally increased \[^{18}F\]FET uptake was shown to be an early and reliable indicator of tumor progression\(^{100}\) (Fig. 5). However, the diagnostic power was higher in an MRS study based on multivoxel 3D acquisition (sensitivity, 94\%; specificity, 100\%).\(^{101}\) Comparable diagnostic accuracy was found for \[^{18}F\]FET PET when additional dynamic data analysis was applied (sensitivity, 100\%; specificity, 93\%),\(^{102}\) which was significantly superior to conventional MRI (sensitivity, 94\%; specificity, 50\%) in discriminating tumor recurrence from posttherapeutic changes. However, the accuracy of amino acid PET is not yet high enough to replace histological verification in patients with MRI-based suspicion of a glioma recurrence or progression but seems to be a useful tool for biopsy planning and patient selection. In this light, a significant decrease of amino acid uptake, correlated with effectiveness of radiotherapy and chemotherapy\(^{103}\) and postoperative elevated amino acid uptake, suggesting remnant glioma tissue is associated with worse survival in malignant glioma.\(^{104}\)

Limited data on \[^{18}F\]FLT indicates that this marker for cell proliferation might also be superior to \[^{18}F\]FDG in evaluating recurrent high-grade gliomas.\(^{30}\) In an animal model of glioma, \[^{18}F\]FLT uptake correlated with changes in tumor growth as well as expression levels of therapeutic genes and has been suggested to be a promising noninvasive parameter to monitor effects of antiproliferative therapy, as \[^{18}F\]FLT uptake levels could be assessed as early as 3 days after therapy onset.\(^{105}\) However, these results have to be confirmed in humans.

New treatment strategies with antivascular agents (e.g., the antivascular endothelial growth factor receptor-1 antibody bevacizumab) are difficult to monitor reliably by conventional imaging techniques, since treatment-induced reduction of contrast enhancement represents predominantly reduced vascular permeability.\(^{106}\) Therefore, contrast-enhanced MRI is considered to be of only limited value to quantify tumor burden after treatment with antivascular agents.\(^{86}\) However, to date none of the current radiographic modalities, neither conventional or diffusion-weighted imaging-based MRI nor MRS, has proven sensitive enough to assess post-bevacizumab treatment effects.

Metabolic imaging has been proposed to be an alternative therapy-response assessment tool. \[^{18}F\]FLT PET proved to be superior compared with contrast-enhanced MRI in predicting treatment response of malignant gliomas to bevacizumab plus chemotherapy,\(^{107}\) albeit in a small group of patients with recurrent malignant gliomas (\(n = 21\)). Yet, the experience to date remains limited, and further prospective studies have to be performed.

PET based on markers of hypoxia like \[^{18}F\]FMISO might be helpful to detect hypoxic areas, which were shown to be associated with poorer therapy response to antiangiogenic treatment.\(^{108}\) However, this assumption remains speculative and has to be proven by prospective studies.

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**Fig. 5.** Postradiogenic contrast enhancement on MRI coupled with pathologically increased tracer uptake on PET were highly suggestive for glioblastoma progression, which was confirmed by means of histology (upper row), whereas contrast enhancement on MRI with only slightly increased and homogeneous \[^{18}F\]FET uptake (lower row) was shown to be treatment associated by follow-up examinations.
Altogether, amino acid PET with dynamic analysis seems to provide additional information, compared with morphological imaging techniques, for the sensitive and specific detection of glioma recurrence. Moreover, PET-based imaging might help to monitor new treatment modalities like antiangiogenic therapies.

Impact of PET-Based Evaluation on Patient Prognosis

Several prognostic factors have been identified in glioma, including patient’s age, location and size of the lesion, histology and grade of the tumor, and neurological status. The clinical course of patients with low-grade gliomas can vary considerably, and valuable tools for an accurate identification of patients with a poor or a favorable prognosis is highly desirable to adjust treatment strategies. A treatment that is too aggressive may cause treatment-related morbidity, whereas insufficient treatment of progressive lesions may significantly decrease overall survival. $^{[18F]}$FET PET in combination with MRI was suggested to be a strong predictor in determining the clinical course and outcome in nonenhancing low-grade gliomas. Within the observation period of the study (up to 65 months), the best outcome was found in circumscribed lesions without tracer uptake (18% progression), which was followed by those with tracer uptake (46% progression). The worst outcome was shown in diffuse glioma with high uptake (100% progression).110 $^{[18F]}$FDG PET uptake was also shown to predict malignant transformation and to correlate with overall survival in a large retrospective study including 331 patients, since 71% of patients with initially high $^{[18F]}$FDG uptake survived for less than 1 year (22% less than 3 years), whereas 94% of patients with initially low $^{[18F]}$FDG uptake had a median survival of more than 1 year (63%; and 39% more than 2 and 3 years respectively).111

Potential New Targets for Glioma Imaging

Several molecular markers involved in glioma progression have recently been characterized. A true molecular imaging would allow visualization of these molecules in situ. This could have a major impact on the understanding of glioma biology, as well as on selection and monitoring of therapies against these targets. The use of radiolabeled biomolecules such as monoclonal antibodies and peptides may potentially enable a more specific assessment of molecular changes in tumor tissue. For instance, glycosylated arginine–glycine–aspartic acid peptide ($^{[18F]}$Galacto-RGD) was demonstrated in glioblastoma to successfully identify the expression of the integrin $\alpha_\beta_3$, which is associated with tumor-induced angiogenesis via basic fibroblast growth factor and is also found in small blood vessels, where it is thought to promote extensive tumor progression. Such a concept has become even more important, as $\alpha_\beta_3$ integrin antagonists are promising new agents currently being tested in clinical trials for supplemental therapy of glioblastoma. Likewise, different antibodies and peptides can be considered as worthwhile ligands that might potentially be interesting for imaging in glioma. Further development might lead to more selective radiotracers, which permit profound and more selective insight into tumor biochemistry in vivo. As an example, the development of antisense oligonucleotides for the visualization of specific mRNA and protein expression would allow targeting of the expression of almost any endogenous gene. However, further technological advancements are needed in order to solve known problems, like low accumulation in the target tissue, for which a more widespread use of antisense imaging technique is currently avoided in favor of a reliable in vivo monitoring of gene expression.

Due to its remarkable sensitivity, molecular imaging with PET allows the use of very low tracer doses in physiological quantities that theoretically enable the application of almost each substance with only a minimal risk of adverse reaction, rather than bulk tracer doses that are necessary for CT or MRI. Therefore, PET appears to be one of the most interesting imaging modalities for further advancement in molecular imaging. One might speculate whether information gained by PET tracer development will be transferrable for the elaboration of injectable targeted MR contrast agents that can cross the blood–brain barrier.

Conclusion

The scientific data justify the use of PET in glioma, especially when radiolabeled amino acids are used. Although information assessed by MRI will remain essential in glioma management, PET by means of amino acids using dynamic PET data acquisition together with assessment of the maximal or mean SUV value was shown to be

- more specific for tumor delineation;
- beneficial for biopsy planning, in particular for inhomogeneous gliomas without contrast enhancement on MRI;
- very helpful for the differentiation between remnant tumor tissue and posttherapeutic changes, as well as for assessment of early treatment response; and
- potentially useful for treatment planning of local therapies.

With the introduction of PET radiopharmaceuticals like $^{[18F]}$FLT and $^{[18F]}$FMISO, additional insight into proliferation rate and oxygen metabolism of gliomas can be obtained. Further prospective studies are needed to evaluate their clinical impact. Molecular imaging techniques might be promising for the selection of patients who might better
respond to targeted therapies, as well as for the evaluation of treatment response, and therefore might enable individualized patient management. PET can therefore be regarded as a relevant tool for the accurate evaluation of new treatment strategies and should be considered in upcoming prospective studies. Early adjustment of patient care can also avoid unnecessary treatment toxicity and reduce treatment costs of ineffective therapies. However, further randomized, prospective multicenter clinical trials are needed to clearly demonstrate the additional value of both PET combined with regular MR compared with regular MR alone.

**Conflict of interest statement.** None declared.

## References


