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Usefulness of Positron Emission Tomographic Studies for Gliomas

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Abstract

Non-invasive positron emission tomography (PET) enables the measurement of metabolic and molecular processes with high sensitivity. PET plays a significant role in the diagnosis, prognosis, and treatment of brain tumors and predominantly detects brain tumors by detecting their metabolic alterations, including energy metabolism, amino acids, nucleic acids, and hypoxia. Glucose metabolic tracers are related to tumor cell energy and exhibit good sensitivity but poor specificity for malignant tumors. Amino acid metabolic tracers provide a better delineation of tumors and cellular proliferation. Nucleic acid metabolic tracers have a high sensitivity for malignant tumors and cellular proliferation. Hypoxic metabolism tracers are useful for detecting resistance to radiotherapy and chemotherapy. Therefore, PET imaging techniques are useful for detecting biopsy-targeting points, deciding on tumor resection, radiotherapy planning, monitoring therapy, and distinguishing brain tumor recurrence or progression from post-radiotherapy effects. However, it is not possible to use only one PET tracer to make all clinical decisions because each tracer has both advantages and disadvantages. This study focuses on the different kinds of PET tracers and summarizes their recent applications in patients with gliomas. Combinational uses of PET tracers are expected to contribute to differential diagnosis, prognosis, treatment targeting, and monitoring therapy.

Key words: glioma, positron emission tomography (PET), L-methyl-[^{11}C]methionine ([^{11}C]MET), 3′-deoxy-3′-[^{18}F]fluorothymidine ([^{18}F]FLT), [^{18}F]fluoromisonidazole ([^{18}F]FMISO)

Introduction

Gliomas, the most common primary brain tumors, constitute a heterogeneous group of histological subtypes, including oligodendrogliomas, astrocytomas, ependymal tumors, and choroid plexus tumors, classified according to the World Health Organization (WHO) grading criteria based on cellular alterations related to tumor aggressiveness.[1,2] Accurate tissue diagnosis of gliomas is important for appropriate treatment planning and prognosis. Final diagnosis and grading are performed by the pathological diagnosis of surgical specimens. However, some glioma cases tend to be diagnosed less stringently than by actual grading done through pathological diagnosis. Therefore, several different imaging modalities are needed for diagnosis, grading, assessment of recurrence, and treatment planning and monitoring. Diagnostic imaging of gliomas uses various methods and has recently advanced. Magnetic resonance imaging (MRI) is the most commonly used method for determining tumor size and location and can delineate secondary phenomena, but the morphological information obtained is limited for diagnostic and prognostic decisions. Unlike morphological imaging, positron emission tomography (PET) uses radiotracers to achieve metabolic and molecular imaging and can improve diagnoses. Depending on the radiotracer, various molecular processes can be visualized. The vast majority of PET tracers take the advantage of the increased intratumor cell proliferation.[3] In the following sections, the most important or promising PET approaches for diagnosis, grading, treatment planning, and prognosis for gliomas are presented.

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PET

Since its advent in 1970, PET has gained importance in evaluating patients with gliomas. PET imaging enables a highly sensitive measurement using biochemical

active molecules labeled with positron emitting radionuclides (radiotracers). Positrons emitted from the nucleus of radioactive isotopes annihilate nearby electrons within the tissue. Each annihilation results in a pair of 511 keV photons traveling in opposite directions can be detected in a ring surrounding the subject. When two opposing detectors simultaneously register a pair of photons, the annihilation event is counted and assigned to a line of response joining the two relevant detectors. PET scans acquire many lines of response, which are used to reconstruct 3D images using standard tomographic techniques.

Four different positron-emitting isotopes (carbon-11 [^{11}C], nitrogen-13 [^{13}N], oxygen-15 [^{15}O], and fluorine-18 [^{18}F]) are mainly produced in a cyclotron. Because, three isotopes (^{15}O, ^{13}N, and ^{11}C) have very short half-lives (2, 10, and 20 min, respectively), their use is restricted to centers with an adjacent cyclotron unit. The longer half-life of ^{18}F (110 min) has permitted the commercial distribution of radiotracers by PET pharmacies placed outside of clinical locations.

The maximal or mean standardized uptake values (SUVs), calculated as the tissue radioactivity concentration divided by the injected dose and patient's body weight, are the most widely used semi-quantitative parameters of radioactivity in target tissues. SUV analysis can be performed voxelwise as well as by means of regions or volumes of interest. For the exact interpretation of tumor tracer uptake, it is essential to determine whether the changes are related to radiotracer transport, metabolism, distribution and/or back-diffusion. This analysis uses dynamic PET data acquisition and requires serial arterial blood samplings. Dynamic image acquisition (measuring the rate of accumulation of radiotracers in the brain over time) allows the modeling of regional radiotracer transport and kinase activity rates.[4] The model separates radiotracer uptake into two compartments with flux rates characterized by kinetic parameters (k_1, k_2, k_3, and k_4),[5] but the analysis is not amenable to routine clinical use.

Diagnosis and Grading of Gliomas

Glucose metabolism

2-Deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) has been widely used as a PET radiotracer to measure local glucose metabolism that represents a common pathway of brain neuro-chemical activity.[6] Intravenously injected [^{18}F]FDG enters the cells by the same glucose transporters (GLUTs) as glucose. Although more than 10 GLUTs have been identified, only GLUT-1 and GLUT-3 are considered in the normal and tumorous brain.[7] After GLUT transport, [^{18}F]FDG and glucose are phosphorylated by hexokinase. Unlike glucose-6-phosphate, [^{18}F]FDG-6-phosphate is not a substrate of glucose-6-phosphate isomerase and does not undergo further metabolism in the glucose pathway; therefore, it is trapped inside the cells. Consequently, [^{18}F]FDG accumulation increases in highly malignant tumors.[8] [^{18}F]FDG PET is applicable for the imaging of gliomas because of increased glucose metabolism in high-grade gliomas and the positive correlation between glycolysis rate and malignancy.[9] However, because of high physiological glucose metabolism in normal brain tissue (cerebral cortex, basal ganglia, and thalamus) and inflammatory tissue (i.e., macrophages), glioma identification in such tissues is difficult. Thus, the decreased sensitivity of lesion detection of [^{18}F]FDG PET is a major limitation for assessing gliomas.[10] Conversely, [^{18}F]FDG uptake by a typical primary central nervous system lymphoma (PCNSL) is about 2.5 times higher than that in the normal gray matter; therefore, it is useful for the differentiation and diagnosis of typical PCNSLs.[11]

Amino acid metabolism

Radiolabeled amino acids have been used as suitable PET tracers in brain tumors,[12] which play a key role in cell proliferation.[13] Therefore, various radiolabeled amino acids, such as L-methyl-[^{11}C]methionine([^{11}C]MET)[14] and aromatic amino acid analogues like [^{18}F]fluoroethyltyrosine ([^{18}F]FET)[15] and [^{18}F]fluorodopa ([^{18}F] FDOPA),[16] have been proposed. [^{11}C]MET is one of the essential amino acids and is used for evaluating protein synthesis and cell proliferation in gliomas. The presence of glioma cells has been confirmed in areas with an increased accumulation of [^{11}C]MET despite no change on MRI and no increased accumulation of [^{18}F]FDG. [^{11}C]MET accumulation has been correlated not only with microvessel density and blood volume in tumors, but also with expression levels of amino acid transporters (L-type amino acid transporter 1; LAT1) in vascular endothelial and tumor cells;[3] therefore, increased [^{11}C]MET uptake in non-tumor lesions, including inflammation, infarction, and hemorrhage, may lead to false positives.[17] Moreover, it has been reported that [^{11}C]MET uptake is high in oligodendrogliomas because of their high cell density[18] and in pilocytic astrocytomas despite being a WHO grade I glioma, because of increased vascularization and the high density of transporters in its vascular endothelial cells.[3] Thus, it is difficult to diagnose gliomas using only [^{11}C]MET. One of the disadvantages of [^{11}C]MET is that the half-life of ^{11}C is 20 min. This relatively short half-life limits the use of [^{11}C]MET to PET centers with a cyclotron and makes [^{11}C]MET less useful in routine clinical practice. To have a

longer half-life of positron emitters, [18F]FET and [18F]FDOPA were developed. These molecules are 18F-labeled amino acid tracers and have a half-life of 110 min, which is clinically advantageous when compared with [11C]MET.[15,19] Although [18F]FET and [18F]FDOPA can delineate tumor extent and provide excellent tumor-to-background contrast, they have some disadvantages.[20] Because the physiological uptake of [18F]FDOPA is in the corpus striatum, margins of tumors may not be distinguished from invasion into the basal ganglia. In [18F]FET imaging, because of slower renal elimination, detectable amounts of tracer have been confirmed in the blood pool for a long period, which may lead to difficult differentiation between blood vessels and metabolically active tumors. Conversely, dynamic PET imaging of [18F]FET can be helpful in clinical brain tumors and allows differentiation between low- and high-grade gliomas.[21]

In recent years, *trans*-1-amino-3-[18F]fluorocyclobutanecarboxylic acid (*anti*-[18F]FACBC) is a newly developed PET tracer that accumulates inside cells via an amino acid transporter.[22] Previous studies have shown that the accumulation of *anti*-[18F]FACBC was high in gliomas and low in normal tissues and inflammatory regions.[23,24] We expected that *anti*-[18F] FACBC PET may be useful for the diagnosis of low and high-grade gliomas.

Nucleic acid metabolism

Evaluation of cell proliferation is considered to be useful for therapeutic guidance and therapeutic effect assessment. Thus, radiolabeled nucleosides, such as the thymidine analog, 3′-deoxy-3′-[18F] fluorothymidine ([18F]FLT), has been developed.[25] Thymidine is rapidly transported into cells by a nucleoside transporter and phosphorylated by thymidine kinase-1 (TK-1), a principle enzyme in the salvage pathway of DNA synthesis, to thymidine nucleotides. [18F]FLT is trapped inside the cells, although only trace amounts of it can be recovered from DNA extracts.[26] Thus, [18F]FLT has been thought to be a helpful biomarker of cell proliferation, and the correlation between [18F]FLT accumulation and Ki-67 labeling index has been found to be significant.[27] Because, [18F]FLT accumulation in normal brain tissue is very low, it provides excellent tumor-to-background contrast. One of the disadvantages of [18F]FLT is that it is less useful in assessing noncontrast-enhancing tumor proliferation regardless of histopathological grading. Because of [18F]FLT leakage in radiation necrosis and disruption of the blood–brain barrier (BBB), [18F]FLT accumulation can increase,[10] which may make it difficult to differentiate from metabolically active tumors. A kinetic assay of [18F]FLT related to TK-1 expression was expected to evaluate cell proliferation, but the phosphorylation rate constant k_3 determined using this assay did not accurately reflect TK-1 expression in the tissue.[28] Rather, [18F]FLT accumulation has been associated with vascular permeability and BBB disruption. Further, the value of the [18F]FLT tracer in gliomas needs to be prospectively evaluated.

4′-[Methyl-11C]thiothymidine ([11C]4DST) is a newly developed PET-imaging thymidine analog for cell proliferation that is resistant to degradation by thymidine phosphorylase and is incorporated into DNA synthesis.[29] We expected [11C]4DST to be superior to [18F]FLT in evaluating cell proliferation and treatment response and in predicting prognosis by [11C]4DST uptake, which reflects the whole DNA synthesis process, and to be useful for PET imaging of gliomas.[30]

Hypoxic metabolism

Malignant tumors are characterized by hypoxic tissue (lower oxygen concentration), which results from the insufficient blood supply that occurs with aberrant tumor cell proliferation[31] and vascular occlusion of blood vessels within the tumor.[32] Hypoxia promotes neovascularization through various molecular signals,[33] may drive the peripheral growth of a tumor, and is associated with tumor progression and resistance to chemotherapy[34] and radiotherapy.[35] One of the most widely used PET radiotracers for molecular imaging of hypoxia is [18F]fluoromisonidazole ([18F]FMISO), which is a nitroimidazole derivative[36] and is exclusively trapped in hypoxic cells.[37] In cellular environments with a high partial pressure of oxygen (normoxic tissue), the radical anion is reduced back to the parent compound before further reaction. In hypoxic environments, the radical anion persists long enough to react with other electrons in the cell to form the two-electron reduction product. This can react further with intracellular macromolecules, trapping the tracer in the hypoxic environment and providing a contrast between hypoxic and normoxic regions.[38] In our results, [18F]FMISO showed high accumulation in WHO grade IV gliomas but not in WHO grade II and III gliomas, and an [18F]FMISO PET study discriminated WHO grade IV gliomas from WHO grade II and III gliomas.[39] These results are consistent with those of recent studies in which the volume and intensity of hypoxia in WHO grade IV gliomas before radiotherapy were strongly associated with shorter time to progression and survival.[40] Based on biological links between hypoxia and tumor-induced neoangiogenesis, [18F]FMISO uptake has been shown to significantly correlate with vascular endothelial growth factor (VEGF) expression in tumors and has

potential as an antiangiogenic treatment biomarker in newly diagnosed malignant gliomas.[40] Moreover, because hypoxic regions are associated with resistance to both chemotherapy and radiotherapy, [^{18}F]FMISO PET imaging is expected to be helpful for glioma tratment evaluation. However, considering the low target-to-background ratio and slow uptake in malignant tissues, [^{18}F]FMISO use has been limited in routine clinical examinations. Other PET tracers are 1-α-D-(5-[^{18}F]fluoro-5-deoxyarabinofuranosyl)-2-nitroimidazole ([^{18}F]FAZA)[41] and ^{64}Cu-diacetyl-bis-(*N*-*N*-*N*-*N*-methylthiosemicarbazone) ([^{64}Cu]ATSM).[38] Further study of these tracers would be of valuable for the prognosis of glioma patients.

Table 1 summarizes the advantages and disadvantages of the four kinds of PET tracers.

Representative cases

Figure 1 shows representative cases of [^{18}F]FDG, [^{11}C]MET, [^{18}F]FLT, and [^{18}F]FMISO PET studies in diffuse astrocytoma, anaplastic astrocytoma, and glioblastoma.

Treatment Planning

Biopsy planning

Brain tumor diagnosis can be performed at the time of surgical resection or through stereotactic biopsy. Biopsy is performed to obtain a diagnosis in *de novo* cases when the tumor is located in an eloquent brain region and resection cannot be performed without compromising normal function.

The combined use of CT and MRI and stereotactic framing devices allows neurosurgeons to perform biopsies with continuous and accurate intraoperative tumor localization. However, we sometimes estimate lower malignancy grading in gliomas with weak edema and no enhanced area on MRI only by performing target selection by stereotactic MRI-guided biopsy.[42] Thus, PET may be a valuable tool for identifying the most malignant areas in the heterogeneous tumors.

[^{18}F]FDG, the most widespread radiotracer, was shown to be superior for the target selection of stereotactic image-guided biopsy to CT or MRI alone.[43] However, in low-grade gliomas, [^{18}F]FDG accumulation is low and unclear and is a limitation of biopsy targeting of [^{18}F]FDG-positive regions. Previously, combined modalities of [^{11}C]MET and MRI have been shown to significantly enhance the accuracy for the identification of active tumors relative to that of [^{18}F]FDG.[44] Particularly in low-grade gliomas, [^{11}C]MET is better suited for biopsy targeted lesions than is [^{18}F]FDG. Although [^{18}F]FET has been shown to accurately identify malignant tumors, [^{18}F]FET alone could not detect more active tumors within presumed WHO grade II gliomas.[45] However, when the dynamic analysis of [^{18}F]FET was applied, it was possible to differentiate WHO grade II gliomas from grade III within the same lesion and detect a malignant tumor.[46]

Table 1 Summary of PET tracers

Tracer	Advantage	Weak point
Glucose metabolism	Glycolytic metabolism Sensitivity for malignant lymphoma	Poor sensitivity and specificity for lesion detection and malignant grading Not reflect cellular proliferation
Amino acid metabolism	High accumulation related to amino acid transporter Protein synthesis Cellular proliferation marker Better delineation of tumor Dynamic imaging of FET Long half-life of [^{18}F] FET and FDOPA	Short half-life limits the use of [^{11}C] MET to PET center with a cyclotron High uptake of MET and FET for oligodendroglioma, pilocytic astrocytoma and inflammatory cells Physiological uptake of FDOPA in the basal ganglia
Nucleic acid metabolism	High sensitivity for malignant glioma DNA synthesis Cellular proliferation marker Examination of kinetic analysis	Sometimes false positive in regions of BBB disruption
Hypoxic metabolism	Hypoxic marker Detect resistant region of radiation therapy	A few studies for glioma Only taken up into viable cells Not identify necrotic areas

The advantage of glucose metabolism tracers is their sensitivity to malignant lymphomas; however, a limitation is their poor specificity. Better delineation of tumors and cellular proliferation are the advantages of amino acid metabolism tracers. Nucleic acid metabolism tracers are useful for their high sensitivity for malignancies and cellular proliferation; however, false positives are sometimes detected in regions of the blood–brain barrier disruption. Hypoxic metabolism tracers are useful for detecting regions resistant to radiation therapy.

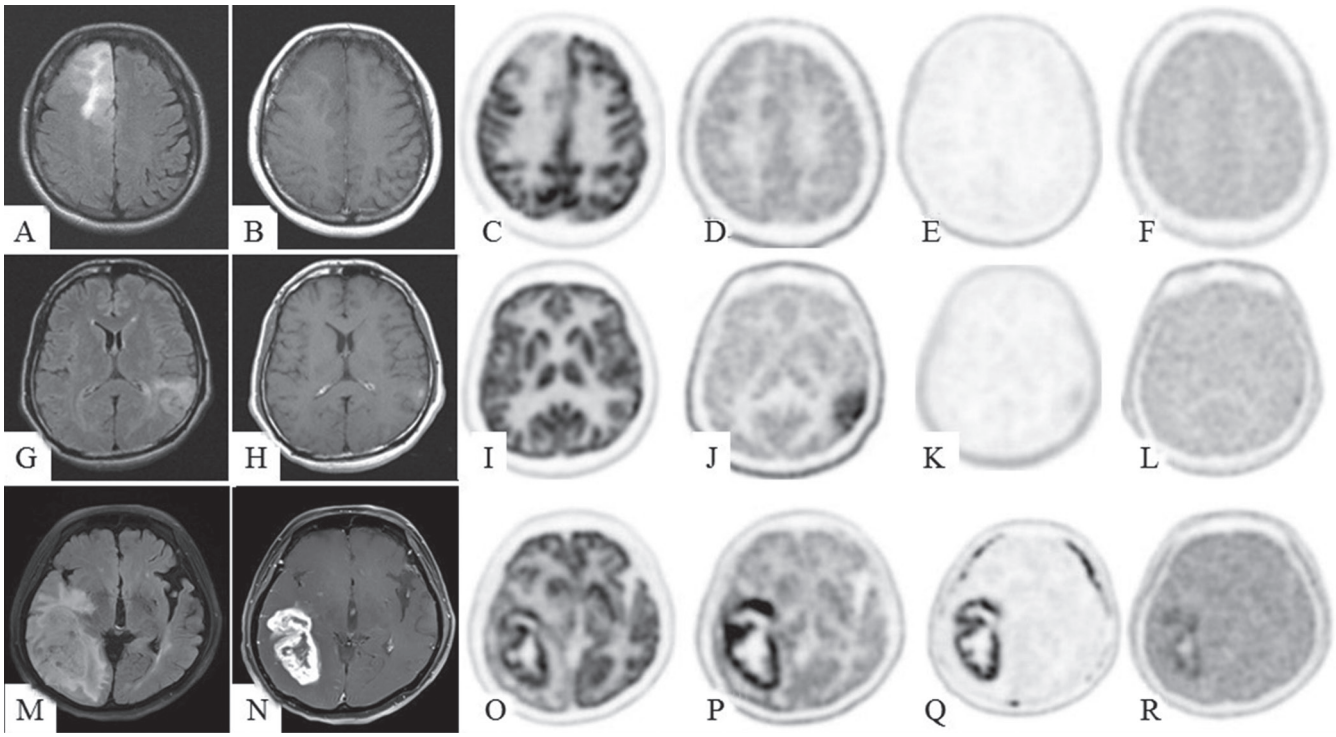

Fig. 1 This Figure shows three illustrative cases. The upper panel shows a WHO grade II case (diffuse astrocytoma) (A, B, C, D, E, and F). The middle panel shows a WHO grade III case (anaplastic astrocytoma) (G, H, I, J, K, and L). The lower panel shows a WHO grade IV case (glioblastoma) (M, N, O, P, Q, and R). FLAIR images (A, G, and M), enhanced-T_1WI (B, H, and N), FDG PET images (C, I, and O), MET PET images (D, J, and P), FLT PET images (E, K, and Q), and FMISO PET images (F, L, and R) are shown. Comparison of T/N or T/B ratios and WHO grade of gliomas showing that increased WHO grade of the gliomas tended to be associated with increased T/N ratios of FDG, but there was no significant difference in the T/N ratios between each WHO grade of gliomas. The differences in MET T/N ratios were statistically significant between grades II and IV gliomas. The differences in FLT T/N ratios were statistically significant between grades II and III gliomas and between grades III and IV gliomas. And also the differences in FMISO T/B ratios were statistically significant between grades III and IV gliomas but not between grades II and III gliomas. Analysis of the correlation between the T/N ratios or T/B ratios and Ki-67 labeling index shows a significant correlation between the Ki-67 labeling index with MET, FLT, and FMISO. The most significant correlation of the Ki-67 labeling index was with the FLT T/N ratio. Using MET, FLT, and FMISO PET, we could distinguish between different WHO grades of gliomas. The upper panel case involves a 55-year-old woman with high intensity in the right frontal lobe on FLAIR MRI (A). Weak uptake of FDG (C) and MET (D), and no uptake of FLT (E) and FMISO (F) are shown; this case was diagnosed as WHO grade II glioma. The middle panel shows a case involving a 46-year-old man with a slight enhancement in the left temporal lobe on enhanced-T_1WI (H). The MET uptake increase is more in the tumor lesion than in the white matter (J), and the uptakes of FLT are slightly increased (K). This case was diagnosed as a WHO grade III glioma. The lower panel case involves a 64-year-old man with a strong enhancement in the right temporo-occipital lobe in the enhanced-T_1WI (N). High uptakes of all PET tracers are shown (O, P, Q, and R); this case was diagnosed as a WHO grade IV glioma.

In high-grade gliomas, it is arguable that PET-guided biopsy is useful. Because of their metabolic and vascular properties based on increased proliferation, high-grade gliomas generally exhibit high uptake values for all well-established radiotracers. Therefore, [^{18}F]FDG,[43] [^{11}C]MET,[44] and [^{18}F]FET,[45] as well as [^{18}F]FLT, which can identify regions of tumors with increased proliferation rates, could be implemented for combined PET/MRI guidance in high-grade gliomas.[47]

Resection planning

In heterogeneous gliomas, resection, including the most malignant part of the tumor, should be performed for correct histopathological evaluation and improvement of prognosis (Fig. 2). However, only three studies have investigated the value of PET-guided resection to date.[47–49] A multimodal navigation system, including several PET tracers and MRI, has been suggested to be more useful than the

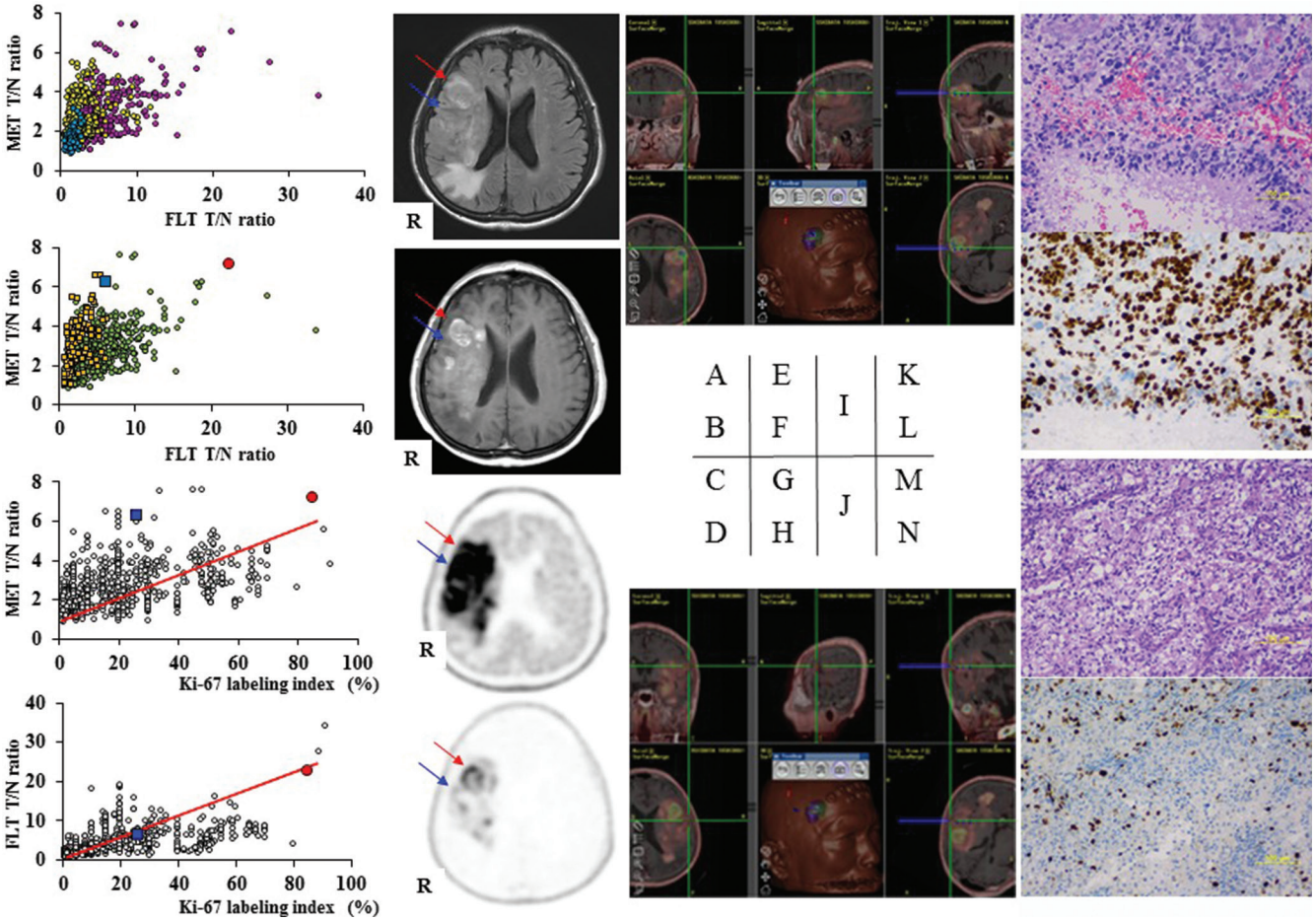

Fig. 2 Surgical management of glioma patients using PET tracers. In the same glioma patient, the cellular component shows heterogeneity. We evaluated the heterogeneity of gliomas using PET tracers. In a pre-determined region of interest (ROI), the T/N ratios of FDG, MET, and FLT and the T/B ratio of FMISO were used to compare the values from each of the four PET studies. Linear regression analysis of the T/N ratio between MET and FLT was performed (*sky blue circle*: WHO grade II, *yellow circle*: WHO grade III, *pink circle*: WHO grade IV) (A). This relationship between MET and FLT is divided into two parts. For the analysis of the oligodendroglioma component, the T/N ratio of MET tended to be high without correlating with an increased T/N ratio of FLT (B, *orange square*). The *green circle* shows the correlation between MET and FLT for an astrocytoma (B). A high accumulation of MET appears to indicate an oligodendroglioma component. The correlations between the T/N ratio for MET (C) or FLT (D) and the Ki-67 labeling index were determined. Analysis showing the significant correlations between the Ki-67 labeling index and MET T/N ratio ($r = 0.444$, $p < 0.001$) and FLT T/N ratio ($r = 0.530$, $p < 0.001$). This case involved a 69-year-old man with a ringed enhancement on enhanced T_1WI (E) and a high-intensity area on FLAIR (F) in the right fronto-parietal lobe. MET PET image showing an increased uptake over a huge area (G). FLT PET image showing increased uptake in the lesion. MR and FLT PET fusion images on the navigation system during surgery (I, J). The *red arrow* indicates that the MET uptake is high (T/N ratio, 7.16) and the FLT uptake is the highest (T/N ratio, 22.5) (B, *red circle*). These PET studies led to a diagnosis of a high-grade astrocytoma. This area was selected for tumor sampling using a fusion image of the navigation system (I). Histopathological analysis identified a glioblastoma (K, hematoxylin-eosin stain; L, Ki-67 labeling index of 85%, *scale bars* = 100 μm). The correlation between the T/N ratio for MET (C, *red circle*) or FLT (D, *red circle*) and the Ki-67 labeling index is shown. The *blue arrow* indicates that MET uptake is high (T/N ratio, 6.25) and FLT uptake is slightly high (T/N ratio, 6.19) (B, *blue square*). These PET studies led to a diagnosis of a high-grade glioma with an oligodendroglioma component. This area was selected for tumor sampling using a fusion image of the navigation system (J). Histopathological analysis identified a glioblastoma with an oligodendroglioma component (M, hematoxylin-eosin stain; N, Ki-67 labeling index of 26%; *scale bars* = 100 μm). The correlation between the T/N ratio for MET (C, *blue square*) or FLT (*blue square*) and Ki-67 labeling index is shown.

conventional navigation system in determining the resection area by providing clearer enhanced lesions of MRI. Resections performed using these systems have resulted in decreased remnant tumor mass and have been associated with improved postsurgical prognosis. Further investigations are needed to assess not only the degree of association between PET-guided resection and patient outcomes, but also the procedures related to morbidity in comparison with those for MRI-based resection.

Radiation therapy planning

Radiation therapy for gliomas performed on the basis of CT and MRI information has developed and is useful for the local control of gliomas. However, the recurrence site is observed within 2–3 cm of the margin of the original lesion in ~80% of glioma patients.[50] Therefore, the usefulness of PET-based biological target volume (BTV) for radiation therapy planning has been reported.[51,52] Particularly for high-grade gliomas, treatment planning based on [^{18}F]FET combined with CT/MRI has also been associated with improved survival in comparison with that based on CT/MRI alone.[50,53] Therefore, biological treatment planning based on amino acid PET appears to be very promising.

Because the tumor hypoxic region is highly resistant to radiation therapy, it is very important to evaluate images in the tumor hypoxic region prior to radiation therapy.[54] However, only a few clinical studies have assessed hypoxia-marker uptake and treatment response to radiotherapy.

Assessment of treatment response to chemotherapy

For glioma patients treated with chemotherapy, [^{11}C]MET and [^{18}F]FET PET may improve response assessment. The assessment of treatment response to adjuvant temozolomide chemotherapy has been demonstrated using [^{11}C]MET in patients with recurrent high-grade glioma.[55] Similarly, [^{18}F]FET PET has been used to assess the effects of temozolomide chemotherapy and may provide earlier indications of a successful treatment than can standard MRI for this patient group.[56]

Since 2013, it has been possible to introduce antiangiogenic drugs, such as bevacizumab, for malignant gliomas in Japan. However, a previous study has shown that the problem of pseudoresponse cannot be solved by the treatment evaluation of images based on the Macdonald criteria alone.[57] For rapidly reducing enhanced lesions after bevacizumab treatment initiation, it would be incorrect to conclude that the response rate is high.[58] The reduction of enhanced lesions in MRI is caused by the rapid normalization of abnormal vascular permeability of BBB, which previously was partially broken. In other words, the reduced enhancement of lesions may not fully reflect the true antitumor activity of antiangiogenic therapy.[59] To overcome the limitations of the Macdonald criteria for antiangiogenic therapy assessment, the Response Assessment in Neuro-Oncology (RANO) group has proposed new recommendations for evaluating responses.[60] For the assessment of treatment response to antiangiogenic therapy, additional metabolic PET imaging provides an important and valuable addition to standard MRI. [^{18}F]FLT is most useful for evaluating cell proliferation and grading of gliomas. However, [^{18}F]FLT is significantly dependent on BBB permeability and is mainly restricted to contrast-enhancing tumor lesions. Thus, the assessment of treatment response to antiangiogenic therapy based on [^{18}F]FLT needs to be carefully interpreted.[61] However, amino acid PET tracers have been evaluated for the assessment of treatment response to antiangiogenic therapy.[62] Compared with the MRI-based RANO criteria, [^{18}F]FET and [^{18}F]FDOPA PET are useful for determining antiangiogenic treatment failure with bevacizumab earlier[63] and have been used to predict a favorable outcome for responders to bevacizumab.[64] A case study showed that [^{18}F]FMISO was useful for the evaluation of the dynamic biological effects of tissue hypoxia on vascular normalization within recurrent high-grade gliomas treated using bevacizumab.[65]

Patient Prognosis

Prognosis prediction

Several prognostic factors have been identified in gliomas, including patient's age, location, and size of the lesion, histology and grade of the tumor, and neurological status.[66] Aggressive treatment can cause treatment-related morbidity, whereas, inadequate treatment of progressive lesions may significantly decrease overall survival time. Several imaging modalities need to be used to adjust treatment strategies for the accurate identification of patients with poor or better prognosis because the clinical course of patients with low- or high-grade gliomas varies considerably. Widespread [^{18}F]FDG PET uptake has been shown to predict malignant transformation and to correlate with overall survival in a retrospective study.[67] [^{18}F]FET PET in combination with MRI has been suggested to enable good prediction of the clinical course and outcome in non-enhanced low-grade gliomas.[68] Within the observation period of this study, the best outcome was found for circumscribed lesions without tracer uptake. Conversely, the worst outcome was found

in diffuse gliomas with high uptake. A recent study showed an association between volume-based tumor measurements and patient prognosis because [11C]MET uptake reflected tumor expansion more accurately than did MRI (Figs. 3, 4).[69] Another promising tracer for tumor grade and cellular proliferation evaluation in gliomas is [18F]FLT. Increased [18F]FLT uptake in untreated patients with low-grade gliomas is a strong predictor of overall survival.[70] The proliferative volume and [18F]FLT tumor-to-normal ratio are independent predictors of survival in patients with recurrent malignant gliomas. The proliferative volume of [18F]FLT appears to be more predictive than tumor volume on MRI for overall survival.[71]

Differential Diagnosis of Pseudoprogression

Post-radiation treatment effects can be divided into acute effects (i.e., immediately after or even during radiotherapy), subacute (early-delayed) effects (i.e., pseudoprogression), or late effects, such as radiation necrosis.[72] Pseudoprogression has commonly been defined as a subacute post-treatment reaction

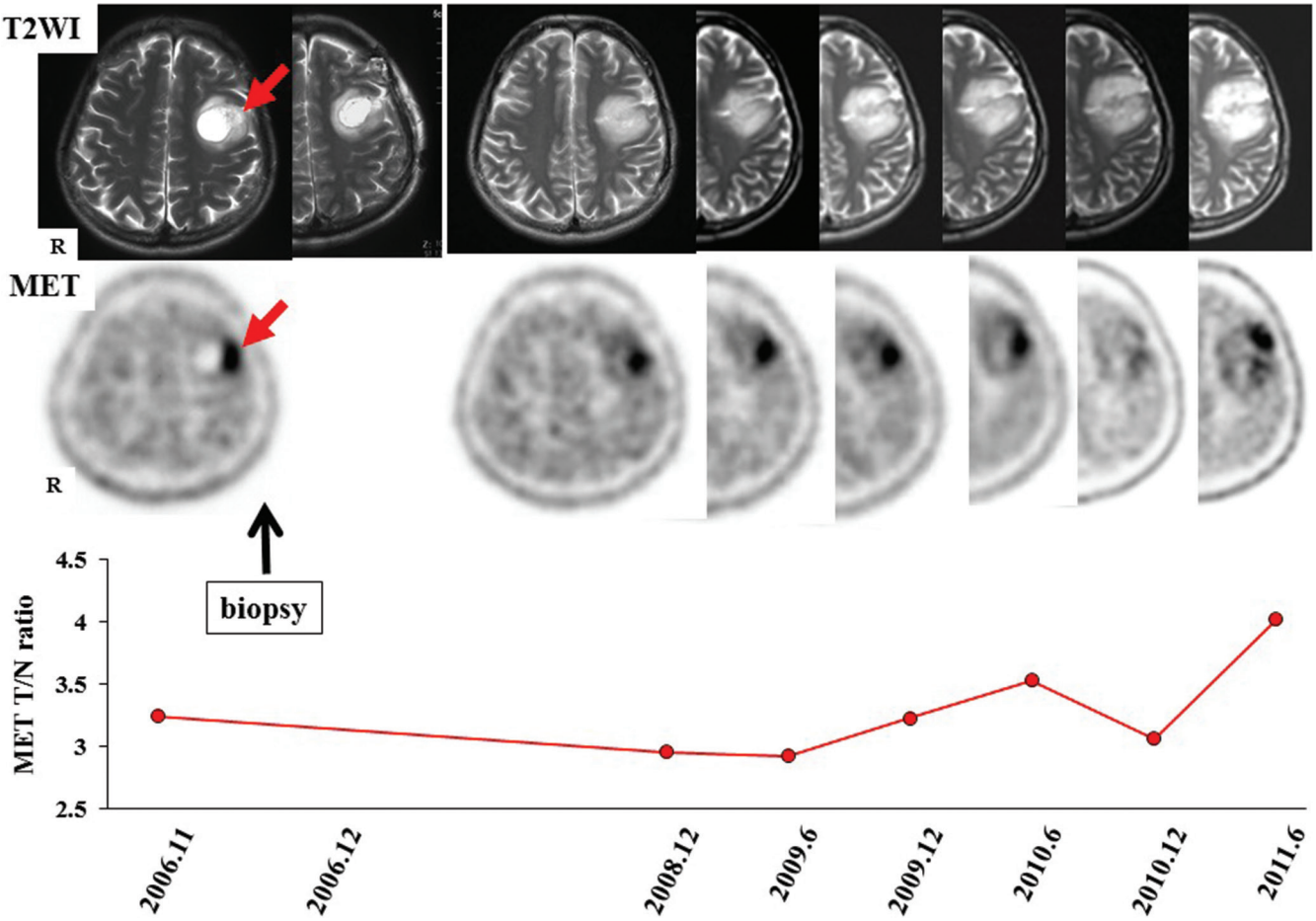

Fig. 3 Representative case examined using PET for treatment monitoring. This case involved a 39-year-old woman with a high-intensity area, including a cyst, on T_2WI (November 2006) in the left frontal lobe. MET PET image showing increased uptake in the lesion (T/N ratio, 3.24). For the diagnosis of the lesion, a left fronto-parietal craniotomy was performed, the high MET uptake area was selected for tumor sampling (*red arrow*), and the cyst was opened. Histopathological analysis showing a diffuse astrocytoma with a Ki-67 labeling index of 1–2%. Therefore, imaging was performed for observation. T_2WI after surgery is shown (December 2006). T_2WI and MET PET images during the observation and the graph of the MET T/N ratio are shown. We could not detect a change in the high-intensity area on T_2WI. We observed a change in the MET uptakes from December 2008 and December 2010 (December 2008, 2.95; June 2009, 2.92; December 2009, 3.23; June 2010, 3.53; December 2010, 3.06). On June 2011, we could not detect increased high-intensity area on T_2WI. However, in the MET PET study, we detected an increased MET uptake area within the high-intensity area of T_2WI (T/N ratio, 4.02). We suspected that this high uptake area indicated a recurrent tumor or a malignant transformation of tumor.

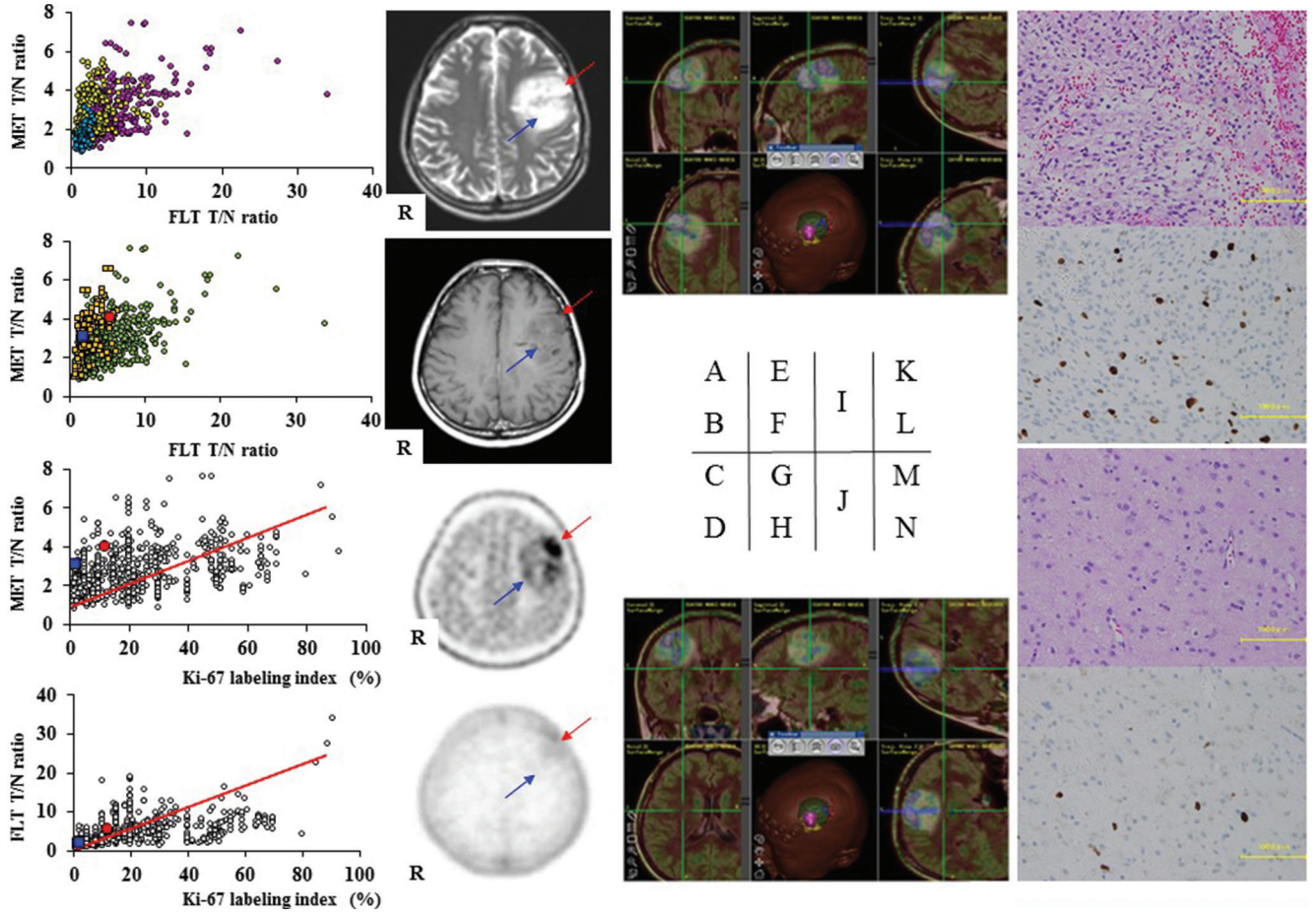

Fig. 4 On June 2011, we could not detect an increased high-intensity area on T_2WI (E) and an enhanced lesion on enhanced-T_1WI (F). Linear regression analysis of the T/N ratio between MET and FLT was performed (*sky blue circle*: WHO grade II, *yellow circle*: WHO grade III, *pink circle*: WHO grade IV) (A). A comparison between the astrocytoma and oligodendroglioma component is shown (B). The correlation between the T/N ratio for MET (C) or FLT (D) and the Ki-67 labeling index was determined. MET PET image showing an increased uptake area in the weak uptake area of the previous PET study (G), and FLT PET showing increased uptake in the lesion. MR and MET PET fusion images of the navigation system acquired during surgery (I and J). The *red arrow* indicates that MET uptake is higher (T/N ratio, 4.02) than the previous value and FLT uptake is slightly high (T/N ratio, 5.45) (B, *red circle*). The results of these PET studies led to a diagnosis of a malignant transformation from WHO grade II to III. This area was selected for tumor sampling using a fusion image of the navigation system (I). Histopathological analysis identified an anaplastic oligoastrocytoma (K, hematoxylin-eosin stain; L, Ki-67 labeling index of 12%; *scale bar* = 100 μm). The correlation between the T/N ratios for MET (C, *red circle*) or FLT (D, *red circle*) and Ki-67 labeling index are shown. The *blue arrow* indicates that MET uptake was slightly high (T/N ratio, 3.06) and similar to that shown by previous data. The FLT uptake is not very high (T/N ratio, 1.85) (B, *blue square*). These PET studies led to a tentative diagnosis of a low-grade glioma with an oligodendroglioma component. This area was selected for tumor sampling using a fusion image of the navigation system (J). Histopathological analysis identified a low-grade astrocytoma (M, hematoxylin-eosin stain; N, Ki-67 labeling index of 2%; *scale bar* = 100 μm). The correlation between the T/N ratios for MET (C, *blue square*) or FLT (D, *blue square*) and Ki-67 labeling index are shown. This tumor was diagnosed as a malignant transformation. Therefore, the PET study was considered to be very useful for treatment monitoring of low-grade gliomas.

with an increased enhanced lesion and edema that mimics tumor progression and recurrence but subsequently stabilizes and regresses without further additional treatment.[73] However, radiation necrosis belongs to the late post-radiation treatment effects category and may appear more than 3 months to several years after radiation therapy, which is later than the typical time period for pseudoprogression;[74] radiation necrosis can also be progressive and irreversible.[75]

Because radio-chemotherapy with temozolomide is the current standard for glioblastoma treatment, it has led to a sudden increase in contrast-enhancing lesions on MRI that are not related to tumor progression but rather to treatment effects, such as pseudoprogression. Pseudoprogression is typically regarded as a phenomenon of the first 12 weeks after radiotherapy,[75] and this time-dependent definition has been incorporated into the new criteria for RANO.[60] However, it is not possible to distinguish tumor recurrence and pseudoprogression in conventional MRI. [^{18}F]FET PET may be useful for this indication within the short time frame of the first 12 weeks after radio-chemotherapy with temozolomide[76] because the sensitivity and specificity of [^{18}F]FET have been found to be >90% for differentiating pseudoprogression from tumor recurrence in glioblastoma patients.[77] Similarly, [^{18}F]FDOPA PET may also be useful for identifying pseudoprogression and distinguishing tumor recurrence from treatment-related changes.[78] However, treatment-related changes between pseudoprogression and radiation necrosis are difficult to distinguish. It is important that [^{18}F]FET and [^{18}F]FDOPA may facilitate the diagnosis of pseudoprogression following radio-chemotherapy for malignant glioma.

Conclusion

PET is a non-invasive molecular imaging examination method that enables measurement of metabolic and molecular processes. Although information assessed using MRI will remain essential in glioma management, several studies using the PET tracers ([^{18}F]FDG, [^{11}C]MET, [^{18}F]FET, [^{18}F]FDOPA, [^{18}F]FLT, and [^{18}F]FMISO) have shown that PET is more specific for tumor delineation, beneficial for biopsy planning, and useful for differentiation between remnant tumor tissue and post-therapeutic changes. Moreover, these PET tracers are suitable for early treatment response assessment and potentially useful for treatment planning of local therapies. PET should be regarded as a useful tool for the accurate evaluation of new treatment strategies and should be considered for use in future prospective studies to evaluate the clinical impact of the treatments. Early adjustment of patient care can also avoid unnecessary treatment toxicity and reduce treatment costs of ineffective therapies. However, further randomized and prospective multicenter clinical trials are needed to clearly demonstrate the additional value of multiple PET studies.

Conflicts of Interest Disclosure

The authors have no personal, financial, or institutional interest. All authors are the members of the Japan Neurosurgical Society (JNS), and have registered online self-reported COI disclosure statements forms through website for JNS members.

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