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), 1-methyl-11C]methionine ([11C]MET), 3′-deoxy-3′-[18F]fluorothymidine ([18F]FLT), [18F]fluoromisonidazole ([18F]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.

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 [11C], nitrogen-13 [13N], oxygen-15 [15O], and fluorine-18 [18F]) are mainly produced in a cyclotron. Because, three isotopes (15O, 13N, and 11C) 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 18F (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. The model separates radiotracer uptake into two compartments with flux rates characterized by kinetic parameters (k1, k2, k3, and k4), but the analysis is not amenable to routine clinical use.

**Diagnosis and Grading of Gliomas**

**Glucose metabolism**

2-Deoxy-2-[18F]fluoro-D-glucose ([18F]FDG) has been widely used as a PET radiotracer to measure local glucose metabolism that represents a common pathway of brain neuro-chemical activity. Intravenously injected [18F]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. After GLUT transport, [18F]FDG and glucose are phosphorylated by hexokinase. Unlike glucose-6-phosphate, [18F]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, [18F]FDG accumulation increases in highly malignant tumors. [18F]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. 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 [18F]FDG PET is a major limitation for assessing gliomas. Conversely, [18F]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.

**Amino acid metabolism**

Radiolabeled amino acids have been used as suitable PET tracers in brain tumors, which play a key role in cell proliferation. Therefore, various radiolabeled amino acids, such as L-methyl-[11C]methionine ([11C]MET) and aromatic amino acid analogues like [18F] fluoroethyltyrosine ([18F]FET) and [18F]fluorodopa ([18F] FDOPA), have been proposed. [11C]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 [11C]MET despite no change on MRI and no increased accumulation of [18F]FDG. [11C]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; therefore, increased [11C]MET uptake in non-tumor lesions, including inflammation, infarction, and hemorrhage, may lead to false positives. Moreover, it has been reported that [11C]MET uptake is high in oligodendrogliomas because of their high cell density 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. Thus, it is difficult to diagnose gliomas using only [11C]MET. One of the disadvantages of [11C]MET is that the half-life of 11C is 20 min. This relatively short half-life limits the use of [11C]MET to PET centers with a cyclotron and makes [11C]MET less useful in routine clinical practice. To have a
longer half-life of positron emitters, \(^{[18}\text{F}]\text{FET}\) and \(^{[18}\text{F}]\text{FDOPA}\) were developed. These molecules are \(^{18}\text{F}\)-labeled amino acid tracers and have a half-life of 110 min, which is clinically advantageous when compared with \(^{[11}\text{C}]\text{MET}\).\(^{15,19}\) Although \(^{[18}\text{F}]\text{FET}\) and \(^{[18}\text{F}]\text{FDOPA}\) can delineate tumor extent and provide excellent tumor-to-background contrast, they have some disadvantages.\(^{20}\) Because the physiological uptake of \(^{[18}\text{F}]\text{FDOPA}\) is in the corpus striatum, margins of tumors may not be distinguished from invasion into the basal ganglia. In \(^{[18}\text{F}]\text{FET}\) 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 \(^{[18}\text{F}]\text{FET}\) can be helpful in clinical brain tumors and allows differentiation between low- and high-grade gliomas.\(^{21}\)

In recent years, \(\text{trans-1-amino-3-}[^{18}\text{F}]\text{fluorocyclo-}
\text{butane-carboxylic acid (anti-}[^{18}\text{F}]\text{FACBC) is a newly
developed PET tracer that accumulates inside cells via an amino acid transporter.}\)\(^{22}\) Previous studies have shown that the accumulation of \(\text{anti-}[^{18}\text{F}]\text{FACBC}\) is high in gliomas and low in normal tissues and inflammatory regions.\(^{23,24}\) We expected that \(\text{anti-}[^{18}\text{F}]\text{FACBC}\) 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-\(3’-[^{18}\text{F}]\text{fluorothymidine ([}^{18}\text{F}]\text{FLT})\), 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. \(^{[18}\text{F}]\text{FLT}\) is trapped inside the cells, although only trace amounts of it can be recovered from DNA extracts.\(^{26}\) Thus, \(^{[18}\text{F}]\text{FLT}\) has been thought to be a helpful biomarker of cell proliferation, and the correlation between \(^{[18}\text{F}]\text{FLT}\) accumulation and Ki-67 labeling index has been found to be significant.\(^{27}\) Because, \(^{[18}\text{F}]\text{FLT}\) accumulation in normal brain tissue is very low, it provides excellent tumor-to-background contrast. One of the disadvantages of \(^{[18}\text{F}]\text{FLT}\) is that it is less useful in assessing noncontrast-enhancing tumor proliferation regardless of histopathological grading. Because of \(^{[18}\text{F}]\text{FLT}\) leakage in radiation necrosis and disruption of the blood–brain barrier (BBB), \(^{[18}\text{F}]\text{FLT}\) accumulation can increase,\(^{10}\) which may make it difficult to differentiate from metabolically active tumors. A kinetic assay of \(^{[18}\text{F}]\text{FLT}\) related to TK-1 expression was expected to evaluate cell proliferation, but the phosphorylation rate constant \(k\) determined using this assay did not accurately reflect TK-1 expression in the tissue.\(^{28}\) Rather, \(^{[18}\text{F}]\text{FLT}\) accumulation has been associated with vascular permeability and BBB disruption. Further, the value of the \(^{[18}\text{F}]\text{FLT}\) tracer in gliomas needs to be prospectively evaluated.

\(4’\)-[Methyl-\(^{11}\text{C}\)thiothymidine ([\(^{11}\text{C}\)]\text{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 \([^{11}\text{C}]\text{4DST}\) to be superior to \(^{[18}\text{F}]\text{FLT}\) in evaluating cell proliferation and treatment response and in predicting prognosis by \([^{11}\text{C}]\text{4DST}\) 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 and vascular occlusion of blood vessels within the tumor.\(^{31}\) Hypoxia promotes neovascularization through various molecular signals,\(^{32}\) may drive the peripheral growth of a tumor, and is associated with tumor progression and resistance to chemotherapy\(^{33}\) and radiotherapy.\(^{34}\) One of the most widely used PET radiotracers for molecular imaging of hypoxia is \(^{[18}\text{F}]\text{fluoromisonidazole ([}^{18}\text{F}]\text{FMISO})\), which is a nitroimidazole derivative\(^{35}\) and is exclusively trapped in hypoxic cells.\(^{36}\) 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.\(^{37}\) In our results, \(^{[18}\text{F}]\text{FMISO}\) showed high accumulation in WHO grade IV gliomas but not in WHO grade II and III gliomas, and an \(^{[18}\text{F}]\text{FMISO}\) PET study discriminated WHO grade IV gliomas from WHO grade II and III gliomas.\(^{38}\) 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.\(^{39}\) Based on biological links between hypoxia and tumor-induced neoangiogenesis, \(^{[18}\text{F}]\text{FMISO}\) uptake has been shown to significantly correlate with vascular endothelial growth factor (VEGF) expression in tumors and has
PET Scan Studies for Gliomas

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, $[^{18}\text{F}]$FMISO PET imaging is expected to be helpful for glioma treatment evaluation. However, considering the low target-to-background ratio and slow uptake in malignant tissues, $[^{18}\text{F}]$FMISO use has been limited in routine clinical examinations. Other PET tracers are $1\alpha$-$[^{18}\text{F}]$fluoro-5-deoxyarabinofuranosyl)-2-nitroimidazole ($[^{18}\text{F}]$FAZ)$^{41}$ and $[^{64}\text{Cu}]$diacetyl-bis-(N-N-N-methylthiosemicarbazone) ($[^{64}\text{Cu}]$ATSM).$^{42}$ 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 $[^{18}\text{F}]$FDG, $[^{11}\text{C}]$MeT, $[^{18}\text{F}]$FLT, and $[^{18}\text{F}]$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.

$[^{18}\text{F}]$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, $[^{18}\text{F}]$FDG accumulation is low and unclear and is a limitation of biopsy targeting of $[^{18}\text{F}]$FDG-positive regions. Previously, combined modalities of $[^{11}\text{C}]$MET and MRI have been shown to significantly enhance the accuracy for the identification of active tumors relative to that of $[^{18}\text{F}]$FDG.$^{44}$ Particularly in low-grade gliomas, $[^{11}\text{C}]$MET is better suited for biopsy targeted lesions than is $[^{18}\text{F}]$FDG. Although $[^{18}\text{F}]$FET has been shown to accurately identify malignant tumors, $[^{18}\text{F}]$FET alone could not detect more active tumors within presumed WHO grade II gliomas.$^{45}$ However, when the dynamic analysis of $[^{18}\text{F}]$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                          | Poor sensitivity and specificity for lesion detection and malignant grading |
|                      | Sensitivity for malignant lymphoma             | Not reflect cellular proliferation              |
| Amino acid metabolism| High accumulation related to amino acid transporter | Short half-life limits the use of $[^{11}\text{C}]$MET to PET center with a cyclotron |
|                      | Protein synthesis                               | High uptake of MET and FET for oligodendroglioma, pilocytic astrocytoma and inflammatory cells |
|                      | Cellular proliferation marker                   | Physiological uptake of FDOPA in the basal ganglia |
|                      | Better delineation of tumor                    |                                               |
|                      | Dynamic imaging of FET                         |                                               |
|                      | Long half-life of $[^{18}\text{F}]$FET and FDOPA |                                               |
| Nucleic acid metabolism | High sensitivity for malignant glioma DNA synthesis | Sometimes false positive in regions of BBB disruption |
|                      | Cellular proliferation marker                   |                                               |
|                      | Examination of kinetic analysis                |                                               |
| Hypoxic metabolism  | Hypoxic marker                                  | A few studies for glioma                       |
|                      | Detect resistant region of radiation therapy   | 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.

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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, \[^{18}\text{F}\] FDG, \[^{11}\text{C}\] MET, and \[^{18}\text{F}\] FLT, which can identify regions of tumors with increased proliferation rates, could be implemented for combined PET/MRI guidance in high-grade gliomas.

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,WI (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. Therefore, the usefulness of PET-based biological target volume (BTV) for radiation therapy planning has been reported. 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. 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. 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]MEM and [18 F]FET PET may improve response assessment. The assessment of treatment response to adjuvant temozolomide chemotherapy has been demonstrated using [11 C]MEM in patients with recurrent high-grade glioma. 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.

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 pseudoprogression cannot be solved by the treatment evaluation of images based on the Macdonald criteria alone. For rapidly reducing enhanced lesions after bevacizumab treatment initiation, it would be incorrect to conclude that the response rate is high. 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. 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. 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. However, amino acid PET tracers have been evaluated for the assessment of treatment response to antiangiogenic therapy. 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 and have been used to predict a favorable outcome for responders to bevacizumab. 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.

**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. 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. [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. 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 $[^{11}\text{C}]$MET uptake reflected tumor expansion more accurately than did MRI (Figs. 3, 4). Another promising tracer for tumor grade and cellular proliferation evaluation in gliomas is $[^{18}\text{F}]$FLT. Increased $[^{18}\text{F}]$FLT uptake in untreated patients with low-grade gliomas is a strong predictor of overall survival. The proliferative volume of $[^{18}\text{F}]$FLT appears to be more predictive than tumor volume on MRI for overall survival.\\n
**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. Pseudoprogression has commonly been defined as a subacute post-treatment reaction.
with an increased enhanced lesion and edema that mimics tumor progression and recurrence but subsequently stabilizes and regresses without further additional treatment.\textsuperscript{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;\textsuperscript{74} radiation necrosis can also be progressive and irreversible.\textsuperscript{75}

**Fig. 4** On June 2011, we could not detect an increased high-intensity area on T2WI (E) and an enhanced lesion on enhanced-T1WI (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.
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 pseudoprogession. Pseudoprogession 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 pseudoprogession 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 pseudoprogession from tumor recurrence in glioblastoma patients.\(^77\) Similarly, \(^{[18} F\)FDOPA PET may also be useful for identifying pseudoprogession and distinguishing tumor recurrence from treatment-related changes.\(^78\) However, treatment-related changes between pseudoprogession and radiation necrosis are difficult to distinguish. It is important that \(^{[18} F\)FET and \(^{[18} F\)FDOPA may facilitate the diagnosis of pseudoprogession 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.

**References**

1. Kleihues P, Soylemezoglu F, Schauble B, Scheithauer BW, Burger PC: Histopathology, classification, and grading of gliomas. *Glia* 15: 211–221, 1995
2. Louis DN, Holland EC, Cairncross JG: Glioma classification: a molecular reappraisal. *Am J Pathol* 159: 779–786, 2001
3. Okubo S, Zhen HN, Kawai N, Nishiyama Y, Haba R, Tamiya T: Correlation of \(l\)-methyl-\(11\)C-methionine (MET) uptake with \(l\)-type amino acid transporter 1 in human gliomas. *J Neurooncol* 99: 217–225, 2010
4. Schaller B: Usefulness of positron emission tomography in diagnosis and treatment follow-up of brain tumors. *Neurol Biol Dis* 15: 437–448, 2004
5. Spence AM, Muzi M, Graham MM, O'Sullivan F, Krohn KA, Link JM, Lewellen TK, Lewellen B, Freeman SD, Berger MS, Ojemann GA: Glucose metabolism in human malignant gliomas measured quantitatively with PET, \(1\)-\(\text{[C-11]}\)glucose and FDG: analysis of the FDG lumped constant. *J Nucl Med* 39: 440–448, 1998
6. Di Chiro G: Positron emission tomography using \(^{[18} F\)fluorodeoxyglucose in brain tumors: a powerful diagnostic and prognostic tool. *Invest Radiol* 22: 360–371, 1987
7. Boado RJ, Black KL, Pardridge WM: Gene expression of GLUT3 and GLUT1 glucose transporters in human brain tumors. *Brain Res Mol Brain Res* 27: 51–57, 1994
8. Colavolpe C, Guedj E, Metellus P, Barrie M, Figarella-Branger D, Mundler O, Chinot O: FDG–PET to predict different patterns of progression in multicentric glioblastoma: a case report. *J Nucl Med* 90: 47–51, 2008
9. Di Chiro G, DeLapaz RL, Brooks RA, Sokoloff L, Kornblith PL, Smith BH, Patronas NJ, Kifta CV, Kessler RM, Johnston GS, Manning RG, Wolf AP: Glucose utilization of cerebral gliomas measured by \(^{[18} F\)fluorodeoxyglucose and positron emission tomography. *Neurology* 32: 1323–1329, 1982
10. Herholz K, Coope D, Jackson A: Metabolic and molecular imaging in neuro-oncology. *Lancet Neurol* 6: 711–724, 2007
11. Kawai N, Miyake K, Yamamoto Y, Nishiyama Y, Tamiya T: 18F-FDG PET in the diagnosis and treatment of primary central nervous system lymphoma. *Biomed Res Int* 2013: 247152, 2013
12. Hubner KF, Purvis JT, Mahaley SM Jr, Robertson JT, Rogers S, Gibbs WD, King P, Partain CL: Brain tumor imaging by positron emission computed tomography using \(11\)C-labeled amino acids. *J Comput Assist Tomogr* 6: 544–550, 1982
13. Isselbacher KJ: Sugar and amino acid transport by cells in culture: differences between normal and malignant cells. *N Engl J Med* 286: 929–933, 1972
14) Derlon JM, Bourdet C, Bustany P, Chatel M, Theron J, Darcel F, Syrota A: [11C] l-methionine uptake in gliomas. Neurosurgery 25: 720–728, 1989
15) Wester HJ, Herz M, Weber W, Heiss P, Senekowitsch-Schmidtke R, Schweiger M, Stocklin G: Synthesis and radiopharmacology of O-[2-([18]F]fluoroethyl]-l-tyrosine for tumor imaging. J Nucl Med 40: 205–212, 1999
16) Chen W, Silverman DH, Delaloye S, Czerniak J, Kamdar N, Pope W, Satyamurthy N, Schiepers C, Cloughesy T: 18F-FDOPA PET imaging of brain tumors: comparison study with 18F-FDG PET and evaluation of diagnostic accuracy. J Nucl Med 47: 904–911, 2006
17) Nakagawa M, Kuwabara Y, Sasaki M, Koga H, Chen T, Kaneko H, Hayashi K, Morioka T, Masuda K: 11C-methionine uptake in cerebrovascular disease: a comparison with 18F-FDG PET and 99mTc-HMPAO SPECT. Ann Nucl Med 16: 207–211, 2002
18) Torii K, Tsuyuguchi N, Kawabe J, Sunada H, Hara M, Shiomai S: Correlation of amino-acid uptake using methionine PET and histological classifications in various gliomas. Ann Nucl Med 19: 677–683, 2005
19) Langen KJ, Hamacher K, Weckesser M, Floeth F, Stoffels G, Bauer D, Coenen HH, Pauliet D: O-[2-[18]F]fluoroethyl]-l-tyrosine: uptake mechanisms and clinical applications. Nucl Med Biol 33: 287–294, 2006
20) Kratochvil C, Combs SE, Leotta K, Afshar-Oromieh A, Rieken S, Debus J, Haberkorn U, Giesel FL: Intra-individual comparison of (1)(8)F-FLT and (1)(8)F-DOPA in PET imaging of recurrent brain tumors. Neuro Oncol 16: 434–440, 2014
21) Kunz M, Thon N, Eigenbrod S, Hartmann C, Egensperger R, Herms J, Geisler J, la Fougere C, Lutz J, Linn J, Kreth S, von Deimling A, Tonn JC, Kretzschmar HA, Popperl G, Kreth FW: Hot spots in dynamic (18)FET–PET delineate malignant tumor parts within suspected WHO grade II gliomas. Neuro Oncol 13: 307–316, 2011
22) Ono M, Oka S, Okudaira H, Schuster DM, Goodman MM, Kawai K, Shirakami Y: Comparative evaluation of transport mechanisms of trans-1-amino-3-[(1)(8)F] fluorocarbocarboxylic acid and l-[methyl-(1)(1)C]methionine in human glioma cell lines. Brain Res 1535: 24–37, 2013
23) Ono T, Sasajima T, Doi Y, Oka S, Ono M, Kanagawa M, Baden A, Mizoi K, Shimizu H: Amino acid PET tracers are reliable markers of treatment responses to single-agent or combination therapies including temozolomide, interferon-beta, and/or bevacizumab for glioblastoma. Nucl Med Biol 42: 598–607, 2015
24) Doi Y, Kanagawa M, Maya Y, Tanaka A, Oka S, Nakata N, Toyama M, Matsumoto H, Shirakami Y: Evaluation of trans-1-amino-3-[18F]fluorocarbocarboxylic acid accumulation in low-grade glioma in chemically induced rat models: PET and autoradiography compared with morphological images and histopathological findings. Nucl Med Biol 42: 664–672, 2015
25) Shields AF, Grierson JR, Dohmen BM, Machulla HJ, Stayanoff JC, Lawhern-Crews JM, obradowich JE, Muzik O, Mangner TJ: Imaging proliferation in vivo with [F-18]FLT and positron emission tomography. Nat Med 4: 1334–1336, 1998
26) Seitz U, Wagner M, Neumaier B, Wawra E, Glatting G, Leder G, Schmid RM, Reske SN: Evaluation of pyrimidine metabolising enzymes and in vitro uptake of 3′-[(18)F]fluoro-3′-deoxythymidine ([(18)F]FLT) in pancreatic cancer cell lines. Eur J Nucl Med Mol Imaging 29: 1174–1181, 2002
27) Hatakeyama T, Kawai N, Nishiyama Y, Yamamoto Y, Sasaki Y, Ichikawa T, Tamiya T: 11C-methionine (MET) and 18F-fluorothyridine (FLT) PET in patients with newly diagnosed glioma. Eur J Nucl Med Mol Imaging 35: 2009–2017, 2008
28) Shinomiya A, Kawai N, Okada M, Miyake K, Nakamura T, Kushida Y, Haba R, Kudomi N, Yamamoto Y, Tokuda M, Tamiya T: Evaluation of 3′-deoxy-3′-[(18)F]-fluorothyridine (18F-FLT) kinetics correlated with thymidine kinase-1 expression and cell proliferation in newly diagnosed gliomas. Eur J Nucl Med Mol Imaging 40: 175–185, 2013
29) Toyohara Y, Okada M, Toramatsu C, Suzuki K, Irie T: Feasibility studies of 4′-[methyl-(11)C]thiotymidine as a tumor proliferation imaging agent in mice. Nucl Med Biol 35: 67–74, 2008
30) Toyota Y, Miyake K, Kawai N, Hatakeyama T, Yamamoto Y, Toyohara Y, Nishiyama Y, Tamiya T: Comparison of 4′-methyl-[11)C]thiotymidine (11C-4DST) and 3′-deoxy-3′-[(18)F]fluorothyridine (18F-FLT) PET/CT in human brain glioma imaging. EJNMMI Res 5: 7, 2015
31) Rajendran JG, Mankoff DA, O’Sullivan F, Peterson LM, Schwartz DL, Conrad EU, Spence AM, Muzi M, Farwell DG, Krohn KA: Hypoxia and glucose metabolism in malignant tumors: evaluation by [18F]fluoromisonidazole and [18F]fluorodeoxyglucose positron emission tomography imaging. Clin Cancer Res 10: 2245–2252, 2004
32) Brat DJ, Castellano-Sanchez AA, Hunter SB, Pecot M, Cohen C, Hammond EH, Devi SN, Kaur B, Van Meir EG: Pseudopalisades in glioblastoma are hypoxic, express extracellular matrix proteases, and are formed by an actively migrating cell population. Cancer Res 64: 920–927, 2004
33) Fischer I, Gagner JP, Law M, Newcomb EW, Zagzag D: Angiogenesis in gliomas: biology and molecular pathophysiology. Brain Pathol 15: 297–310, 2005
34) Wilson WR, Hay MP: Targeting hypoxia in cancer therapy. Nat Rev Cancer 11: 393–410, 2011
35) Denny WA: Prodrug strategies in cancer therapy. Eur J Med Chem 36: 577–595, 2001
36) Swanson KR, Chakraborty G, Wang CH, Rockne R, Harpold HL, Muzi M, Adamsen TC, Krohn KA, Spence AM: Complementary but distinct roles for MRI and 18F-fluoromisonidazole PET in the assessment of human glioblastomas. J Nucl Med 50: 36–44, 2009
PET Scan Studies for Gliomas

37) Whitmore GF, Varghese AJ: The biological properties of reduced nitroheterocyclics and possible underlying biochemical mechanisms. *Biochem Pharmacol* 35: 97–103, 1986

38) Krohn KA, Link JM, Mason RP: Molecular imaging of hypoxia. *J Nucl Med* 49: 129S–148S, 2008

39) Kawai N, Maeda Y, Kudomi N, Miyake K, Okada M, Yamamoto Y, Nishiyama Y, Tamiya T: Correlation of biological aggressiveness assessed by 11C-methionine PET and hypoxic burden assessed by 18F-fluoromisonidazole PET in newly diagnosed glioblastoma. *Eur J Nucl Med Mol Imaging* 38: 441–450, 2011

40) Kawai N, Lin W, Cao WD, Ogawa D, Miyake K, Haba R, Maeda Y, Yamamoto Y, Nishiyama Y, Tamiya T: Correlation between (1)(8)F-fluoromisonidazole PET and expression of HIF-1alpha and VEGF in newly diagnosed and recurrent malignant gliomas. *Eur J Nucl Med Mol Imaging* 41: 1870–1878, 2014

41) Souvatzoglou M, Grosu AL, Piert M, Weber WA, Jeremic B, Picchio M, Weber DC, Casanova N, Zilli T, Buchegger F, Rouzaud M, Nouet P, Vees H, Ratib O, Dipasquale G, Miralbell R: Recurrence pattern after [(18)F]fluoroethyltyrosine-posi- tion emission tomography-guided radiotherapy for high-grade glioma: a prospective study. *Radiation Oncol* 93: 586–592, 2009

42) Götz I, Grosu AL: [(18)F]FET–PET imaging for treatment and response monitoring of radiation therapy in malignant glioma patients: a review. *Front Oncol* 3: 104, 2013

43) Cher LM, Murone C, Lawrentschuk N, Ramdave S, Papenfuss A, Hannah A, O'Keefe GJ, Sachinidis II, Berlangieri SU, Fabinyi G, Scott AM: Correlation of hypoxic cell fraction and angiogenesis with glucose metabolic rate in gliomas using 18F-fluoromisonidazole, 18F-FDG PET, and immunohistochemical studies. *J Nucl Med* 47: 410–418, 2006

44) Galldiks N, Schruder T, Walder B, Schuller M, Molls M, Wallner K, Schwaiger M, Molls M: Positron emission tomography for radiation treatment planning. *Strahlenther Onkol* 181: 483–499, 2005

45) Piriotte BJ, Levivier M, Goldman S, Massager N, Wikler D, Dewitte O, Bruneau M, Rorive S, David P, Brochi J: Positron emission tomography-guided volumetric resection of supratentorial high-grade gliomas: a survival analysis in 66 consecutive patients. *Neurosurgery* 64: 471–481: discussion 481, 2009

46) Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galalis E, Degroot J, Wick W, Ahluwalia MS, Wen PY: Antiangiogenic therapy for patients with glioblastoma: current challenges in imaging and future directions. *Expert Rev Anti-cancer Ther* 11: 653–656, 2011

47) Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galalis E, Degroot J, Wick W.
Gilbert MR, Lassman AB, Tsien C, Mikkelsen T, Wong ET, Chamberlain MC, Stupp R, Lamborn KR, Vogelbaum MA, van den Bent MJ, Chang SM: Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol 28: 1963–1972, 2010

Nowosielski M, DiFranco MD, Putzer D, Seiz M, Recheis W, Jacobs AH, Stockhammer G, Hutterer M: An intra-individual comparison of MRI, [18F]-FET and [18F]-FLT PET in patients with high-grade gliomas. PLoS One 9: e95830, 2014

Reithmeier T, Lopez WO, Spehl TS, Nguyen T, Mader I, Nikkahh G, Pinskyer MO: Bevacizumab as salvage therapy for progressive brain stem gliomas. Clin Neurol Neurosurg 115: 165–169, 2013

Galldiks N, Rapp M, Stoffels G, Dunkl V, Sabel M, Langen KJ: Earlier diagnosis of progressive disease during bevacizumab treatment using O-(2-[18F]-fluoroethyl)-l-tyrosine positron emission tomography in comparison with magnetic resonance imaging. Mol Imaging 12: 273–276, 2013

Hutterer M, Hattingen E, Palm C, Proescholdt MA, Hau P: Current standards and new concepts in MRI and PET response assessment of antiangiogenic therapies in high-grade glioma patients. Neuro Oncol 17: 784–800, 2015

Barajas RF Jr, Pampaloni MH, Clarke JL, Seo Y, Savic D, Hawkins RA, Behr SC, Chang SM, Berger M, Dillon WP, Cha S: Assessing biological response to bevacizumab using 18F-fluoromisonidazole PET/CT imaging in a patient with recurrent anaplastic astrocytoma. Case Rep Radiol 2015: 731361, 2015

Claus EB, Black PM: Survival rates and patterns of care for patients diagnosed with supratentorial low-grade gliomas: data from the SEER program, 1973-2001. Cancer 106: 1358–1363, 2006

Padma MV, Saïd S, Jacobs M, Hwang DR, Dunigan K, Satter M, Christian B, Ruppert J, Bernstein T, Kraus G, Mantl JC: Prediction of pathology and survival by FDG PET in gliomas. J Neurooncol 64: 227–237, 2003

Floeth FW, Pauleit D, Sabel M, Stoffels G, Reifenberger G, Riemenschneider MJ, Jansen P, Coenen HH, Steiger HH, Eble MJ, Piroth MD: Assessment of treatment response in patients with glioblastoma using O-(2-[18F]-fluoroethyl)-l-tyrosine PET in comparison to MRI. J Nucl Med 53: 1048–1057, 2012

Galldiks N, Dunkl V, Stoffels G, Hutterer M, Rapp M, Sabel M, Reifenberger G, Kebir S, Dorn F, Blau T, Herrlinger U, Hau P, Ruge MI, Kocher M, Goldbrunner R, Fink GR, Drzezga A, Schmidt M, Langen KJ: Diagnosis of pseudoprogression in patients with glioblastoma using O-(2-[18F]-fluoroethyl)-l-tyrosine PET. Eur J Nucl Med Mol Imaging 42: 685–695, 2015

Herrmann K, Czernin J, Cloughesy T, Lai A, Pomykala KL, Benz MR, Buck AK, Phelps ME, Chen W: Comparison of visual and semiquantitative analysis of 18F-FDOPA–PET/CT for recurrence detection in glioblastoma patients. Neuro Oncol 16: 603–609, 2014

Belohlavek O, Fencl P, Majovský M, Jarusková M, Benes V: FLT-PET in previously untreated patients with low-grade glioma can predict their overall survival. Nucl Med Rev Cent East Eur 17: 7–12, 2014

Zhao F, Cui Y, Li M, Fu Z, Chen Z, Kong L, Yang G, Yu J: Prognostic value of 3′-deoxy-3′-[18F]-fluorothymidine ([18F] FLT PET) in patients with recurrent malignant gliomas. Nucl Med Biol 41: 710–715, 2014

Walker AJ, Ruzevick J, Malayeri AA, Rigamonti D, Lim M, Redmond KJ, Kleinberg L: Postradiation imaging changes in the CNS: how can we differentiate between treatment effect and disease progression? Future Oncol 10: 1277–1297, 2014

Kruser TJ, Mehta MP, Robins HI: Pseudoprogression after glioma therapy: a comprehensive review. Expert Rev Neurother 13: 389–403, 2013

Yoshiura T, Higano S, Rubio A, Shrier DA, Kwok WE, Iwanaga S, Numaguchi Y: Heschl and superior temporal gyri: low signal intensity of the cortex on T2-weighted MR images of the normal brain. Radiology 214: 217–221, 2000

Brandtma D, Stalpers L, Taal W, Sminia P, van den Bent MJ: Clinical features, mechanisms, and management of pseudoprogression in malignant gliomas. Lancet Oncol 9: 453–461, 2008

Galldiks N, Langen KJ, Holy R, Pinkawa M, Stoffels G, Nolte KW, Kaiser HJ, Filss CP, Fink GR, Coenen HH, Eble MJ, Piroth MD: Assessment of treatment response in patients with glioblastoma using O-(2-[18F]-fluoroethyl)-l-tyrosine PET in comparison to MRI. J Nucl Med 53: 1048–1057, 2012

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