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From the clinician's point of view - What is the status quo of positron emission tomography in patients with brain tumors?

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The most common type of primary brain tumor is malignant glioma. Despite intensive therapeutic efforts, the majority of these neoplasms remain incurable. Imaging techniques are important for initial tumor detection and comprise indispensable tools for monitoring treatment. Structural imaging using contrast-enhanced MRI is the method of choice for brain tumor surveillance, but its capacity to differentiate tumor from nonspecific tissue changes can be limited, particularly with posttreatment gliomas. Metabolic imaging using positron-emission-tomography (PET) can provide relevant additional information, which may allow for better assessment of tumor burden in ambiguous cases. Specific PET tracers have addressed numerous molecular targets in the last decades, but only a few have achieved relevance in routine clinical practice. At present, PET studies using radiolabeled amino acids appear to improve clinical decision-making as these tracers can offer better delineation of tumor extent as well as improved targeting of biopsies, surgical interventions, and radiation therapy. Amino acid PET imaging also appears useful for distinguishing glioma recurrence or progression from postradiation treatment effects, particularly radiation necrosis and pseudoprogression, and provides information on histological grading and patient prognosis. In the last decade, the tracers *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET) and 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine (FDOPA) have been increasingly used for these indications. This review article focuses on these tracers and summarizes their recent applications for patients with brain tumors. Current uses of tracers other than FET and FDOPA are also discussed, and the most frequent practical questions regarding PET brain tumor imaging are reviewed.

Keywords: FDOPA, FET, MET, MRI, PET.

The annual incidence of malignant gliomas is approximately 5–6 cases per 100 000 people. Gliomas are associated with disproportionately high morbidity and mortality.[1] Despite all treatment efforts including maximal surgical resection, radiotherapy, and/or chemotherapy, results as measured by survival time and quality of life remain unsatisfactory. Median survival is only 15–17 months for patients with glioblastoma[2,3] and 2–5 years for patients with anaplastic glioma[1] WHO grade III, with the exception of anaplastic gliomas with oligodendroglial component and 1p/19q codeletion treated with radiotherapy and PCV (procarbazine, lomustine, and vincristine chemotherapy[4]).

Contrast-enhanced MRI, with its excellent soft tissue contrast, high spatial resolution, and multiplanar reconstruction capabilities, is currently the method of choice for detection and differential diagnosis of brain masses. With this widely available technique, tumors can be reliably identified and well characterized in terms of their location, extent, mass effect, and potential disruption of the blood-brain barrier (BBB). However, contrast enhancement resulting from BBB permeability is nonspecific and may not always be an accurate surrogate for tumor grade, burden, or treatment response.[5,6]

Positron-emission tomography (PET) is one of the most promising techniques for imaging specific molecular processes in vivo. This method uses biologically active molecules labeled with short-lived positron-emitting isotopes at micromolar or nanomolar concentrations. Molecular imaging using PET may provide relevant additional information on tumor metabolism and may be helpful for clinical decision-making, especially in the setting of ambiguous MRI findings.

This review article focuses predominantly on the PET tracers *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET) and 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine (FDOPA) and summarizes

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investigations of their recent applications in patients with brain tumors. A brief review of advances for other tracers is also included. Lastly, the most frequent practical questions regarding PET brain tumor imaging are discussed.

Molecular Probes for Pet Imaging of Gliomas

The classic and most common PET tracer for oncologic imaging, both neurologic and nonneurologic, has traditionally been ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG). FDG is accumulated in the majority of tumors due to increased energy demand and consequently elevated glucose metabolism. FDG uptake has been well characterized for tumors outside the brain and has also been applied to brain tumor imaging for many years. The relationship of FDG uptake to tumor glioma grade and prognosis has been reported in several studies.[7] As newer PET tracers have become available, the use of FDG for neuro-oncologic imaging has declined, in part due to several important limitations as discussed below.

Radiolabeled amino acids have been used in neuro-oncological practice since the early 1980s. The most experience with this class of PET tracers for brain tumor imaging has been gained with ^{11}C-methyl-L-methionine (MET). MET is an essential amino acid labeled with the positron-emitting isotope carbon-11, which has a half-life of 20 minutes.[7] This relatively short half-life limits the use of MET to PET centers with a cyclotron. More recently, amino acid tracers labeled with positron emitters, which have longer half-lives, have been synthesized. This has resulted in improved clinical reach, efficiency, and cost-effectiveness.[8] For example, FET was developed in the late 1990s and is an ^{18}F-labeled amino acid tracer (half-life, 110 min), resulting in logistic advantages for clinical practice compared with MET.[9,10] The use of FET has grown rapidly in recent years, especially in Western Europe. Clinical results in brain tumors with PET using MET and FET appear similar.[11–13] Another ^{18}F-labeled amino acid analogue, FDOPA, which was primarily developed to measure dopamine synthesis in the basal ganglia, has also been used increasingly as a tracer for brain tumor imaging.[14]

In addition to FDG and radiolabeled amino acids, several other radiopharmaceuticals have been used to image brain tumors. The thymidine nucleoside analogue 3′-deoxy-3′-^{18}F-fluorothymidine (FLT) reflects thymidine kinase-1 activity, which is the principle enzyme in the pathway of DNA synthesis, and therefore depicts cell proliferation. Although FLT is a promising tool for glioma diagnosis and grading[15,16] and has been shown to be predictive of survival after bevacizumab treatment,[17] it has limitations for clinical use because of permeability restrictions of the intact blood-brain barrier (BBB) and nonspecific flow-related activity.[5]

Imaging of hypoxia in brain tumors has been performed with the tracer ^{18}F-fluoromisonidazole (FMISO).[18] FMISO enters tumor cells by passive diffusion and becomes trapped in cells with reduced tissue oxygen partial pressure by nitroreductase enzymes. Clinically, this tracer is of interest for identifying hypoxic tumor areas, which are thought to be more resistant to irradiation.[19] However, to date FMISO has predominantly been used in a preclinical setting.[20]

Another target of growing interest in molecular imaging is the translocator protein (TSPO), a mitochondrial molecule expressed specifically in proliferating glioma and other cells including activated microglia and macrophages. Imaging with the TSPO ligand ^{11}C-(R)PK11195 demonstrates increased binding in tumor cells of high-grade gliomas compared with low-grade gliomas and normal brain.[21,22] However, ^{11}C-(R)PK11195, like MET, is limited to PET centers with a cyclotron due to its short half-life.

The Most Frequent Questions Regarding Practical Considerations for PET Brain Tumor Imaging

What are the Disadvantages of FDG PET Imaging in Patients with Brain Tumors?

Despite the potential benefits of grading and prognostication for brain tumors, FDG PET has considerable limitations in the evaluation of intracranial neoplasms.[23] Because of the high rate of physiologic glucose metabolism in normal brain tissue (ie, high background uptake), the identification of tumors with only modest increase of glucose metabolism (eg, low-grade gliomas and, in some cases, high-grade gliomas) is difficult. FDG uptake in low-grade tumors is usually similar to that of normal white matter, and uptake in high-grade tumors can be less than or similar to that of normal gray matter (Fig. 1), thus decreasing the sensitivity of lesion detection.[23] Furthermore, due to spillover effects related to high glucose consumption of normal brain parenchyma, small brain tumors may be inconspicuous. Thus, low tumor-to-background contrast limits the use of FDG PET for assessing brain tumors.

What are Advantages and Disadvantages of Amino Acid PET Tracers for Brain Tumor Imaging?

Amino acid PET tracers, including MET, FET, and FDOPA, are transported via the L amino acid transporter type 1 (LAT1) system and are particularly attractive for brain tumor imaging because of high uptake in neoplastic tissue and relatively low uptake in healthy brain parenchyma, which result in high tumor-to-background contrast.[7,24] LAT1 is upregulated in cerebral gliomas, but the expression at the normal BBB is considerably lower. Due to the fact that these amino acid tracers are also transported into the normal brain, disruption of the BBB is not a prerequisite for intratumoral accumulation of MET, FET, or FDOPA. Consequently, uptake of these tracers has been reported for low-grade gliomas without BBB leakage.[25,26]

Several disadvantages of FET and FDOPA should also be noted. In the case of FDOPA, physiologic uptake in the corpus striatum[27] may obscure margins of tumors that extend into the basal ganglia (Fig. 2). For FET, slower renal elimination results in detectable amounts of tracer being present in the blood pool for longer periods of time. This may lead to nonspecific tracer uptake. For example, the FET signal is physiologically increased in vascular malformations and dural venous sinuses. Thus, for tumors located in close proximity to brain sinuses, differentiation between blood vessel and metabolically active tumor may be challenging. Coregistration of PET images with higher spatially resolved images from contrast-enhanced MRI may help to ameliorate this difficulty. Nevertheless, lower spatial resolution of PET remains an important limitation. Current

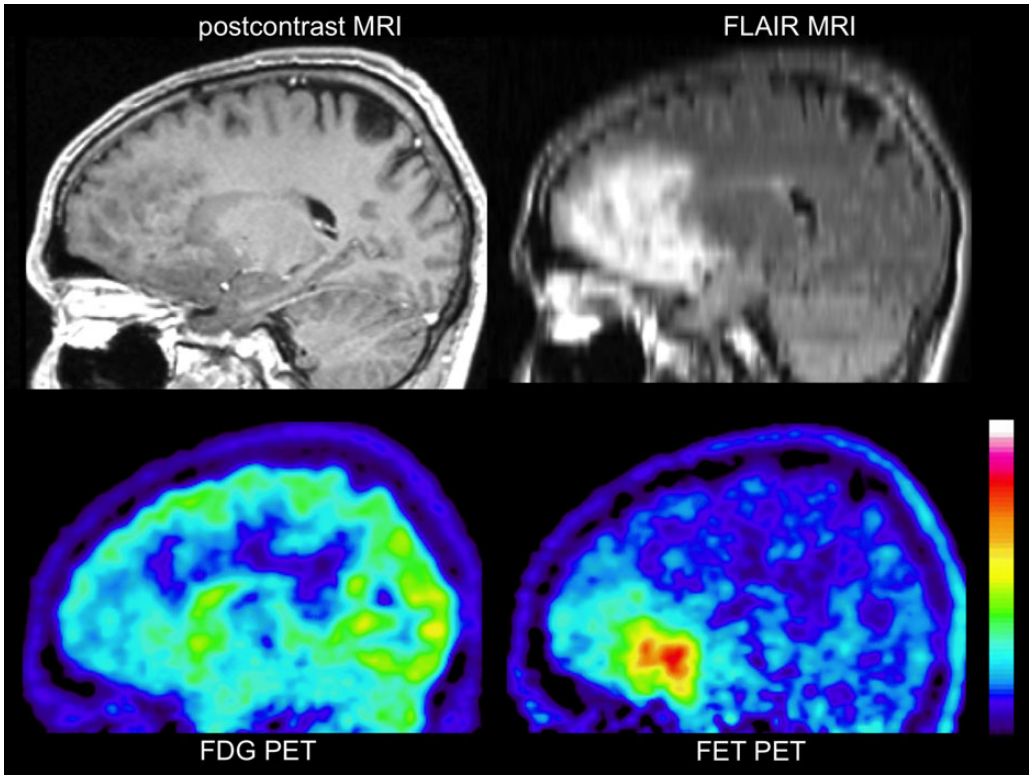

Fig. 1. Patient with a newly diagnosed frontal brain tumor. MRI depicts no clear pathological contrast enhancement and a widespread, diffuse FLAIR signal. Thus, the tumor cannot be well delineated by MRI alone. Additional FDG PET imaging shows no hypermetabolic activity. Only FET PET is able to identify the hypermetabolic hotspot of the tumor. FET PET-guided stereotactic biopsy revealed an anaplastic oligoastrocytoma, WHO grade III. Abbreviations: FDG, ^{18}F-2-fluoro-2-deoxy-D-glucose, FET, *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine FLAIR, fluid-attenuated inversion recovery.

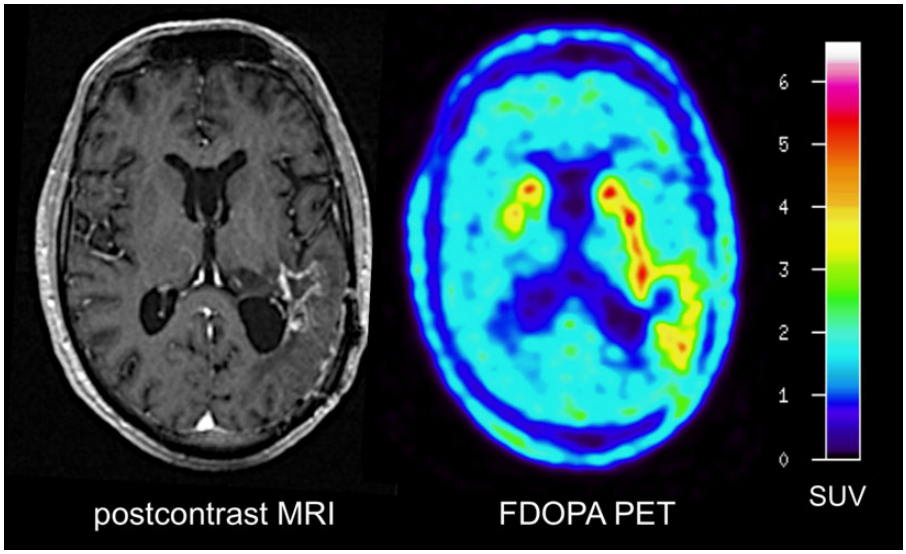

Fig. 2. Patient with a recurrent oligodendroglioma, WHO grade II. MRI shows an area with contrast enhancement in the left hemisphere. In contrast, FDOPA PET identifies metabolically active tumor, which is larger than the area with contrast enhancement. Furthermore, tumor delineation is difficult due to physiological FDOPA uptake in the striatum (courtesy of Dr. Francesco Cicone, Dept. of Nuclear Medicine, Sant'Andrea Hospital, "Sapienza", University of Rome, Italy). Abbreviations: FDOPA, 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine.

scanners achieve a resolution of about 4–6 mm compared with about 2 mm for MRI. This can lead to false-negative findings because small lesions may be undetectable with PET.

Are the PET Tracers MET, FET, and FDOPA Comparable?

In general, amino acid tracers that are transported via the LAT1 system have been shown to yield similar results for brain tumor

imaging. Several papers have compared PET scans of brain tumor patients using various tracers. The delineation of tumor extent using MET, FET, and FDOPA appears comparable based on the metabolically active tumor volume.[13,14,27,28] Furthermore, these tracers all provide excellent tumor-to-background contrast. In addition to visual interpretation, semiquantitative analysis of tracer uptake using region-of-interest analysis on the basis of static PET scans has become important in amino acid PET interpretation.[29] Although standardized uptake values of MET and FET are not directly comparable, they are strongly correlated.[13] In high-grade gliomas, standardized uptake values and tumor-to-background contrast tend to be higher for FET compared with FDOPA, but this does not appear to impact tumor visualization.[28]

Is Dynamic PET Imaging Helpful in Clinical Neuro-oncology?

Dynamic PET imaging for brain tumor visualization involves the collection of a series of frames of PET data over contiguous time intervals, usually in the range of 1–5 minutes. Data from each of the frames is independently reconstructed to form a set of images. These images can then be used to characterize the temporal pattern of tracer uptake by deriving a time-activity curve. Time-to-peak, defined as time from the beginning of the dynamic acquisition up to the maximum tumor uptake, can also be calculated.[30]

A number of studies have indicated that time-activity curves of FET uptake contain biological information beyond that of static images, and this data may be helpful for glioma grading. For example, it has been reported that high-grade gliomas are characterized by an early activity peak around 10–15 minutes after injection, followed by a decrease of FET uptake, while low-grade gliomas typically exhibit delayed and steadily increasing tracer uptake.[30–34] These patterns were observed for primary as well as recurrent tumors[32,34,35] and appear to be a special characteristic of FET since they were not observed for other amino acid tracers such as MET and FDOPA.[27,36] Using dynamic FET PET, the accuracy of differentiating high-grade from low-grade gliomas (both primary tumors and recurrent) was initially reported to be greater than 90%,[30,32,33,35,37] whereas more recent data suggest a value of around 80%.[34,38] In either case, the results suggest the ability to improve noninvasive tumor grading over MRI images alone. Other uses of dynamic FET PET that are less well studied include applications for determining patient prognosis[38–40] and for differentiating brain metastasis recurrence from treatment-related changes after radiosurgery.[41] One caveat is that differences in data processing of dynamic FET scans in different PET centers limit the comparability of the results. Thus, standardization of data processing is needed to make clinical results comparable.

Recent Advances in PET Imaging for Brain Tumors

Previously, amino acid PET was mainly used for several indications including detection of neoplastic tissue (especially when standard MRI is inconclusive) (Fig. 3), the delineation of brain tumor extent for improved treatment planning and biopsy-guidance, and the differentiation of glioma recurrence or progression from post-radiation treatment effects, particularly radiation necrosis. For these indications, the tracer MET has predominantly been used, and the value of PET for these classical indications has been summarized in several review articles.[7,20,24,42,43] In the last few years, application of FET and FDOPA PET imaging has been expanded to additional diagnostic problems in neuro-oncology, as discussed below.

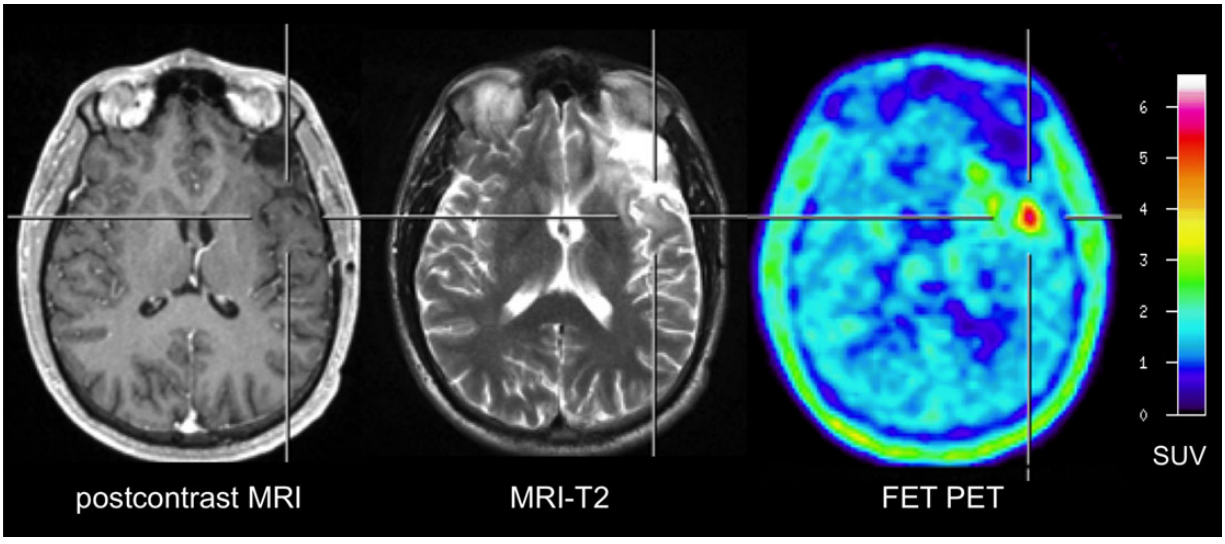

Fig. 3. Patient with an anaplastic oligoastrocytoma (WHO grade III) in the temporal lobe. T1-weighted MRI shows no clear pathological contrast enhancement, and the tumor cannot be delineated. T2-weighted MRI shows widespread abnormalities and is also not helpful for depicting the tumor. In contrast, FET PET identifies a tumor with increased tracer uptake in the left temporal lobe. After tumor resection, the recurrence of an anaplastic oligoastrocytoma could be confirmed histologically. Abbreviation: FET, *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine.

Pseudoprogression

Postradiation treatment effects can be divided into acute effects (ie, immediately after or even during radiotherapy), subacute (early-delayed) effects (ie, pseudoprogression), or late effects such as radiation necrosis.[44] Pseudoprogression has commonly been defined as a subacute, posttreatment reaction with increased contrast enhancement and edema that mimics tumor progression but subsequently stabilizes and/or regresses without further intervention.[45] In contrast, radiation necrosis belongs to the late postradiation treatment effects category and may appear months to several years after radiation therapy (later than the typical time period for pseudoprogression[46]). Radiation necrosis can also be progressive and irreversible.[47]

Since the introduction of radiochemotherapy with temozolomide as the current standard of care for patients with glioblastoma, there has been increasing awareness of progressive enhancing lesions on MRI that are not related to tumor progression but rather are due to treatment effect (ie, pseudoprogression). Pseudoprogression is typically regarded as a phenomenon of the first 12 weeks after radiotherapy,[47–49] and this time-dependent definition has been incorporated into the new criteria for Response Assessment in Neuro-Oncology (RANO).[48] Although pseudoprogression most often occurs within the first 12 weeks after completion of therapy, some cases of later-onset pseudoprogression have been observed, especially after radiochemotherapy using temozolomide in combination with lomustine.[50] Depending on the literature, pseudoprogression occurs in 10%–30% of patients with malignant glioma.[47,51,52] This is of great importance because a successful treatment might be erroneously terminated in patients with pseudoprogression, potentially reducing their survival.

Conventional MRI does not allow a reliable distinction between tumor recurrence and pseudoprogression. Several preliminary reports have suggested that FET PET might be helpful for this indication within the narrow time frame of the first 12 weeks after completing radiochemotherapy.[13,53,54] Compared with conventional MRI, a more recent study with a larger patient cohort ($n = 22$) reported a sensitivity and specificity of FET PET of more than 90% for differentiating pseudoprogression from tumor progression in glioblastoma patients after standard radiochemotherapy.[55] Similarly, FDOPA PET may also be useful for identifying pseudoprogressors. A study with 110 glioblastoma patients showed a diagnostic accuracy of 82% for FDOPA PET in distinguishing recurrent disease from treatment-related changes.[56] However, treatment-related changes such as early-delayed effects/pseudoprogression versus late effects/radiation necrosis were not further specified in that study. Thus, despite the lack of confirmatory PET studies investigating the 12-week time frame after radiochemotherapy with more subjects, the present data on amino acid PET suggest that this technique may facilitate the diagnosis of pseudoprogression following radiotherapy of malignant glioma.

Differentiation of Radiation-induced Changes From Recurrent Brain Metastasis After Radiosurgery

In view of (i) the sociodemographic changes of industrialized society with an increasing elderly population and (ii) the improved therapeutic regimens for extracranial tumors (eg, biomarker-guided patient stratification, immunotherapy) resulting in an overall improvement of survival, the number of patients diagnosed with brain metastases is expected to increase. Besides neurosurgical resection, various types of radiation therapy such as radiosurgery, brachytherapy, and whole-brain radiation therapy are commonly used to treat secondary brain neoplasms.

Neuro-oncologists are often confronted with the clinical problem that conventional MRI cannot reliably differentiate brain metastasis recurrence or progression from radiation-induced changes (eg, radiation necrosis) after radiation therapy and particularly after radiosurgery. In gliomas, radiation necrosis usually manifests within 6 months after standard radiotherapy and occurs in approximately 5%–25% of these patients.[46,57] For patients with brain metastasis treated by radiosurgery, a similar fraction of radiation necrosis (24% of 310 cerebral metastases) has been reported,[58] although the risk of radiation necrosis may be as high as 47% depending on the irradiated volume receiving a specific radiation dose.[58]

Amino acid PET has been recently investigated as a problem-solving tool to address this highly relevant problem in clinical practice. For instance, MET PET may be effective in differentiating recurrent metastatic brain tumor from radiation-induced changes since a simple semiquantitative regions-of-interest analysis for the calculation of tumor/brain ratios demonstrated a sensitivity and specificity of 70%–80%.[59,60] FDOPA PET has been shown to differentiate recurrent or progressive brain metastasis from radiation-induced changes with high sensitivity (81%) and specificity (84%).[61] Another study has reported an FDOPA PET accuracy of 91% for differentiating radiation-induced changes from progressive disease in patients with brain metastases after stereotactic radiosurgery, outperforming MRI-derived perfusion metrics 91% to 76%.[62] Similar diagnostic accuracy has also been reported for FET PET: using the tumor/brain ratios and the evaluation of FET kinetic studies, FET PET differentiated local recurrent brain metastasis from radiation-induced changes with a sensitivity of 95% and specificity of 91%[41] (Fig. 4).

Assessment of Treatment Response to Antiangiogenic Treatment and Alkylating Chemotherapy

Since the introduction of antiangiogenic drugs such as bevacizumab, the problem of pseudoresponse has complicated the assessment of treatment based on the Macdonald criteria[63] alone. Bevacizumab can rapidly decrease contrast enhancement after initiation of therapy,[64] producing an erroneously high response rate. Some of the improvement observed on contrast-enhanced MRI results from a rapid normalization of abnormally permeable blood vessels that restores, at least in part, the integrity of the BBB. Hence, the extent of reduction of contrast enhancement may not fully reflect the true antitumor activity of the antiangiogenic agent.[6] Not infrequently, radiographic images after antiangiogenic therapy suggest a response that is more impressive than the clinical benefit derived from the therapy. Thus, it appears that the use of antiangiogenic drugs alters the image characteristics of enhancing tumor more noticeably than that of nonenhancing tumor.[6] In order to overcome the limitations of the Macdonald criteria for assessment of antiangiogenic treatment, the RANO group proposed new recommendations for evaluating response.[48] In the setting of antiangiogenic therapy, the group recommends

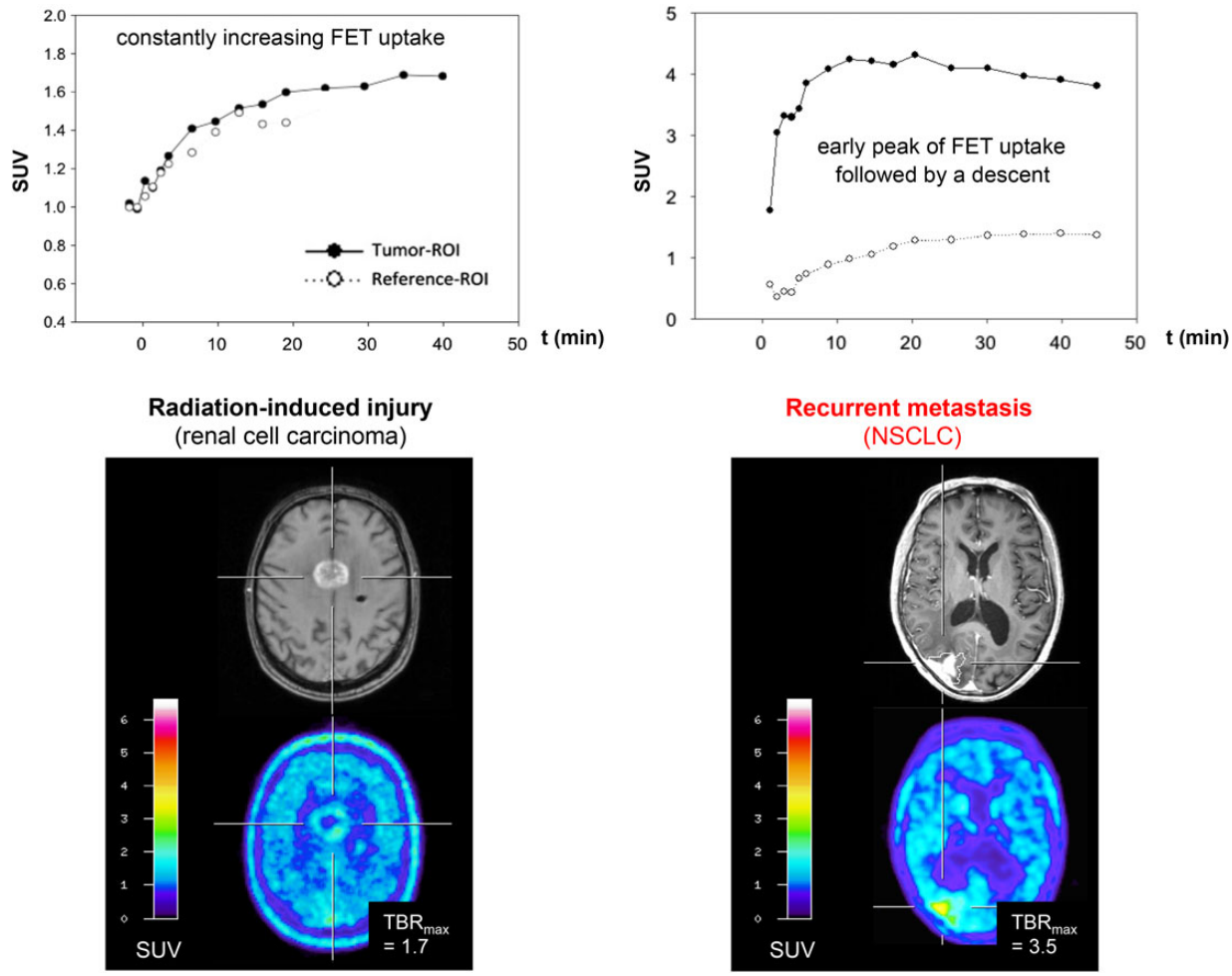

Fig. 4. (Left) A patient with a brain metastasis of a renal cell carcinoma (left side), which was treated by radiosurgery. Four months after intervention, MRI suggests recurrent disease. In contrast, FET PET shows only minimal metabolic activity, and the time-activity curve shows a constantly increasing uptake pattern, consistent with radiosurgery-induced changes. Ten months after radiosurgery, the patient is still clinically stable and asymptomatic. (Right), A patient with a histologically proven recurrence of a metastasis of a non–small cell lung cancer in the right occipital region 12 months after radiosurgery (right side). FET PET shows increased metabolic activity, and the time-activity curve shows an early peak around 20 minutes after injection followed by a decrease of FET uptake, consistent with brain metastasis recurrence. Abbreviation: FET, *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine.

fluid-attenuated inversion recovery (FLAIR) or T2 hyperintensity as a surrogate for nonenhancing tumor to help determine progression, thereby including nonenhancing disease as a criterion for determining tumor response.[48] However, RANO does not quantify the degree of FLAIR or T2 change necessary to define progression because of difficulties in achieving reproducible measurements of nonenhancing tumor. Tumor-related edema or ischemia, radiation effect, demyelination, and infection can all result in increased FLAIR or T2 signal, thereby diminishing the specificity of these abnormalities and making the confident identification of nonenhancing tumor difficult.[6]

Consequently, amino acid PET as an alternative imaging method has been evaluated for the assessment of treatment response to antiangiogenic therapy.[65] Recent studies and case reports suggest that changes in FET and FDOPA PET parameters such as the metabolically active tumor volume is useful for determining treatment failure of antiangiogenic treatment with bevacizumab earlier than MRI-based RANO criteria.[66,67] FET and FDOPA PET have also been used to predict a favorable outcome for responders to bevacizumab.[68–70]

For patients treated with cytotoxic rather than antiangiogenic therapy, MET and FET PET may improve response assessment. For instance, MET PET has been extensively evaluated to assess the effects of alkylating chemotherapy. Reliable monitoring of adjuvant temozolomide and PCV chemotherapy has been demonstrated with MET in patients with recurrent high-grade glioma.[71–73] Similarly, FET PET has been used to assess effects of cytotoxic chemotherapy (ie, temozolomide chemotherapy) according to the EORTC protocol 22033–26033 (75 mg/m^2 temozolomide per day over 21 days of every 28-day cycle). In a prospective study, FET PET was compared with FLAIR-weighted MRI for evaluation of response to the temozolomide regimen in 11 patients with progressive, nonenhancing low-grade glioma (WHO grade II).[74] A reduction of the

metabolically active tumor volume after initiation of treatment could be observed substantially earlier in responding patients than volume reductions on FLAIR sequences, suggesting that FET PET may be an earlier marker of successful treatment than standard MRI for this patient group.

Prognostication

The prognostic potential of amino acid PET in untreated glioma patients has been explored for both high-grade and low-grade tumors. In patients with low-grade glioma at initial diagnosis, low tumoral MET uptake is associated with longer survival compared with patients exhibiting higher MET uptake.[75–77] Furthermore, only patients with high MET uptake tumors appear to benefit from surgery.[75] Combining FET PET and tumor morphological features derived from MRI can be used to predict survival of patients with newly diagnosed low-grade glioma[78] because low baseline FET uptake and a circumscribed (rather than a diffuse) growth pattern on T2-weighted MR images are associated with favorable outcome. More recent studies using dynamic FET PET suggest that untreated patients with both low-grade and high-grade glioma with decreasing time-activity curves of FET uptake at initial diagnosis may have an unfavorable prognosis.[38–40] During follow-up of low-grade gliomas, a change of the FET uptake curve from a positive to a negative slope and increasing FET uptake can indicate malignant progression.[34]

Prognostic accuracy for patients with high-grade gliomas may also benefit from PET imaging. For instance, pretreatment of metabolically active tumor volume, as assessed by MET PET in patients with high-grade glioma, might help determine prognosis.[79] Similarly, FET PET has been used to predict prognosis for glioblastoma both before and after radiotherapy.[80,81]

Radiotherapy Planning, Radiotherapy, and Monitoring of Radiotherapy Effects Under Guidance of Amino Acid PET

Recently, biopsy-guided studies have shown that amino acid PET is a more reliable method for determining the extent of cerebral gliomas than conventional MRI.[82–84] Accordingly, several clinical studies have evaluated amino acid PET for radiotherapy planning in glioma patients in order to delineate the target volume prior to radiotherapy.[85–92] Marked differences of the radiotherapy target volume were observed between amino acid PET and MRI/CT. It is still a matter of debate whether the amino acid PET-based target volume definition has a positive clinical impact on treatment planning, as assessed by improvement in survival time. However, some evidence indicates that this is indeed the case. For instance, a retrospective study with 44 recurrent high-grade glioma patients compared the effects of radiotherapy on survival after definition of target tumor volume based on MRI/CT in addition to MET PET or MRI/CT alone. The patients with MET PET integrated into their treatment plan had a significantly longer survival time as assessed by univariate analysis compared with patients whose treatment was planned based on MRI/CT alone (median time benefit, 4.5 mo).[93] In a subsequent prospective study of 21 recurrent glioblastoma patients, MET PET was integrated into the planning of an intensity-modulated hypofractionated stereotactic radiotherapy.[94] This protocol was well tolerated and was associated with a favorable overall survival time of 11 months from the start of radiotherapy. Additional studies with comparison to a control group will be required show the impact of MET PET on treatment planning and patient outcomes.

A prospective phase 2 study of 22 newly diagnosed glioblastoma patients evaluated an integrated-boost intensity-modulated dose escalation radiation concept (based on pre-irradiation FET PET-guided target volume delineation; total dose, 72 Gy) with concomitant and adjuvant temozolomide.[53] Compared with the EORTC trial 22981/26981,[2] the authors found that this dose escalation concept incorporating FET PET led to similar overall survival, but no clear survival benefit (14.6 vs 14.8 mo). Currently, an ongoing, randomized phase 2 multicenter trial (with a larger number of patients) is prospectively assessing the value of FET PET versus MRI-guided re-irradiation in patients with recurrent glioblastoma (GLIAA (NOA-10) study; EudraCT-No.: 2012-001121-27) This higher-powered study may provide more definitive data for evaluating the utility of FET PET to guide target volumes.

Amino acid PET has also been investigated as a way to assess response or failure of iodine-125 seed brachytherapy. For instance, one year after seed implantation in patients with low-grade glioma, MET uptake was significantly diminished, whereas glucose metabolism was unchanged as assessed by FDG PET.[95,96] In a more recent FET PET study, tumor/brain ratios, uptake kinetics, and metabolically active tumor volumes were evaluated for their value in monitoring stereotactic brachytherapy using iodine-125 seeds.[97] In that study, FET PET correctly differentiated with high diagnostic accuracy, late post-therapeutic effects after 6 months from local tumor progression in patients with recurrent high-grade glioma.

A prospective study also assessed the prognostic value of early changes of FET uptake after postoperative radiochemotherapy in glioblastoma patients.[54,98] PET responders with a decrease in the tumor/brain ratio of more than 10% had significantly longer progression-free survival and overall survival than patients with stable or increasing tracer uptake after radiochemotherapy. However, the kinetic analysis of FET uptake was not helpful for monitoring the effects of radiochemotherapy.[99]

Use of Amino Acid PET in Meningioma Patients

Amino acid and other PET techniques have also been recently investigated for their diagnostic potential in patients with meningiomas.[100] From the clinical perspective, exact tumor delineation and monitoring response to radiosurgery are highly important for guiding patient management. A promising approach is the use of PET with somatostatin receptor ligands (eg, ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE) since the somatostatin receptor subtype 2 expression is strong in most meningiomas.[101,102] The potential of amino acid PET in meningioma patients is also promising, although not sufficiently evaluated to date. Initial reports suggest that FET PET may provide additional information beyond standard imaging for noninvasive grading of meningiomas and possibly for the discrimination of tumor in critical areas of the skull base.[103,104] However, further confirmatory studies are required before substantive conclusions can be drawn about the utility of FET PET for this indication.

Recommendations for PET Imaging in Patients With Brain Tumors

Despite excellent results in imaging *extracranial* tumors, the application of FDG PET to brain tumor visualization is hampered by poor tumor-to-background contrast. A growing body of data suggest that amino acid PET, using established tracers such as MET, FET, or FDOPA, may have substantial advantages over FDG PET and add value to standard MRI for assessing patients with gliomas and other intracranial neoplasms. These amino acid tracers all depict primary and recurrent gliomas with better tumor-to-background contrast than FDG. According to the current literature, amino acid PET appears to provide additional diagnostic information in the following clinical situations: (i) the detection of neoplastic tissue, especially when MRI is inconclusive; (ii) the delineation of glioma extent for treatment planning and biopsy guidance; (iii) the differentiation of glioma recurrence or progression from postradiation treatment effects, particularly radiation necrosis; and (iv) the monitoring of treatment effects (ie, alkylating chemotherapy, antiangiogenic treatment). The delineation of tumor extent and the tumor-to-background contrast are similar for all of these amino acid tracers. However, due to logistical disadvantages of MET (ie, necessity of cyclotron unit on site, short half-life of ^{11}C), FET or FDOPA are preferable for routine clinical practice. For these aforementioned indications, dynamic PET scans are not necessary. However, dynamic FET PET may have indications for glioma grading, prognostication of untreated gliomas, and differentiation of brain metastasis recurrence from radiation-induced changes, pending additional confirmatory studies. It is important to note that dynamic PET appears to provide additional diagnostic information only when using FET. Besides amino acid PET, a number of advanced MRI techniques such as MR spectroscopy and MR perfusion-and diffusion-weighted imaging also may also improve the evaluation of brain tumor patients. The optimal combination of advanced MR and PET imaging for specific clinical indications remains to be determined.[105,106]

At present, FET seems to be the most promising amino tracer for PET imaging of brain tumors and should be given special consideration for prospective validation. Key benefits of FET are the logistical advantages of F-18 labeling compared with C-11-methionine, the differential FET kinetics in high-grade and low-grade gliomas (which have not been previously observed with other amino acids), and the lack of physiological uptake in the striatum when compared with FDOPA. These properties may account for the fact that FET is the best-studied F-18 labeled amino acid for brain tumor assessment today.

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