

Current Radiopharmaceuticals for Positron Emission Tomography of Brain Tumors

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Brain tumors represent a diverse spectrum of histology, biology, prognosis, and treatment options. Although MRI remains the gold standard for morphological tumor characterization, positron emission tomography (PET) can play a critical role in evaluating disease status. This article focuses on the use of PET with radiolabeled glucose and amino acid analogs to aid in the diagnosis of tumors and differentiate between recurrent tumors and radiation necrosis. The most widely used tracer is ^{18}F -fluorodeoxyglucose (FDG). Although the intensity of FDG uptake is clearly associated with tumor grade, the exact role of FDG PET imaging remains debatable. Additionally, high uptake of FDG in normal grey matter limits its use in some low-grade tumors that may not be visualized. Because of their potential to overcome the limitation of FDG PET of brain tumors, ^{11}C -methionine and ^{18}F -3,4-dihydroxyphenylalanine (FDOPA) have been proposed. Low accumulation of amino acid tracers in normal brains allows the detection of low-grade gliomas and facilitates more precise tumor delineation. These amino acid tracers have higher sensitivity and specificity for detecting brain tumors and differentiating recurrent tumors from post-therapeutic changes. FDG and amino acid tracers may be complementary, and both may be required for assessment of an individual patient. Additional tracers for brain tumor imaging are currently under development. Combinations of different tracers might provide more in-depth information about tumor characteristics, and current limitations may thus be overcome in the near future. PET with various tracers including FDG, ^{11}C -methionine, and FDOPA has improved the management of patients with brain tumors. To evaluate the exact value of PET, however, additional prospective large sample studies are needed.

Key Words Brain tumors; Positron emission tomography-computed tomography; ^{18}F -FDG; C-11 methionine; ^{18}F -FDOPA.

INTRODUCTION

Brain tumors can originate from different cells both from within the brain and from systemic tumors that have metastasized to the brain. Primary brain tumors most commonly arise from glial cells [1]. With an annual age-adjusted incidence rate of 28 per 100,000 in adults, gliomas account for approximately 27.2% of all brain and other central nervous system tumors, and approximately 81.3% of all malignant tumors [2].

Gliomas can be categorized into different pathologic subtypes. In addition to the pathologic type, World Health Orga-

nization classifications also provide histologic grades based on cellular alterations related to cancer aggressiveness. Grades I and II are considered low-grade tumors that have a prolonged clinical course. Grade III and IV tumors are considered high-grade lesions rapidly leading to death when left untreated [3].

Despite multimodal treatment strategies, the prognosis for patients with glioma is poor. The median survival for patients varies according to tumor grade, location, and age at diagnosis. Therefore, adequate tumor diagnosis and grading is thus crucial to initiate appropriate treatment and improve long-term outcomes [4].

MRI with gadolinium contrast enhancement is the gold standard imaging modality for assessing the morphological characteristics of brain tumors, such as location, mass effect, and contrast enhancement; however, it has several limitations. It cannot always distinguish gliomas from non-neoplastic le-

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sions such as those resulting from vascular processes or inflammatory reactions. Because the absence of contrast enhancement does not always correspond to low-grade tumors, MRI is not perfect for grading gliomas. Furthermore, distinguishing tumor recurrence from post-surgical or post-radiotherapeutic changes remains a major challenge in brain imaging studies [5]. In recent decades, molecular imaging with positron emission tomography (PET) has gained increasing importance in identifying and delineating areas of increased tumor growth activity. Various PET tracers have been developed to visualize tumors using the hallmarks of cancers, such as metabolic derangement and replicative immortality. The tracer ^{18}F -fluorodeoxyglucose (FDG) visualizes glucose metabolism, radiolabeled amino acids [e.g., ^{11}C -methionine, ^{18}F -3,4-dihydroxyphenylalanine (FDOPA), and O-(2- ^{18}F -Fluoroethyl)-L-Tyrosine (FET)] perform protein synthesis, and ^{18}F -fluorothymidine (FLT) performs DNA replications. PET fused with computed tomography (PET/CT) can obtain detailed anatomical information on PET results and provides clinically invaluable information regarding primary detection and differentiation between various underlying tumor types, initial tumor grading and risk stratification, therapy planning, selection of biopsy site, response evaluation, and recurrence detection [6-8]. The current article discusses some of the positive aspects of the contemporary use of PET or PET/CT in primary brain tumors.

FDG PET

FDG PET imaging was first used to detect and differentiate between low- and high-grade tumors [9]. Similar to most ma-

lignancies elsewhere in the body, malignant brain tumors generally have increased glucose metabolism and increased FDG uptake, and FDG is actively transported across the intact blood-brain barrier (BBB) (Fig. 1). Anaerobic glycolysis has been shown to occur in advanced cancers, even with an abundance of oxygen, a process named the Warburg effect. The high glycolytic rate of cancerous lesions results from various biological changes, including high levels of the membrane glucose transporter and increased cytosolic glycolytic enzymes such as hexokinase. Consequently, the greater demand for glycolytic substrates causes increased transport of the glucose analog FDG into malignant cells [10-12].

FDG PET can be used to identify differences in glucose uptake among healthy brains, low- and high-grade gliomas, and radionecrosis [13,14]. FDG uptake is generally considered to reflect both tumor cell viability and density, and is directly related to tumor grade [15,16]. FDG uptake in low-grade tumors is similar to that of white matter, whereas Grade III and IV tumors exhibit glucose metabolic activity comparable to or higher than that of grey matter (Fig. 2). A meta-analysis conducted by Zhao et al. [17] revealed that FDG PET was able to detect brain tumors with a sensitivity of 71% and a specificity of 77%, whereas another study on detecting high-grade gliomas found that FDG PET had a sensitivity of 94% and a specificity of 77% [9]. Because the similarities in glucose metabolic activity between tumors and grey matter cause difficulties in the analysis of FDG-PET images, several studies have shown that delaying scanning times by 3 hours after FDG injection considerably improves the contrast between malignant brain tumors and normal brain tissue [18,19].

Because treatment-induced changes such as radionecrosis

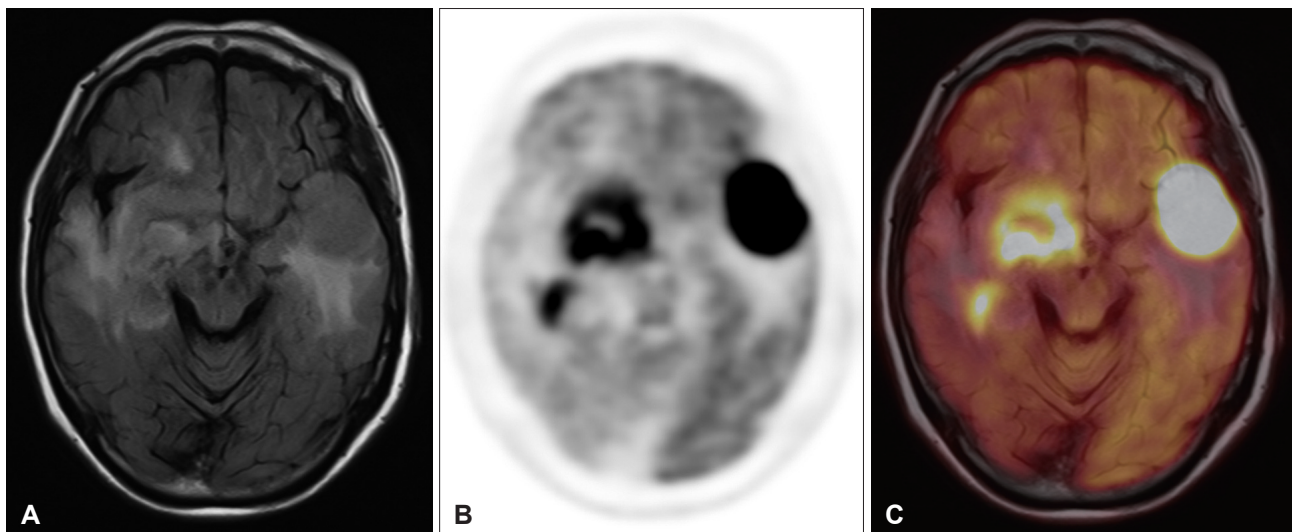


Fig. 1. FDG PET/MR for CNS lymphoma. 79-year-old woman diagnosed as CNS lymphoma. T2 fluid attenuated inversion recovery MRI shows multiple lesions with high signal in both hemisphere (A). FDG PET (B) and FDG PET/MR (C) show intense tracer uptake at the lesions. FDG, ^{18}F -fluorodeoxyglucose; PET, positron emission tomography; CNS, central nervous system.

and post-surgical changes are highly difficult to distinguish from tumor recurrence, evaluation of disease status after treatment is challenging with MRI alone [20]. Conversely, FDG PET can detect recurrent high-grade tumors. Chao et al. [14] reported sensitivity of 75% and specificity of 81% for FDG PET in differentiating recurrent tumors from post-radiation changes. They also observed an improvement in the sensitivity of tumor recurrence detection after stereotactic radiotherapy, from 65% to 85%, when FDG PET was added to standard MRI. Previous studies have reported high sensitivities and specificities for FDG PET of 81–86% and 40–94%, respectively, for distinguishing radionecrosis from residual or recurrent tumors whereas those for contrast enhanced MRI were 95% and 23%, respectively [21,22].

Wang et al. [23] defined the criteria for positive and negative FDG PET scans as tracer uptake above or below the expected uptake in the adjacent brain tissue, which achieved high overall sensitivity and accuracy of 80% and 87%, respectively, with regard to differentiating recurrent tumors from post-radiation changes.

However, values of FDG PET are inherently limited by the FDG avidity of normal brain tissue. The physiologic glucose consumption in the normal brain generates a high background uptake of FDG, which is generally high in gray matter, and moderate to high in white matter [24-26]. In addition, various non-malignant intracerebral lesions also have varying levels of increased FDG uptake (e.g., with inflammatory or infectious causes), and this also applies to normal brain tissue adjacent to tumor lesions. Thus, differentiating between malignant and non-malignant causes of increased FDG uptake is difficult [27-29].

Although FDG remains the most widely used radiotracer for PET imaging, radiopharmaceutical development is an

evolving domain, promising higher sensitivity as well as higher specificity for certain tumor entities [30]. Because of physiologically low uptake in healthy brain tissue and absent or low uptake in inflammatory lesions, radiolabeled amino acids or their analogs have been demonstrated to overcome the limitations of FDG [31,32].

AMINO ACID PET

Because of the limitations of FDG PET in assessing brain tumors, amino acid-based radiotracers have been developed. The most popular amino acid tracer is ^{11}C -methionine, which has been investigated in many studies on brain tumors (Fig. 3). The use of ^{11}C -methionine provides a high detection rate for brain tumors and good lesion delineation because of the low physiological uptake of the amino acid in healthy brains with high contrast between normal and cancerous tissue [33-38]. Increased ^{11}C -methionine uptake is associated with upregulation of L-type amino acid transporter 1 (LAT1) and proliferation of the tumor microvasculature [39-42]. Although methionine PET has been shown to have high sensitivity for gliomas, false-positive results may be seen under benign conditions, such as cases of demyelination, leukoencephalitis, or abscess [43].

Several studies diagnosing untreated brain tumors with methionine PET have reported relatively high sensitivities, ranging from 76% to 91%, and specificities ranging from 75% to 100% [35,38,44-47]. A recent meta-analysis found a 91% sensitivity and an 86% specificity [17]. Methionine PET is more suitable than FDG PET alone for diagnosing and managing patients, particularly those with low-grade tumors [38,48,49].

In high-grade gliomas, tracer leakage from a disrupted BBB contributes considerably to amino acid uptake. However, in low-grade gliomas, amino acid uptake occurs without sub-

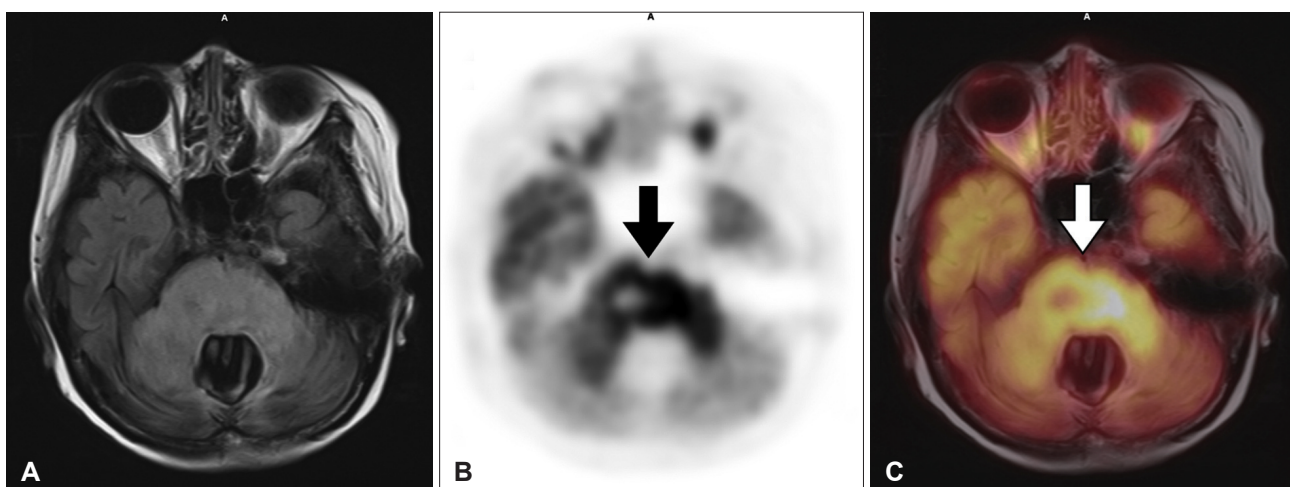


Fig. 2. FDG PET/MR for high-grade glioma. 18-year-old woman diagnosed as a glioblastoma, WHO grade IV. T2 fluid attenuated inversion recovery MRI shows high signal in pontine lesion (A). FDG PET (B) and FDG PET/MR (C) show increased tracer uptake at the lesion (arrows). FDG, ^{18}F -fluorodeoxyglucose; PET, positron emission tomography.

stantial BBB breakdown, corresponding to an upregulation of LAT1 [45]. Therefore, the relationship between tumor grade and the intensity of amino acid analog uptake remains subject to speculation; some studies have reported strong correlation between the two parameters [50-52], whereas others have reached the opposite conclusion [53-55].

Methionine PET can also detect recurrent tumors with high sensitivity and specificity, allowing differentiation between tumor recurrence and radionecrosis. A recent meta-analysis of methionine PET reported a summary sensitivity of 70% and specificity of 93% for high-grade gliomas in the detection of recurrent tumors [56].

However, because of the short half-life of ^{11}C , ^{18}F -labeled amino acid tracers were developed, such as FDOPA and FET [4,31,57,58]. Whereas FDOPA is widely spread in the United States, FET is more common in Europe [59].

Similar to radiolabeled methionine, uptake of FDOPA is mediated by amino acid transporters and does not require disruption of the BBB. Therefore, FDOPA and ^{11}C -methionine have similar distribution in tumors [60,61].

Despite published series having involved mixed patients populations, FDOPA PET reportedly has high sensitivity and specificity for detecting brain tumors, ranging from 85% to 100% and from 86% to 90%, respectively [60,62-64]. Accumulation of FDOPA does not vary substantially within different tumor grades, and the amino acid analog is clearly superior to ^{18}F -FDG for diagnosing low- and high-grade gliomas [64,65].

Because FDOPA uptake in brain tumors does not depend on the BBB, delineation of tumor extent is reportedly more accurate, and areas with increased uptake on PET are often larger than areas with contrast-enhanced lesions on MRI [66]. There-

fore, amino acid PET can be useful for treatment planning, and Grosu et al. [67] reported better outcomes for patients with radiotherapy planned on the basis of tumor extent as defined using amino acid PET.

FDOPA PET provides crucial information for the detection of recurrent brain tumors as well as initial diagnosis. It is a valuable tool for treatment monitoring because it helps in assessing treatment response and evaluating patient prognosis after therapy. Previous studies have reported sensitivity and specificity of FDOPA PET for detecting tumor recurrence as ranging from 90% to 92% and from 92% to 95%, respectively [32,68,69].

FLT PET

The pyrimidine analog 3'-deoxy-3'-FLT has been studied as a marker of tumor proliferation rate by reflecting thymidine kinase-1 activity, which is the principle enzyme in the pathway of DNA synthesis. Because no transporter has sufficient capacity, uptake of FLT in the brain depends on BBB permeability. In brain tumors with a damaged BBB, therefore, FLT provides highly reliable tumor-to-background contrast but cannot be used in low-grade gliomas with an intact BBB [70,71].

Whereas the sensitivity of FLT PET for detecting high-grade gliomas can reach 100%, a lower overall sensitivity of 83% has been shown because of major differences in uptake between high- and low-grade tumors [72,73]. Hence, the sensitivity of all grades is typically lower than with FDG PET [74] and methionine PET [75]. Conversely, FLT PET seems to be superior to methionine PET in tumor grading and assessment of proliferation activity in gliomas of different grades [76,77].

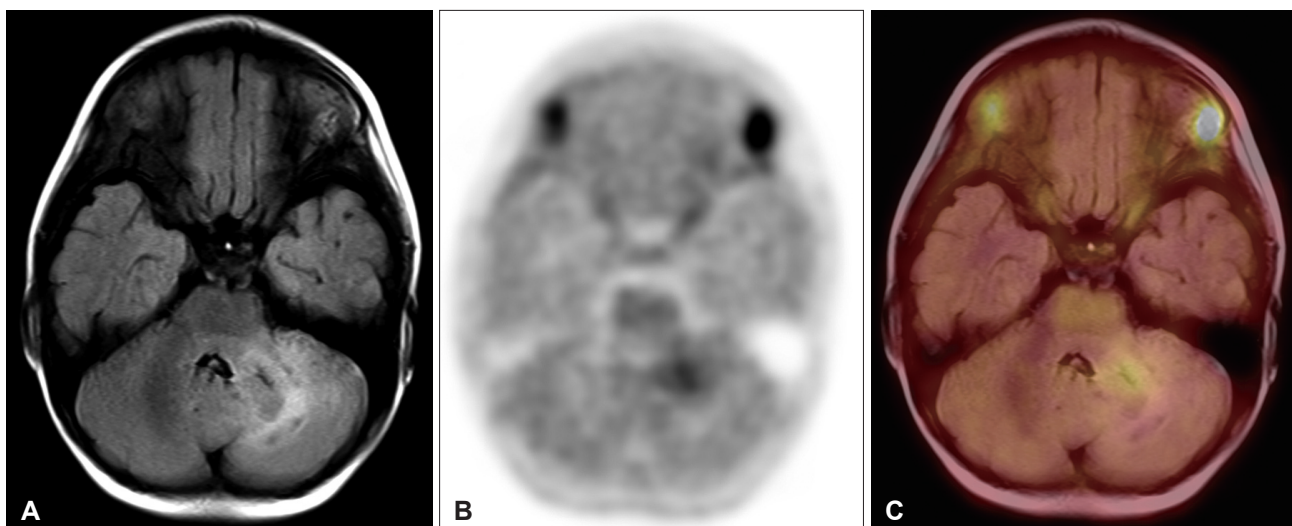


Fig. 3. ^{11}C -methionine PET/MR. 5-year-old girl diagnosed low-grade glioma in cerebellum. T2 fluid attenuated inversion recovery MRI shows high signal in a cerebellar lesion (A). ^{11}C -methionine PET (B) and ^{11}C -methionine PET/MR (C) show increased tracer uptake at the cerebellar lesion. PET, positron emission tomography.

FUTURE PERSPECTIVES

Because the information gained by different imaging methods is complementary and brain PET scans generally should not be interpreted without access to the corresponding MRI scans, combining all imaging methods might provide optimal results for assessment of tumor characteristics [78-83]. Combined PET/MR can readily be achieved using standard software and is provided more directly and conveniently by hybrid PET/MR machines (Fig. 1-3). Although the effect of image fusion does not play an essential role in the case of brain imaging, accurate image fusion can be easily obtained through image co-registration based on fixed points. PET/MR also has the advantage of low radiation exposure compared to PET/CT, rendering it particularly attractive for pediatric patients.

The nitroimidazole derivative tracer ¹⁸F-Fluoromisonidazole (F-MISO) has been developed as a PET tracer, to visualize intratumoral hypoxic areas before and during radiation therapy [84,85]. In addition, F-MISO is able to diffuse freely across the BBB, it is useful imaging tracer for brain tumor. Dual-phase F-MISO PET has been used; early F-MISO distribution reflects blood flow, while later tracer is accumulated in hypoxic area [86,87]. Hypoxia measurements have been shown to correlate with invasion, tumor recurrence, the probability of metastatic spread and decreased patient survival as well as resistance to radiation and chemotherapy. However, the biggest obstacle for using F-MISO is limited availability, and further clinical studies are still needed for verifying clinical usefulness of F-MISO PET. Nevertheless, the majority of PET studies have been limited to small sample size and retrospective designs, lacking comparability because of different acquisition and data evaluation methods. Therefore, the clinical value of PET in brain tumors might still be underestimated. Multicenter clinical trials of PET are crucial to elucidate the optimal PET setting for assessing brain tumors, which can be useful for guiding optimal diagnostic and therapeutic decision making and ultimately improving the prognosis of brain tumors.

Additional tracers for brain tumor imaging are under active development, and PET tracers using other metabolic processes, such as phospholipid membrane biosynthesis, hypoxia, receptor binding, and oxygen metabolism and blood flow, will be crucial for forming personalized therapeutic strategies using targeted agents. The combination of different tracers might provide more accurate information on the characteristics of various brain tumors, and the current limitations may thus be overcome in the near future.

CONCLUSION

PET imaging with oncologic radiotracers can visualize vari-

ous biological statuses of brain tumors and improves diagnostic and therapeutic planning in certain patients with brain tumors. Advancement of PET chemistry and development of imaging technologies will broaden the applications of PET imaging in the field of brain tumors.

Conflicts of Interest

The authors have no financial conflicts of interest.

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