Clinical value of O-(2-[¹⁸F]-fluoroethyl)-L-tyrosine positron emission tomography in patients with low-grade glioma

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Progress in morphological imaging has facilitated the diagnosis of low-grade glioma (LGG) and plays a decisive role in therapeutic decisions. To date, the method of choice is contrast-enhanced MRI including T1-/T2-weighted and FLAIR sequences. However, tumor delineation and the differentiation between neoplastic and normal brain tissue can be difficult when using morphological MRI and may complicate the identification of anaplastic foci for biopsy and further treatment planning. Furthermore, therapy monitoring and the differentiation of tumor recurrence from unspecific post-therapeutic changes in the tissue are challenging. Additional information about tumor metabolism may be very helpful for the diagnostic assessment of LGG and can be provided by PET. In recent years, the PET amino acid tracer O-(2-[¹⁸F]-fluoroethyl)-L-tyrosine (¹⁸F-FET) has been clinically validated for brain tumor diagnosis. This tracer has logistical advantages over the widely used PET tracer ¹¹C-methyl-L-methionine due to the longer half-life of the ¹⁸F-label (109 vs 20 minutes, respectively). Additionally, it has been demonstrated that both tracers provide comparable diagnostic information. The authors provide an overview of the recent literature regarding the value of various clinical applications of ¹⁸F-FET PET in patients with LGG.
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THE term “low-grade glioma” includes all WHO Grade I and II gliomas. According to the WHO classification,³⁶ the most important WHO Grade II histological subtypes are astrocytomas, oligodendrogliomas, and oligoastrocytomas. The incidence of LGG in Europe is approximately 1.5/100,000 patients/year (astrocytic LGG, 1.2/100,000 patients/year; oligodendroglial LGG, 0.3/100,000 patients/year),⁶ accounting for nearly 15% of all primary brain tumors. At the time of diagnosis, patients with LGG are typically affected at an average age of 40 years.⁴⁸ Regarding the anatomical localization, there is a predilection for eloquent areas such

as the insula or the supplementary motor area.⁷ In up to 80%–90% of all patients with LGG, the most common initial clinical presentation is partial or generalized epileptic seizures.⁵⁷ Epileptic seizures are more frequently associated with cortically based tumors, particularly in frontal, temporal, and insular locations and with oligodendroglial tumors. Depending on histological subtype, the 5-year survival rate is approximately 40%–50% in astrocytoma patients and 65%–80% in oligodendroglioma patients.^{6,28} The 3 largest randomized trials (EORTC 22844, EORTC 22845, and the NCCTG trial) together studied more than 800 patients with LGG, and 58%–72% of patients were alive at 5 years from the time of diagnosis.¹⁷ Furthermore, it could be demonstrated that several factors may affect survival negatively: age greater than 40 years, astrocytoma histology, maximum tumor diameter ≥ 6 cm, tumor crossing the corpus callosum, and the presence of a neurological deficit (except epileptic seizures) before surgery.⁴²

Treatment remains challenging, and to date there is

Abbreviations used in this paper: EORTC = European Organisation for Research and Treatment of Cancer; HGG = high-grade glioma; LGG = low-grade glioma; MRS = MR spectroscopy; NCCTG = North Central Cancer Treatment Group; NPV = negative predictive value; PPV = positive predictive value; 5-ALA = 5-aminolaevulinic acid; ¹¹C-MET = ¹¹C-methyl-L-methionine; ¹⁸F-FET = O-(2-[¹⁸F]-fluoroethyl)-L-tyrosine.

no randomized prospective study defining the impact of gross-total surgery, chemotherapy, or radiotherapy.^{3,48,56,57}

Today, a general consensus for treatment is radical tumor resection if possible and subsequent chemotherapy, especially in high-risk patients with incomplete resection. The chemosensitivity of oligodendroglial tumors is higher than that of astrocytic tumors and is associated with the loss of heterozygosity on chromosome 1p/19q.⁵⁰ Furthermore, postoperative radiotherapy may be considered as it leads to longer symptom-free survival, with no influence on overall survival but with reduced quality of life.^{4,29,54,64}

To date, morphological MRI is the most important diagnostic tool for assessing LGG. Signal alterations of LGG are usually characterized by homogeneous iso- to hypointense signal changes on T1-weighted images and hyperintense signal changes on T2-weighted or FLAIR images (Fig. 1). Furthermore, oligodendrogliomas in particular exhibit calcifications in 20% of all cases,²³ which can be observed best on CT scans. Contrast enhancement is infrequently seen, in approximately 30% of LGG patients¹⁶ (Fig. 2). The risk of anaplasia in nonenhancing lesions increases with patient age.²

Basing the diagnosis of an LGG on the aforemen-

FIG. 1. **A:** Studies obtained in a 29-year-old woman with a right parietal astrocytoma (WHO Grade II). The sagittal MR images reveal a large, circumscribed, and nonenhancing lesion with ^{18}F -FET uptake below the cortical level in the corresponding PET scan indicating a favorable prognosis. **B:** Studies obtained in a 54-year-old man with a left insular oligoastrocytoma (WHO Grade II). The transaxial MR images demonstrate a hyperintense, circumscribed lesion without contrast enhancement. In contrast to the lesion size on MRI, the corresponding PET scan shows a smaller, circumscribed lesion with increased ^{18}F -FET uptake, facilitating biopsy guidance. **C:** Studies obtained in a 44-year-old woman with a left frontal oligodendroglioma (WHO Grade II). The transaxial MR images demonstrate a diffuse and nonenhancing lesion, with inhomogeneous and increased ^{18}F -FET uptake on the PET scan, which helps to guide biopsy.

FIG. 2. Studies obtained in a 34-year-old man with a left temporal lesion. **A:** The MR images show a large, diffuse, nonenhancing lesion suspicious for a diffuse LGG. Differentiation of tumor extent, edema, and peritumoral brain tissue is not possible, and information derived from the MR images does not provide a favorable biopsy target. The corresponding PET scan demonstrates a small area of focally increased ^{18}F -FET uptake at the medial aspect of the temporal lobe within the large area of hyperintense signal alterations on MRI. **B:** Serial stereotactic biopsies were performed and titanium markers (black points within red circles on the T1-weighted images) are left for exact documentation of the biopsy sites. The first biopsy was performed within the area of abnormal signal on MRI and normal ^{18}F -FET accumulation on the PET scan (blue arrows). The photomicrograph reveals peritumoral tissue with edema and reactive astrogliosis without tumor cells. **C:** The second biopsy was performed within the area of abnormal signal on MR images and high accumulation of ^{18}F -FET on the PET scan (red arrows). The photomicrograph shows tumor tissue with all the features of an anaplastic astrocytoma (WHO Grade III). H & E, original magnification $\times 400$ (B and C).

tioned MRI findings alone is, however, a common source of error. Kondziolka and colleagues³⁰ reported a false-positive rate of 50% for the prediction of glioma histology based on the typical MRI appearance. Additionally, low sensitivity (range 72%–93%) and specificity (range 50%–80%) values have been reported for standard morphological MRI protocols of suspected LGG.³¹ Thus, the results of these studies indicate that morphological MRI alone cannot be used as a reliable tool to predict the histological diagnosis in patients with LGG. Consequently, alternative diagnostic methods are needed to improve the diagnostic accuracy. Metabolic imaging using PET with radiolabeled amino acids might help to overcome some of these limitations.

O-(2- ^{18}F -fluoroethyl)-L-tyrosine PET

The most widely used tracer for amino acid PET is ^{11}C -MET, but because of its short physical half-life (20 minutes), the use of ^{11}C -MET remains restricted to a few

¹⁸F-FET PET in patients with low-grade glioma

PET centers possessing a cyclotron unit onsite and could not be established in routine clinical practice despite convincing clinical results. In contrast, ¹⁸F-FET is one of the first ¹⁸F-labeled amino acids that can be produced in large amounts for clinical purposes and is applicable in PET studies using a satellite concept similar to that of the widely used PET tracer ¹⁸F-FDG (¹⁸F-2-fluoro-2-deoxy-D-glucose).^{19,69}

Although ¹⁸F-FET is not incorporated into proteins (in contrast to ¹¹C-MET), uptake by tumor cells is stereospecific and mediated by amino acid transporters.^{22,34} Initial studies using ¹⁸F-FET PET for the analysis of human brain tumors and rat gliomas have shown results similar to those obtained with ¹¹C-MET PET.^{18,34,66}

Comparative studies of ¹⁸F-FET and ¹¹C-MET have shown that tumor-to-brain contrast of ¹⁸F-FET appears to be very similar to that of ¹¹C-MET,⁶⁶ so that clinical experiences gained with both tracers can be considered together. In contrast to ¹¹C-MET, animal experiments have shown that ¹⁸F-FET exhibits no uptake in inflammatory cells and in inflammatory lymph nodes, promising a higher specificity for the detection of tumor cells.³³ Nevertheless, false-positive uptake has been observed for both tracers in brain abscesses, demyelinating processes, cerebral ischemia, and hematomas. Therefore, increased uptake of the tracers is not specific for cerebral gliomas, although high amino acid uptake has a high PPV for cerebral gliomas. For both tracers, a patient's radiation exposure remains within the same order of magnitude as that of conventional radiological studies.³⁵ No side effects have been reported to date with the use of these tracers after several thousand studies have been performed worldwide. The duration of tracer uptake and image acquisition with any of these radiopharmaceuticals is about 30–50 minutes. The costs of ¹⁸F-FET PET are comparable to those of ¹⁸F-FDG PET. An ¹¹C-MET PET study is more expensive because only very few patients can be examined with one synthesis due to the short half-life of ¹¹C.

Clinical Applications of ¹⁸F-FET PET

Preoperative Detection of LGG and Differentiation From HGG

In morphological MRI, nonenhancing space-occupying lesions are often suspicious for LGG (Figs. 1 and 2). However, these lesions constitute a heterogeneous group of diseases, including HGGs and nonneoplastic lesions, such as cerebral hematoma, ischemia, and inflammatory processes. Incorrect interpretation of morphological MRI features may result in necessary treatment being deferred or otherwise unnecessarily exaggerated. Regarding the diagnostic accuracy of morphological MRI, it was demonstrated in a biopsy-controlled study that morphological MRI had a high sensitivity of 96% for the detection of tumor tissue but a specificity of only 53%.³⁹ Similar results for morphological MRI alone were observed in a study with a larger number of patients (n = 176).³⁷ In comparison with morphological MRI, the sensitivity of ¹⁸F-FET PET to detect LGG is lower because increased ¹⁸F-FET exhibits increased uptake is present in only 60%–80% of

the patients.^{10,27,40,41} However, the results of previous studies suggest a clearly higher specificity of ¹⁸F-FET PET for detecting high-grade tumors and differentiating them from LGG than morphological MRI.

In a large patient series, 88 patients underwent ¹⁸F-FET PET for evaluation of an untreated and undiagnosed intracerebral mass or lesion detected on MRI.⁴¹ In 60 patients the diagnosis was confirmed histologically, and 19 of the 60 patients had an LGG. In the remaining 28 patients, the diagnosis was confirmed by clinical follow-up. Despite the large number of patients without histological confirmation of the diagnosis (n = 28), the sensitivity of ¹⁸F-FET PET for detecting a high-grade tumor entity was 93%, with a low specificity of 56% due to the number of LGGs. The PPV was 67% and the NPV was 89%.

In a recent study with a larger patient population, the diagnostic performance of ¹⁸F-FET PET was evaluated in a series of 174 newly diagnosed cerebral lesions suspected to be primary brain tumors, which included 77 histologically confirmed LGGs.⁴⁹ Furthermore, 72 high-grade tumors and 25 nonneoplastic lesions were diagnosed histologically. In that study, the diagnostic value of simple maximum tumor-to-background ratios for differentiation between high-grade tumors and LGGs was evaluated using receiver-operating-characteristic curve analyses. At a threshold of 2.5, the sensitivity was 80% and the specificity was 65%. The PPV was 66% and the NPV was 79%.

Furthermore, Jansen and colleagues²⁷ investigated the discriminative value of the additional ¹⁸F-FET PET imaging parameter in patients with newly diagnosed cerebral lesions suspicious for LGG. The authors evaluated ¹⁸F-FET PET kinetics. HGGs were characterized by an early peak of the time-activity curve at 10–15 minutes after tracer injection, followed by a decrease of ¹⁸F-FET uptake. In contrast, slightly and steadily increasing time-activity curves were frequently found in LGGs.⁶⁷ In the retrospective study by Jansen and colleagues, the authors evaluated the diagnostic value of kinetic ¹⁸F-FET PET in 127 patients with newly diagnosed MRI-suspected LGGs prior to histopathological assessment.²⁷ They found in the patients with MRI-suspected LGGs that kinetic analysis of ¹⁸F-FET uptake enabled the detection HGGs with high accuracy (sensitivity 95%, specificity 72%, PPV 74%, and NPV 95%).

It should be noted, that the specificity of ¹⁸F-FET PET for neoplastic lesions may be affected by possible tracer uptake in the area of benign processes (for example, cerebral hematoma, ischemia, and inflammatory processes).^{9,41,51–53}

In summary, compared with morphological MRI, ¹⁸F-FET PET adds valuable information to the data acquired in cases of newly diagnosed cerebral lesions suspicious for LGGs. However, a histological biopsy-based evaluation of suspicious brain lesions remains necessary in most circumstances.

¹⁸F-FET PET–Guided Stereotactic Biopsy and Planning of Resection

A stereotactic biopsy is often performed for diagnostic purposes before treating patients whose imaging studies highly suggest LGG, especially when an open neurosurgi-

cal resection for medical reasons, such as eloquent regions and diffuse lesions invading multiple brain lobules, is not possible. However, regarding stereotactic needle biopsy, there is a certain risk of inaccuracy. It could be demonstrated that WHO Grade I gliomas have been “overgraded” in up to 11% and WHO Grade III gliomas “undergraded” in 28% of all cases.³⁸ Therefore, methods to improve stereotactic biopsy are essential. Since the tumor biology is defined by the most aggressive part of the glioma, representative tissue samples are vitally important for histological tumor diagnosis (Fig. 2). Biopsy-controlled studies have shown that ¹⁸F-FET uptake correlates with microvessel and cell density, which is linked to malignant transformation in noncontrast-enhancing gliomas.^{61,62} Biopsy guidance is based on quantitative radioactivity concentration on brain scans as displayed by color-coded radioactivity maps of standardized uptake values (that is, radioactivity concentration divided by the radioactivity injected per gram of body weight). These quantitative scans are coregistered with the corresponding MR images, and biopsies are targeted to the maximum radioactivity concentration in the tumor area. For example, ¹⁸F-FET PET has been shown to significantly improve the diagnostic efficacy of targeted biopsies, with an accuracy of tumor detection by biopsy of 68% when using MRI alone, which increased to 88% when ¹⁸F-FET PET information was incorporated.¹¹ In a subsequent study, similar results were observed.³⁹

Analysis of ¹⁸F-FET PET kinetics may also be helpful in the distinction between HGG and LGG tissue and therefore for treatment planning. A recent biopsy-controlled study reported that a homogeneous pattern of uptake kinetics within the tumor is linked to homogeneous histopathological findings, whereas a heterogeneous pattern of uptake kinetics in different parts of the tumor was associated with histopathological heterogeneity. In that study, hot spots exhibiting malignant glioma characteristics covered 4%–44% of the entire tumor volumes.³¹

When tumor resection is planned, the delineation of tumor extent is crucial. A study in patients with LGGs demonstrated an improvement of overall survival after aggressive resection compared with partial resection.⁵⁶ Patients with at least 90% of their tumors resected had 5- and 8-year overall survival rates of 97% and 91%, respectively, whereas patients with less than 90% of their tumors resected had 5- and 8-year overall survival rates of 76% and 60%, respectively. Thus, predicted overall survival was negatively influenced even by residual tumor volume of more than 10 ml.⁵⁶

In patients with HGG, fluorescence-guided surgery using 5-ALA is an established intraoperative tool to differentiate between tumor infiltration and normal brain tissue, and thus it facilitates achieving a complete tumor resection.⁶³ A biopsy-controlled study in patients with LGG suggested that ¹⁸F-FET PET is more sensitive to detect glioma tissue than 5-ALA fluorescence.¹² The authors found clear differences between ¹⁸F-FET uptake and 5-ALA fluorescence owing to the limited sensitivity of 5-ALA to detecting tumor tissue, especially in LGG. They concluded that ¹⁸F-FET PET should be considered as an additional tool in resection planning.¹² These results were confirmed by a subsequent study.⁸

Using PET for resection planning, recent studies demonstrated that ¹¹C-MET PET imaging provided a final target contour different from that obtained with MRI alone in about 80% of the procedures.⁴⁵ Moreover, it was demonstrated in a subsequent study in patients with HGG that complete resection of the increased ¹¹C-MET uptake prolongs the survival of these patients.⁴⁶ Because ¹¹C-MET and ¹⁸F-FET PET provide comparable diagnostic information on gliomas,¹⁸ these data suggest that resection guided by ¹⁸F-FET PET may increase the amount of cytoreduction and therefore progression-free and/or overall survival. Prospective studies of LGG patients are needed to confirm these observations.

Use of ¹⁸F-FET PET for Assessment of Prognosis

In patients with LGG, treatment decisions can be challenging and may be influenced by several prognostic factors. Unfavorable prognostic factors are age exceeding 40 years, astrocytoma histology, maximum tumor diameter ≥ 6 cm, tumor crossing the corpus callosum, and the presence of a neurological deficit (except epileptic seizures) before surgery.⁴² Furthermore, a prospective RTOG trial identified a preoperative tumor diameter > 4 cm, astrocytoma/oligoastrocytoma histology type, and a residual tumor > 1 cm as predictive of significantly higher recurrence rates.⁵⁵ These factors help to identify patients at low or high risk for rapid tumor progression and to determine when a watchful-waiting approach is justifiable or when LGG patients should be treated early by surgery, radiotherapy, or chemotherapy.

A prospective study in patients with LGG without contrast enhancement on MRI indicated that ¹⁸F-FET PET in combination with MRI provides important prognostic information.¹⁰ Patients with LGG that exhibited increased ¹⁸F-FET uptake on PET and diffuse tumors on MRI (T2-weighted/FLAIR images) had a worse prognosis with shorter life expectancy, rapid tumor progression, and malignant progression to high-grade tumors within only 2–3 years. In contrast, patients with LGG that showed normal or low ¹⁸F-FET uptake and circumscribed tumors on MRI (Fig. 1) had a good prognosis with lower risk for tumor progression and lack of malignant transformation within the first 5 years after diagnosis.¹⁰

Another study analyzed the prognostic impact of ¹⁸F-FET PET on small, incidentally detected cerebral lesions on MRI that were suspected of being cerebral glioma.¹³ The authors demonstrated that patients with circumscribed ¹⁸F-FET PET-negative lesions had an excellent prognosis. At follow-up imaging, most of these lesions vanished (Fig. 3) or remained unchanged (Fig. 4). In the further course of disease, only a minority of patients developed a glioma. In contrast, patients with an initially diffuse pattern of the lesion on MRI and increased ¹⁸F-FET uptake had a clearly higher risk for developing a malignant glioma.¹³

Thus, combined assessment with ¹⁸F-FET PET and MRI can identify subgroups of patients with a stable course in whom a watch-and-wait strategy is reasonable and patients with LGG who should receive early and aggressive treatment to avoid malignant transformation.

FIG. 3. Studies obtained in a 44-year-old man. **Upper:** The MR images show a relatively circumscribed, nonenhancing right temporal lesion (arrowheads) without increased ^{18}F -FET uptake, as shown on the PET scan. **Lower:** The 6-month follow-up MR images demonstrate complete disappearance of the lesion.

Monitoring of Neurooncological Treatment Using ^{18}F -FET PET

The evaluation of treatment response especially in patients with HGG is based on contrast enhancement and volumetric changes of lesion size seen on T2-weighted/FLAIR MR images according to the recently defined Response Assessment in Neuro-Oncology Working Group criteria.⁶⁸ Treatment monitoring of nonenhancing tumors like LGG, however, can be difficult using T2-weighted/FLAIR MR images alone. Malignant tumor portions (for example, those that are WHO Grade III) may not exhibit contrast enhancement⁵ and, furthermore, T2-weighted/FLAIR MRI-based signal hyperintensity represents a combination of infiltrating tumor cells, necrotic areas, tumor edema, and treatment-related leukoencephalopathy, such as that due to radiotherapy.¹ Thus, in addition to morphological MRI there is a need for imaging tools that allow for a better assessment of therapeutic response and disease development.

Alternative targets for treatment monitoring are the change of treatment-related tumor metabolism. Therefore, imaging methods that measure metabolic processes in the tumor, such as the amino acid uptake in ^{18}F -FET PET, may assess and quantify therapeutic response more with more sensitivity than morphological imaging and may provide additional information to morphological MRI. Several studies, particularly in patients with HGG, have successfully evaluated the role of ^{18}F -FET PET in monitoring radiochemotherapy with temozolomide, chemotherapy, or experimental treatment modalities (for example, antiangiogenic treatment).^{14,15,26,43,44,47}

In contrast to the management of HGG, experience with ^{18}F -FET PET for monitoring of treatment in patients with LGG is limited. In a prospective study, ^{18}F -FET PET was compared with MRI in evaluating the response to

FIG. 4. Studies obtained in a 37-year-old man. **Upper:** The MR images show a small and nonenhancing left frontal lesion without increased ^{18}F -FET uptake on the PET scan. No biopsy was performed. **Lower:** The follow-up 4-year MR images reveal a completely unchanged lesion.

a dose-dense temozolomide regimen in 11 patients with progressive nonenhancing LGG WHO Grade II.⁷⁰ According to the EORTC protocol 22033–26033, patients received 75 mg/m² temozolomide per day over 21 days of every 28-day cycle. After initiation of treatment, the authors compared the reduction of the metabolically active tumor volume, as assessed by ^{18}F -FET PET, with the reduction of the tumor volume delineated by FLAIR images. In responding patients, a reduction of the metabolically active tumor volume after initiation of treatment could be observed earlier than volume reductions on FLAIR sequences. The mean time to maximal volume reduction was 8.0 ± 4.4 months for ^{18}F -FET and 15.0 ± 3.0 months for MRI.

The findings highlight the high diagnostic value of ^{18}F -FET PET for detecting treatment response. Furthermore, the identification of nonresponders at an early stage of neurooncological treatment may help to minimize a negative impact on quality of life. However, further prospective treatment monitoring studies using ^{18}F -FET PET in patients with LGG are needed to confirm these observations.

Conclusions and Future Aspects

Diagnostic assessment of LGG using ^{18}F -FET PET permits a more specific representation of the spatial extent of the tumors than is possible using conventional MRI alone. This has been shown to be advantageous for the planning of biopsies, tumor resection, and other treatment options. Valuable prognostic information can be obtained at initial diagnosis to optimize an individual treatment strategy, and the treatment response can probably be judged early in the course of treatment.

Other advanced MRI methods such as MRS may

also yield metabolic information that is markedly more specific than that obtainable by conventional MRI for the differentiation of tumor tissue from nonspecific changes.²⁴ A relationship between increased ¹⁸F-FET uptake and abnormal high choline concentration in gliomas as measured by MRS has been demonstrated.⁶⁰ In contrast to PET, however, MRS can only be used to analyze selected small volumes or partial areas in single planes, and susceptibility artifacts often impair the quality of MRS scans. Furthermore, diffusion-weighted imaging has been considered, but its clinical relevance is not yet established.⁷¹ Other modalities such as perfusion-weighted MRI are more readily available than PET and may yield information that is correlated with the degree of glioma malignancy.²⁴ However, the diagnostic accuracy of this technique in comparison with ¹⁸F-FET PET remains to be investigated.

Diffusion tensor imaging can contribute valuable diagnostic information on the involvement of white matter structures (for example, nerve pathways). Initial studies have demonstrated the potential benefit of integrating fiber tracking by diffusion tensor imaging and ¹⁸F-FET PET.^{58,59} These studies indicated complementary information and more detailed understanding of peritumoral fiber tract alterations in gliomas, which are more complex than previously thought.

The scientifically well-documented utility of ¹⁸F-FET PET of LGG seems to justify its introduction as a routine diagnostic technique for certain indications. The guidelines of the European and the German Association of Nuclear Medicine for brain tumor imaging using labeled amino acid analogs have been published in recent years.^{32,65} The logistical prerequisites for amino acid-based PET have become markedly less difficult to achieve in recent years since the introduction of ¹⁸F-FET PET, and many centers in Europe have already integrated this approach into the routine diagnostic workup of patients with brain tumors.

Furthermore, the costs of ¹⁸F-FET PET imaging are relatively small in relation to the expenses of local or systemic treatment approaches and, consequently, the management of possible adverse effects.^{20,21}

The future will also be strongly influenced by the integration of PET and MRI in one imaging device.²⁵ The advent of hybrid PET-MRI systems offers a multimodal approach for the investigation of brain tumors and improved patient comfort due to a significant reduction in measurement time and improved spatial and temporal coregistration of PET and MRI data.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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