9 PET Imaging in Glioblastoma: Use in Clinical Practice

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Abstract: Positron emission tomography (PET) is a nuclear medicine imaging method with increasing relevance for the diagnosis, prognostication, and monitoring of glioblastomas. PET provides additional insight beyond magnetic resonance imaging (MRI) into the biology of gliomas, which can be used for noninvasive grading, differential diagnosis, delineation of tumor extent, planning of surgery, and radiotherapy and post-treatment monitoring. In clinical practice, two classes of radiotracers have been used predominantly for imaging purposes, namely glucose metabolism tracers and amino acid transport tracers. Both classes of tracers can provide information on grading and prognosis of gliomas, but amino acid tracers, which exhibit lower uptake in normal brain tissue, are better suited for delineation of tumor extent, treatment planning, or follow-up than ^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}F-FDG). Owing to the progress in PET imaging using radiolabeled amino acids in recent years, the Response Assessment in Neuro-Oncology (RANO) working group, an international effort to develop new standardized response criteria for clinical trials in brain tumors, has recently recommended amino acid PET as an additional tool in the diagnostic assessment of brain tumors.

These developments as well as multimodality imaging should improve the diagnostic assessment of these tumors.

Introduction

The incidence of primary malignant brain and central nervous system tumors in the general population was estimated at 3 per 100,000 in 2008, with a higher incidence rate in developed countries than in developing countries (1). Among these tumors, glioblastomas account for approximately 60–70% of malignant gliomas (2, 3). With maximum safe resection, radiotherapy, and concurrent and adjuvant temozolomide, in clinical trial populations, the medium survival is 12-15 months (4-7). Unfortunately, after initial treatment, these tumors invariably recur. Initial diagnosis, prognosis, and targeted treatment of these tumors thus represent very active areas of investigation.

In this setting, neuroimaging plays a key role in the assessment of these tumors (8). Magnetic resonance imaging (MRI), the current imaging gold standard, has offered limited insight to date with regard to grade of malignancy, tumor delineation, differentiation between necrotic tissues and recurrent tumor, as well as the management of therapeutic interventions such as surgery or radiotherapy (9, 10). In fact, although a rapidly enlarging or enhancing lesion on MRI with or without clinical symptoms is usually considered a progressing tumor, imaging the extent of contrast enhancement in malignant gliomas has limited accuracy due to the difficulty in distinguishing between progressive tumor and treatment-induced changes such as radiation necrosis (11).

Positron emission tomography (PET) is a nuclear medicine method with an increasing relevance especially due to the improved availability of radioactively labeled amino acids, allowing widespread applications in diagnosis, therapy planning, and therapy monitoring of glioblastomas (9, 10). PET provides additional insight beyond MRI into the biology of gliomas which can be used for noninvasive grading, differential diagnosis, delineation of tumor extent, planning of surgery and radiotherapy, post-treatment monitoring, and prognostication. Among PET radiotracers, ^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}F-FDG) is the most widely studied and validated tracer to date. In addition, ^{18}F-FDG is widespread in clinical nuclear medicine and is of low cost (8). In instances of suspicious low-grade glioma, it is able to identify anaplastic transformation and displays good prognostic value. Indeed, tumor cells are characterized by increased glycolytic metabolism, in parallel with cell proliferation and loss of differentiation. ^{18}F-FDG is an appropriate, albeit nonspecific radiotracer for noninvasively assessing the biological aggressiveness of tumors *in vivo*, as previously suggested in many cancer types (12). However, a high ^{18}F-FDG uptake in surrounding normal brain tissue limits its use for the imaging of cerebral gliomas which may not be visualized in a large fraction of primary and recurrent tumors (13).

Due to the relatively low tracer uptake in normal gray matter, amino acid PET tracers can detect gliomas with greater sensitivity than ^{18}F-FDG in primary

and recurrent tumors and are helpful in differentiating recurrent tumors from treatment-induced changes (14). ^{11}C-methyl-methionine (^{11}C-MET) is the most studied and validated amino acid tracer. It is a natural amino acid avidly taken up by glioma cells, with only a low uptake in normal cerebral tissue. A smaller portion of ^{11}C-MET is metabolized by decarboxylation. However, several experiments have suggested that during PET studies, tumor uptake of ^{11}C-MET mainly reflects increased amino acid transport (15). Its major drawback lies in the short half-life of the ^{11}C-carbon, only 20 min, and thus requires close proximity to a cyclotron, thereby limiting its use in routine nuclear medicine centers. To overcome the drawbacks of the short-lived MET, ^{18}F-labeled amino acids have been developed in order to expand amino acid tracer utilization, namely O-(2-[18F]-fluoroethyl)-L-tyrosine (^{18}F-FET) and 3,4-dihydroxy-6-[18F]-fluoro-L-phenylalanine (^{18}F-FDOPA). ^{18}F-FET is increasingly used in Europe as a tracer for both high-grade gliomas as well as low-grade gliomas, owing to its several advantages including synthesis by an efficient nucleophilic reaction, elevated uptake by tumor tissues, low uptake by inflammatory tissues, and high stability (16). Similar to ^{11}C-MET and ^{18}F-FET, ^{18}F-FDOPA is incorporated into cells through amino acid transporters that are overexpressed in gliomas, and its transport and uptake are independent of the blood–brain barrier (17). Of note, a striatal uptake has nonetheless been reported in the case of ^{18}F-FDOPA, which may lead to difficulties in delineating gliomas in these areas (17).

The aim of this chapter is to define clinical practice PET indications in glioblastomas for the purposes of diagnosis, delineation of glioma extent, as well as its value in treatment planning, follow-up, and prognostication. The following mainly focuses on imaging tracers of glucose metabolism (^{18}F-FDG) and amino acid transport (^{11}C-MET, ^{18}F-FET, and ^{18}F-FDOPA), since these compounds are already part of current clinical practice. Future perspectives in novel radiotracers and technical improvements are also outlined.

Primary Diagnosis/Differential Diagnosis

^{18}F-FDG is useful for differentiating high-grade gliomas from other types of brain tumors (18). In the specific setting of glioblastomas, ^{18}F-FDG is particularly sensitive at the initial stage of the diagnosis (19, 20), an example of which is given in Figure 1. In a study involving 31 newly diagnosed glioblastomas, Colavolpe et al. found an uptake of ^{18}F-FDG in these tumors with a tumor-to-background ratio max (TBRmax) of 1.4±0.8 (12). However, differential diagnosis at the initial stage with ^{18}F-FDG may be difficult to achieve due to the low specificity of this radiotracer. Indeed, brain lymphomas can display a higher glucose metabolism uptake than high-grade gliomas (21). Moreover, nonneoplastic neurological diseases can mimic brain neoplasms on ^{18}F-FDG, including pyogenic abscesses, tuberculosis, fungal infections, or sarcoidosis (22). Studies comparing the ^{18}F-FDG and amino acid tracer uptake in the assessment of brain tumors demonstrated significantly higher tumor to brain contrast with amino acid PET than with ^{18}F-FDG (23–25), demonstrating a higher sensitivity of amino acid tracers for glioblastoma detection.
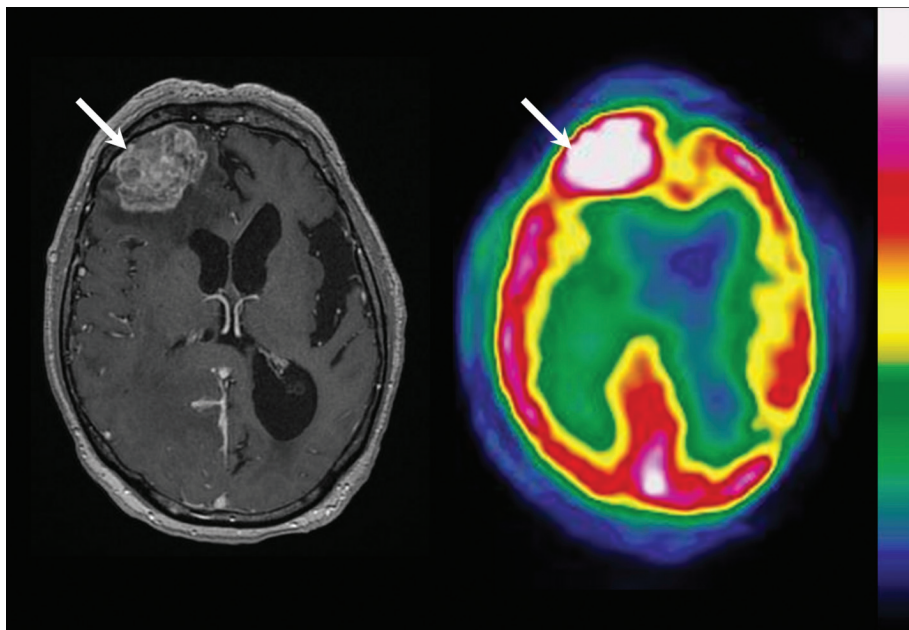
Figure 1 Primary diagnosis of a right frontal glioblastoma in a 79-year-old man following acquisition of axial slices of T1-weighted gadolinium-enhanced MRI (left side) and ^{18}F-FDG PET (right side). The right frontal glioblastoma is contrast-enhanced on MRI (white arrow) and shows an extensive uptake of ^{18}F-FDG PET (white arrow), despite the high uptake in surrounding normal brain tissue.

^{18}F-FET has shown comparable results to ^{11}C-MET in the detection of brain gliomas (26). Approximately 95% of high-grade gliomas, including glioblastomas, display a significant uptake of ^{18}F-FET (27–29), leading to a high sensitivity of ^{18}F-FET for tumor detection. A study conducted in rats demonstrated that ^{18}F-FET uptake was absent in macrophages, a common inflammatory mediator, in contrast to accumulation of ^{18}F-FDG in these cells (30). Nevertheless, in patient studies, unspecific FET uptake has been observed in nonneoplastic brain lesions (28, 31). Despite its limited specificity (32), ^{18}F-FDOPA is also a sensitive tool for diagnosing glioblastomas with similar results to ^{11}C-MET (33). For instance, in a study of 23 histologically confirmed tumors, ^{18}F-FDOPA had a TBRmax of 2.50 ± 0.73 for 18 high-grade tumors, 3 of which were glioblastomas (24).

In the diagnosis of gliomas, noninvasive tumor grading may be helpful in order to define aggressive forms at initial stages with poor prognosis. In this instance, ^{18}F-FDG is helpful to detect glioblastomas, since low-grade gliomas often appear as hypometabolic lesions, particularly when compared with cortical uptake (34). However, due to its high uptake in gray matter, tumor to brain ratios of ^{18}F-FDG uptake are low (1.23 ± 0.69) for high-grade tumors, leading to a poorer tumor imaging contrast in comparison to amino acid tracers (24). ^{18}F-FDOPA uptake was found to be significantly higher in high-grade tumors compared to low-grade tumors in newly diagnosed but nonrecurrent tumors that

had been previously treated in a series of 59 gliomas of which 25 were glioblastomas (35). In another study, ^{18}F-FDOPA uptake was significantly different in high-grade and low-grade gliomas or for both newly diagnosed and recurrent gliomas in a series of 31 gliomas of which 5 were glioblastomas (17). Similarly, several studies, including those on glioblastomas, have shown significantly different TBRmax between high-grade and low-grade gliomas with ^{11}C-MET (36–38), although other study results are more controversial (39, 40).

For ^{18}F-FET, it has been shown that a TBRmax < 2.5 excludes a high-grade tumor with high probability (27). Furthermore, ^{18}F-FET accuracy for tumor grading can be markedly improved by assessing dynamic PET data, which typically show steadily increasing time–activity curves in low-grade gliomas, as opposed to an early activity peak around 10–20 min after injection, followed by decreased uptake in high-grade gliomas (41, 42). Accordingly, in a study combining MRI and dynamic ^{18}F-FET data for initial glioma grading (43), the authors concluded that on multivariate logistic regression analysis, a negative slope of the tumor FET time–activity curve remains the best predictor of high-grade glioma. Analysis of dynamic data was not helpful for tumor grading neither with ^{11}C-MET (44) nor with ^{18}F-FDOPA (45, 46). Altogether, PET is helpful in the diagnostic evaluation of glioblastomas at the initial stage by means of glycolytic or amino acid metabolism-based tracers. Differential diagnosis with nonneoplastic lesions, however, is poorer with ^{18}F-FDG due to its low specificity. On the contrary, all commonly used PET tracers can contribute to the differentiation of glioblastomas from low-grade gliomas, especially ^{18}F-FET, when using dynamic data.

Delineation of Glioma Extent

The accurate definition of initial tumor volume as well as extent of recurrence is essential in treatment planning. Accordingly, PET data provide valuable additional information compared with MRI, which suffers from high interindividual variability in delineation of glioblastoma target volumes (47). Furthermore, multiple histopathological and postmortem series have demonstrated the limitations of conventional MRI in defining the extent of gliomas (48, 49). Amino acid PET tracers are the better candidates for this indication compared with ^{18}F-FDG, which exhibits high uptake in normal brain tissue (13). In a study involving 12 patients with recurrent glioblastoma, the metabolically active tumor volume as defined by ^{11}C-MET PET was substantially underestimated by contrast enhancement in MRI. These findings support the notion that information derived from ^{11}C-MET uptake in addition to contrast-enhanced MRI may be helpful in optimized targeting of the tumor mass by surgery and radiotherapy (50).

Similarly, some studies in which the radiological findings were compared with the histological findings in tissue samples obtained by biopsy or open surgery have provided evidence that FET PET detects the solid mass of gliomas and metabolically active tumor areas more reliably than MRI (51, 52). Furthermore, in a study of initial diagnosis of 56 gliomas, 24 of which were glioblastomas, ^{18}F-FET showed considerably higher TBRmax and larger tumor volumes when compared to regional cerebral blood volume maps derived from perfusion-weighted

MR imaging (53). In addition, postoperative ^{18}F-FET PET has been shown to reveal residual tumor with higher sensitivity than MRI as well as show larger tumor volumes (54). In this latter series of 62 patients with recurrent glioblastoma, ^{18}F-FET was thus recommended as a helpful adjunct in addition to MRI for postoperative assessment of residual tumor (54). Similar results have been obtained with ^{18}F-FDOPA PET in progressive or recurrent glioblastomas where a larger tumor extent was identified when compared with MRI-derived regional cerebral blood volume maps (55). Accordingly, ^{18}F-FDOPA PET-based tumor volumes have been shown to extend beyond the contrast-enhancing volume on conventional MRI (56). In addition, initial nonenhancing glioblastoma areas were also identified with this radiotracer since they were subsequently followed by abnormal MRI contrast enhancement (57).

Value in Treatment Planning

BIOPSY AND RESECTION

PET enables better identification of intra-tumor heterogeneity compared with standard MRI in addition to delineating tumor extent with much greater accuracy. The identification of malignant foci, commonly defined as "hot spots" in heterogeneous gliomas and a specific characteristic of glioblastomas (58), is essential for biopsy planning. The objective is to ensure that the most biologically aggressive portion of the tumor, which ultimately determines the patient's prognosis as well as treatment, is not under-sampled (56, 59). Similar to the delineation of tumor extent, amino acid tracers are more suitable than ^{18}F-FDG in identifying malignant foci in gliomas. In a study aimed at guiding stereotactic brain biopsy of gliomas by using ^{18}F-FDG and ^{11}C-MET, the authors showed that all 32 gliomas, 10 of which were glioblastomas, exhibited an area of abnormal ^{11}C-MET uptake, whereas only 7 glioblastomas showed abnormal ^{18}F-FDG uptake (60). An example of superiority of ^{11}C-MET in comparison to ^{18}F-FDG is given in Figure 2. In another study aimed at comparing performances with MRI, stereotactic PET-guided biopsies were also performed with ^{18}F-FDOPA PET. Thirteen of the 16 high-grade biopsy specimens were obtained from regions of elevated ^{18}F-FDOPA uptake, while MRI contrast enhancement was present in only 6 of the aforementioned 16 samples (56). These observations, in accordance with previous results, thus underscore the potential benefit of using PET amino acid tracers in determining the most aggressive portion of the tumor.

Of particular interest, in a study using a combination of ^{18}F-FDG and ^{11}C-MET, surgical tumor resection based on PET tracer uptake was found to be significantly associated with longer survival in glioblastoma patients when compared with surgical resection based on MRI contrast enhancement (61). Thus, in addition to its value in biopsy planning, PET data provide added prognostic value with regard to surgical resection outcome (61). It has moreover been suggested that patients with glioblastomas may potentially benefit from maximal PET-guided tumor resection since lower biological tumor volume (BTV) before treatment with ^{18}F-FET was independent of clinical prognostic factors: patients with smaller tumor volumes had significantly longer progression-free and overall survival (62).
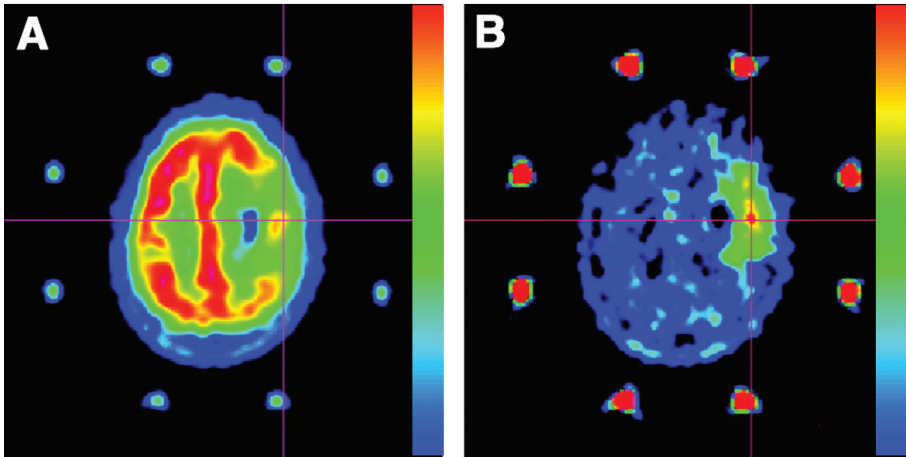
Figure 2 PET performed with ^{18}F-FDG (A) and 11C-MET (B) in a 62-year-old woman with a glioblastoma in the left prerolandic cortical area. Uptake of ^{18}F-FDG was reduced in the tumor area except for one area of uptake equivalent to that in the surrounding gray matter. Uptake of ^{11}C-MET was higher in the tumor than in the surrounding cortex, allowing the definition of a target for biopsy. When PET images obtained with the two tracers were co-recorded, the highest focus of ^{11}C-MET uptake corresponded to the hot spot of ^{18}F-FDG uptake (intersecting lines). (Adapted from J Nucl Med 2004;45:1293–1298. Copyright: The Society of Nuclear Medicine and Molecular Imaging, Inc. Reproduced with Permission.)

RADIATION

In radiotherapy treatment planning, ^{18}F-FDG PET can provide prognostic information. Indeed, ^{18}F-FDG PET volumes are predictive of survival and time to tumor progression in the treatment of patients with glioblastomas (63). However, ^{18}F-FDG uptake abnormalities generally demonstrate a smaller region of uptake contained within the MRI abnormality, with only an occasional extension outside of the MRI target (63). ^{18}F-FDG PET is therefore of limited value for radiation treatment planning except for the definition of target volumes in radiation dose escalation. PET amino acid tracers are thus better suited to delineate tumor volume prior to radiotherapy. Accordingly, in a study of 39 patients with high-grade gliomas before radiotherapy, the region of ^{11}C-MET uptake was larger and detected up to 45 mm beyond MRI contrast enhancement in 29 patients (15). Similarly, high-grade glioma contours obtained with ^{18}F-FDOPA PET-based consensus target volumes were larger than MRI-based volumes (64). ^{11}C-MET PET was also found to provide supplementary information to MRI data, whereby BTV defined with ^{11}C-MET PET included all localizations of recurrences in a series of 52 glioblastomas (65). Thus, these pretreatment ^{11}C-MET PET volumes appear to identify areas at highest risk of recurrence for patients with glioblastomas since inadequate PET-gross-tumor-volume coverage was associated with increased risk of noncentral failures (66).

Of note, in re-irradiated patients, significant longer survival times have been reported using image fusion in treatment planning when compared with treated patients based on MRI/CT alone (67). Large BTC on ^{18}F-FET PET is accordingly

an independent prognostic factor of poor overall survival and of progression-free survival in newly diagnosed glioblastoma patients, to the detriment of other prognosis factors such as clinical factors or MRI-based tumor volume (62, 68). A number of centers have accordingly begun to integrate amino acid imaging into CT-based and MRI-based radiotherapy planning (69), particularly in high-grade gliomas and in instances when high-precision radiotherapy is to be given, or in the setting of dose escalation studies, or for re-irradiation of recurrent tumors (70, 71). In this context, ^{11}C-MET /CT/MRI fusion has also been proposed to optimize hypofractionated stereotactic radiotherapy by intensity-modulated radiation therapy (HS-IMRT) in recurrent glioblastomas, with good treatment tolerance and a median survival time of 11 months (72).

Follow-up: Treatment Response, Progression, Pseudoprogression, and Radionecrosis

The extent of MRI contrast enhancement is usually considered an indicator of treatment response or progression (73). However, contrast enhancement after radiotherapy with or without concomitant temozolomide can mimic tumor progression and is termed "pseudoprogression." This phenomenon typically occurs within the first 12 weeks after chemoradiation with concurrent temozolomide or radiotherapy alone (74, 75). Moreover, contrast enhancement is linked to nonspecific post-therapeutic effects, in the specific setting of post-radiation effects, occurring several months later than pseudoprogression (76). It is relatively similar to that observed in tumor recurrence thus impeding the differential diagnosis between radionecrosis and recurrence. Finally, since the introduction of antiangiogenic agents such as bevacizumab, the phenomenon of pseudoresponse further complicates the assessment of treatment response using standard MRI alone (74, 77).

^{18}F-FDG PET shows a decreased metabolic rate of cerebral glucose after radiotherapy or chemotherapy even if hypermetabolism is observed in the early phase after radiotherapy mostly due to the inflammatory process (20, 78, 79). ^{18}F-FDG nevertheless displays low specificity between radionecrosis and tumor recurrence (80) as well as a weak added value to MRI (81). In contrast, amino acid tracers appear to be better tools to provide sensitive monitoring of the response to various treatment options as well as the early detection of tumor recurrence, including an improved differentiation of tumor recurrence from post-therapeutic effects (82).

[11]C-MET is considered as very helpful in the assessment of these patients because the decrease in amino acid in the metabolically active tumor volume is a sign of treatment response associated with long-term outcome (83, 84). Accordingly, combined assessment with MRI and ^{11}C-MET at 8 weeks can differentiate true responders, that is, those predicted to show a more favorable prognosis, from pseudoresponders (85). F[18] labeled amino acid tracers can also determine treatment response after chemotherapy with a higher accuracy than MRI alone. A comparative illustration between ^{18}F-FET PET and contrast-enhanced MRI is shown in Figure 3. For example, in a study involving 25 patients with glioblastoma after early completion of radiochemotherapy, a decrease in both ^{18}F-FET
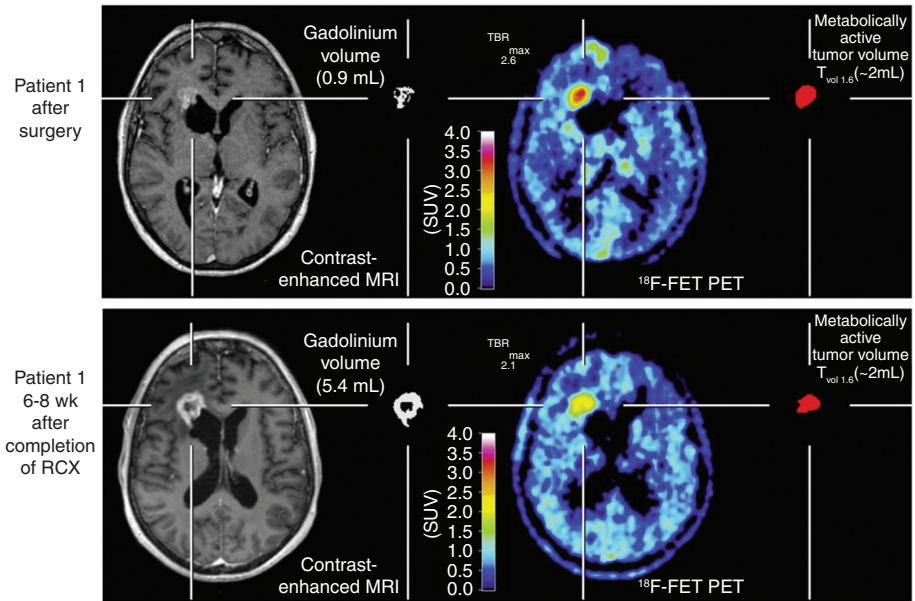
Figure 3 **¹⁸FET-PET in a 59-year-old woman with glioblastoma.** Brain imaging was performed after surgery (upper panel; MRI-/FET-1) and 6–8 weeks after completion of radiochemotherapy (lower panel; MRI-/FET-3). Contrast-enhanced MRI with corresponding contrast-enhanced volume is shown on the left and ¹⁸F-FET PET with corresponding metabolic volume on the right. Enlargement of contrast-enhanced volume on MRI 6–8 weeks after completion of radiochemotherapy (lower panel) is suggestive of tumor progression, whereas ¹⁸F-FET PET conversely indicates responsiveness with decreasing amino acid uptake (reduction of TBRmax) and unchanged metabolic volume. (Adapted from J Nucl Med 2012;53:1048–1057. Copyright: Society of Nuclear Medicine and Molecular Imaging, Inc. Reproduced with Permission.)

TBR(max) and TBR(mean) was found to be a highly significant and independent statistical predictor of progression-free survival and overall survival. On the contrary, contrast enhancement volume changes had no significant predictive value for survival (86).

Otherwise, it has been shown that ¹⁸F-FET PET is able to differentiate pseudo-progression from early tumor progression within the first 12 weeks after completion of radiochemotherapy with concomitant temozolomide. In patients with pseudoprogression, ¹⁸F-FET uptake was found to be significantly lower than in patients with early progression (TBRmax 1.9 ± 0.4 vs. 2.8 ± 0.5, TBRmean 1.8 ± 0.2 vs. 2.3 ± 0.3). Performances for diagnosis of pseudoprogression with ¹⁸F-FET PET were high in sensitivity, specificity, and accuracy by using TBRmax reaching up to respectively, 100, 91, and 96% (87). Moreover, a rapid increase in radiotracer uptake in time activity curves (shorter time to peak) was more frequently present in patients with tumor progression (87). Furthermore, a recent study has even proposed an original method of clustering based on textural ¹⁸F-FET PET features that could distinguish pseudoprogression from true tumor progression (88). In addition, ¹⁸F-FET PET has also been found to provide valuable information in assessing the elusive phenomenon of late pseudoprogression (89).

^{18}F-FDOPA can identify treatment responders to antiangiogenic therapy as early as 2 weeks after treatment initiation and thus could be an efficient tool in case of suspicion of pseudoresponse (90). In a study involving antiangiogenic therapy, a decrease in ^{18}F-FDOPA PET tracer uptake was associated with longer progression-free survival and overall survival (91). Furthermore, in this latter study, the volume fraction of increased ^{18}F-FDOPA PET uptake measured at two time points after bevacizumab treatment also enabled to stratify long-term and short-term progression-free survival as well as overall survival (91). Responders based on ^{18}F-FDOPA PET data survived 3.5 times longer (12.1 months vs. 3.5 months of median overall survival) than nonresponders, which was much higher than responders based solely on MRI (90). Similar results have been reported for ^{18}F-FET (92–94).

With regard to the differential diagnosis between tumor recurrence and radio-necrosis, ^{11}C-MET provides a better sensitivity and clearer delineation of the suspected recurrence (83). In a comparative study, ^{11}C-MET was found to be superior to ^{18}F-FDG for diagnostic accuracy in distinguishing glioma recurrence from radiation necrosis (95). Similarly, in a prospective comparison with ^{18}F-FDG PET, ^{18}F-FDOPA PET had a diagnostic accuracy of 100% for the diagnosis of glioblastoma recurrence versus 92.8% with ^{18}F-FDG PET (96). In addition, in a study of 110 glioblastoma patients, ^{18}F-FDOPA PET detected recurrence with high accuracy while lesion-to-normal-tissue ratios were predictive of progression-free survival (97). Finally, ^{18}F-FDOPA PET is also able to distinguish tumor recurrence from treatment-related changes (24), an example of which is depicted in Figure 4.
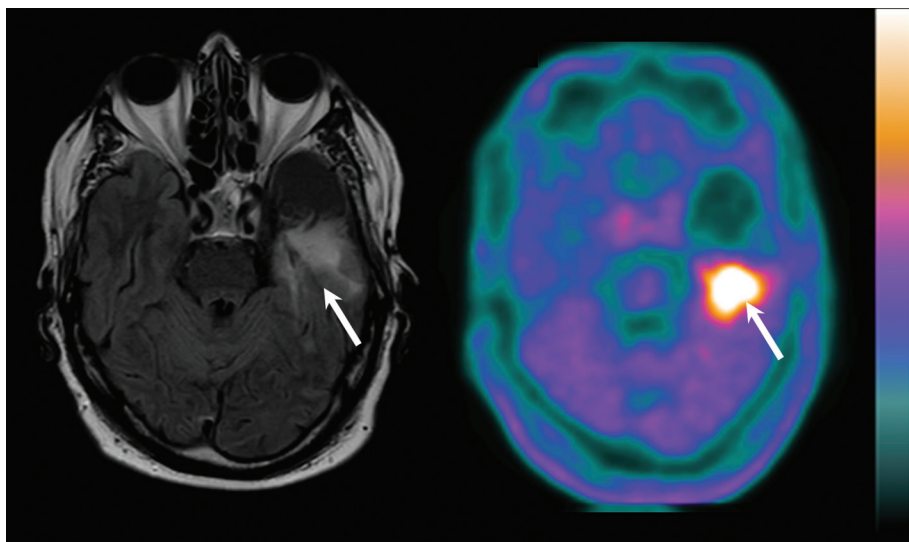

Figure 4 Left temporal glioblastoma recurrence in a 66-year-old man after surgery and adjuvant radiochemotherapy. The axial slice of Fluid-Attenuated Inversion Recovery (FLAIR)-weighted MRI (left side) shows a hypersignal at the posterior area of the exeresis cavity (white arrow), making the distinction between tumor recurrence and post-therapeutic effects somewhat challenging. The axial slice of ^{18}F-FDOPA PET shows an intense uptake in the same area (white arrow), which is strongly in favor of tumor recurrence.

In a similar manner, static and dynamic ^{18}F-FET PET parameters can differentiate progressive or recurrent glioma from treatment-related nonneoplastic changes with a higher accuracy than conventional MRI, especially with regard to glioblastoma recurrence (98, 99).

Prognostication

^{18}F-FDG provides an additional prognostic value to MRI (100) in newly diagnosed (12) or recurrent glioblastomas (101). Indeed, the tumor-to-normal brain tissue ratio has been reported to predict overall survival in a newly diagnosed glioblastoma subgroup, independently of age, Karnofsky performance status, histological grade, and surgery (12). In addition, in a series of 20 recurrent glioblastomas, ^{18}F-FDG uptake was found to be the most powerful predictor of both progression-free survival and overall survival, using either univariate or multivariate analysis, among all variables tested, including histological grade, Karnofsky performance status, steroid intake, and number of previous treatments (101).

Prognostic value is also a feature of amino acid tracers. Indeed, ^{11}C-MET uptake is correlated to prognostic, histological, and molecular parameters in gliomas at initial stage (102). Moreover, a prospective multicenter trial investigating the role of pretreatment ^{18}F-FET PET in newly diagnosed glioblastoma found BTV prior to radiochemotherapy to be highly prognostic of outcome (62). Furthermore, ^{18}F-FET PET time–activity curves before treatment and their changes after radiochemotherapy were also related to outcome, whereby patients with increasing time–activity curves experienced longer overall survival (62). This latter observation is in accordance with results of previous studies investigating amino acid PET in malignant glioma prior to therapy in which volumetry of ^{11}C-MET uptake was a pretreatment prognostic marker in patients with malignant glioma (103). Interestingly, tumor-to-normal brain tissue ratio using ^{18}F-FDOPA PET was also reported as an independent predictor of survival, along with the size of recurrent tumor on MRI in patients with suspected recurrent glioblastomas (104). More recently, a combination of two radiotracers was used to define a metabolic tumor volume in hypoxia, with the latter expressed as the volume of ^{18}F-FDG /^{18}F-fluoromisonidazole (^{18}F-FMISO) double-positive, and ^{18}F-FMISO used as a radiotracer of hypoxia. This metabolic tumor volume in hypoxia was a significant predictor of progression-free survival and overall survival in glioblastoma patients (105).

Future Perspectives: Novel Radiotracers and Multimodality

Several other radiotracers have been developed for diagnosis, prognosis, or follow-up of glioblastomas (106). Among the better-known compounds, the aforementioned ^{18}F-FMISO, a nitroimidazole derivative, was developed as a PET imaging agent of hypoxia (107), through the trapping of its metabolites into hypoxic cells (108). Hypoxia in tumors is a pathophysiological consequence of

structurally and functionally disturbed angiogenesis along with a deterioration in the ability of oxygen to diffuse through the tissues and is associated with progression and resistance to radiotherapy (109). ^{18}F-FMISO uptake has been found in high-grade gliomas, but not in low-grade gliomas, along with a significant relationship between its uptake and expression of the angiogenesis marker VEGF-R1. Thus, ^{18}F-FMISO may have a role in directing and monitoring targeted hypoxic therapy (110).

Another radiotracer, ^{18}F-fluorothymidine (^{18}F-FLT), is a thymidine analog developed for the purpose of imaging tumor cell proliferation (111). ^{18}F-FLT has been used in diagnosis and assessment of glioma grading, in differentiating tumor recurrence from radionecrosis, in assessing response to treatment, and in predicting overall survival (112). In an image-guided biopsy study, results demonstrated that ^{18}F-FLT, while a useful marker of cell proliferation, and although correlated with regional variations in cell proliferation, was unable to identify the margin of gliomas (113). This is due to the fact that ^{18}F-FLT is not able to penetrate the intact blood–brain barrier and normally accumulates only in areas with contrast enhancement on MRI (114, 115).

[11]C-Choline has been used as a marker of cell membrane phospholipids in brain tumors, exhibiting a significant correlation of uptake with the degree of glioma malignancy (116). However, as is the case with ^{18}F-FLT, tracer uptake is limited to areas with blood–brain barrier disruption and therefore this tracer offers limited additional information compared to a contrast-enhanced MRI. It should nevertheless be emphasized that, despite their many advantages, the majority of these radiotracers as well as multiple others are not widely available and are only used in a limited number of centers since they require well-experienced staff with on-site radiochemistry equipment and cyclotron. These radiotracers are currently available only in research centers. Furthermore, future perspectives also include multimodality imaging. Accordingly, technological innovations in glioma imaging assessment such as simultaneous acquisition of anatomic and functional images with the integration of PET–MRI data appear to be of particular promise for research, diagnosis, and treatment of glioblastomas. Fully integrated PET/MRI scanners are now available and the number of scanner installations and published studies is steadily on the rise (117–119). Furthermore, hybrid PET–MRI systems offer improved patient comfort due to a significant reduction in measurement time and improved spatial and temporal co-recording of PET and MRI data. Hybrid PET–MR allows comparing amino acid PET data with advanced MR parameters including perfusion-weighted imaging, magnetic resonance spectroscopy, and diffusion-weighted imaging (118).

In addition to this technical multimodality and the concomitant efforts of using various radiopharmaceuticals to characterize multiple biological targets (61, 105), currently used multiparametric imaging also integrates the development and applications of innovative methods of image processing and analysis (120). While common metrics such as standard uptake value (SUV) or BTV or TBR only partially describes the properties of pathological lesions, novel parameters such as shape and uptake heterogeneity may provide additional information on the biological profile associated with tumor aggressiveness or degree of response to specific treatment and, consequently, with prognosis (121).

Conclusion

In summary, PET is a nuclear medicine imaging method with increasing relevance in diagnosis, therapy monitoring, and prognostication of glioblastomas. In clinical practice, currently used radiotracers are focused on imaging of glucose metabolism and amino acid transport. Both classes of tracers can provide information on grading and prognosis of gliomas, but amino acid tracers, which exhibit lower uptake in normal brain tissue, are better suited for delineation of tumor extent, treatment planning, and follow-up than ^{18}F-FDG. Although the use of PET in the diagnosis of glioblastomas is still at an early stage of development in clinical practice, development of novel radiotracers and recent innovations in multimodality imaging are expected to enhance its use in the assessment of these tumors in the near future.

Conflict of interest: The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

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