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Clinical Utility of Positron Emission Tomography in Patients with Malignant Glioma

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Abstract

Positron emission tomography (PET) is being increasingly utilized for the management of brain tumors. Herein, we primarily review our previous studies on the use of PET in glioma that utilize three types of tracers: ^{11}C-methionine (MET), ^{11}C-choline, and ^{18}F-fluorodeoxyglucose. These studies included aspects such as tumor behavior, diagnosis, grade of malignancy, spread and invasion, viability, and genetic deletions; moreover, they also evaluated PET as a tool for planning radiation therapy (RT) and determining its outcome. MET-PET in particular is considered to be the most informative for diagnosis and therapeutic decision-making for glioma patients; it is therefore considered crucial for brain tumor therapy. MET-PET is expected to be widely used for brain tumor patients going forward.

Key words: positron emission tomography, methionine, fluorodeoxyglucose, choline, glioma

Introduction

There are several modalities used to diagnose brain tumors, among which positron emission tomography (PET) is one of the most reliable and useful for providing clinically important information. The role of PET-based examination in clinical neuro-oncology is growing in importance for tumor diagnosis as well as for the evaluation of tumor malignancy, invasion, and metabolism.[1)] This information is valuable not only to plan therapeutic interventions, but also to evaluate treatment success and predict prognosis.[2)] PET is particularly useful for the diagnosis of glioma; it was previously reported that PET delineates gliomas more accurately than magnetic resonance imaging (MRI).[3)] In this review, we summarize our previous findings regarding the use of PET in gliomas, where we used three types of radiolabeled tracers: ^{11}C-methionine (MET), ^{11}C-choline (CHO), and ^{18}F-fluorodeoxyglucose (FDG). These tracers are retained in tumor cells via mechanisms that are distinct from normal cells.[4)] Moreover, using these three types of tracers in combination can potentially provide more information about a tumor's nature and behavior than MRI is likely to offer.

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MET-PET

MET-PET is critical for evaluating the tumor grade and proliferative activity, as well as to image the size and spread of the glioma. It has advantages in terms of selective labeling of the tumor as distinguished from normal brain tissue, even in cases of no contrast enhancement on MRI.[2)] There are three proposed explanations for the mechanism of MET uptake in tissues: active transport, passive diffusion, and stagnation. First, MET is taken up by tumor cells through an energy-independent L-type amino acid transporter system as well as the sodium-dependent transporter system (A and B^0).[5,6)] This active transport is dependent on cell proliferation and tumor malignancy.[7–12)] Second, passive diffusion of MET is attributed to the disruption of the blood-brain-barrier (BBB) in the lesions. Third, MET stagnation in regional vascular beds depends on the blood volume. These three mechanisms combined lead to the accumulation of MET in tumor cells.[3,6–10,13)]

CHO-PET

Choline is an important component of phospholipids in the cell membrane; accordingly, increased levels of this component are required in highly proliferating brain tumor cells.[14)] The mechanism of CHO uptake in gliomas is thought to be caused BBB

disruption (i.e., passive diffusion) because lesions that accumulate CHO coincide with contrast-enhanced lesions on MRI in which BBB disruption results in the leakage of the contrast agent.[1] In terms of the mechanism of uptake, CHO is dissimilar to MET; therefore, CHO uptake on PET imaging is generally different from CHO levels as assessed by magnetic resonance spectroscopy.[2]

FDG-PET

^{18}F-FDG-PET is generally used to detect systemic cancer. The mechanism of FDG uptake into cells is dependent on the activity of glucose transporters, hexokinases (HKs), and phosphatases. FDG enters cells via glucose transporters and is then phosphorylated by HK to FDG-6-phosphate, which cannot be metabolized further in the glycolytic pathway and remains in the cytoplasm.[15] Accordingly, enhanced uptake of FDG in highly malignant tumors contrasts clearly with normal tissues on ^{18}F-FDG-PET imaging. However, because normal brain tissues also actively absorb glucose, contrast expression of malignant glioma with FDG-PET is less than that with MET-PET.

Tumor detection

MET-PET has an advantage over FDG-PET and CHO-PET because lesions that uptake MET are relatively easy to detect in gliomas of all grades owing to their contrast differences relative to the surrounding normal brain. On the other hand, since FDG is diffusely accumulated in the normal brain and the dynamic state of CHO resembles the gadolinium (Gd)-based contrast medium, both tracers are less effective at identifying low-grade gliomas.

For evaluating lesion viability, the standardized uptake value (SUV) of the tracer in the region of interest (ROI) is analyzed. The SUV is the concentration of the tracer in the ROI at a fixed time point divided by the injected dose, normalized to the patient's measured weight. The tumor-to-normal (T/N) ratios of the MET, CHO, and FDG SUVs are calculated by dividing the maximum SUV of the tumor by the mean SUV of the contralateral normal frontal cortex. The maximum SUVs of the tumors are selected as indicators of the highest tracer accumulation, and are used instead of the mean SUVs to minimize the influence of tumor heterogeneity. In one study, the T/N ratio was used instead of the absolute SUV because of high, unexplained inter-subject SUV variability.[13] Another study investigated the optimal threshold for the mean MET uptake ratio relative to the corresponding contralateral normal brain to discriminate the tumor from the normal brain, and found that using a T/N ratio threshold of 1.3 as an indicator for performing stereotactic biopsy demonstrated a sensitivity and specificity of 87% and 89% for the detection of astrocytic tumors, respectively.[16]

Tumor grading

Our previous study showed that FDG-PET was useful for differentiating glioblastoma multiforme (GBM) from a diffuse astrocytoma (DA) and anaplastic astrocytoma (AA).[2] The FDG T/N ratios in DA, AA, and GBM were 0.79 ± 0.08, 1.27 ± 0.46, and 1.88 ± −0.78, respectively. Significant differences were observed between DA and GBM (P = 0.001), and between AA and GBM (P = 0.05). However, FDG-PET could not distinguish between oligodendroglial tumors (oligodendroglioma [OD]: 1.03 ± 0.40 vs. anaplastic OD [AOD]: 1.71 ± 1.09) or between oligoastrocytic tumors (oligoastrocytoma [OA]: 1.00 ± 0.45 vs. anaplastic OA [AOA]: 0.85 ± 0.15). In a previous study, Kim et al.[17] reported that significant differences in glioma grades could not be detected with FDG-PET; conversely, other reports[3,18–20] have shown significant correlations between the glioma grade and FDG uptake.

Similarly, it was reported that MET-PET could differentiate GBM from DA and AA. MET T/N ratios in DA, AA, and GBM were 2.24 ± 0.90, 3.03 ± 1.02, and 5.03 ± 1.65, respectively. Significant differences were observed between DA and GBM (P < 0.001) and between AA and GBM (P < 0.001). Significant differences were not observed between oligodendroglial tumors (OD: 3.95 ± 1.60; AOD: 4.46 ± 1.55) or between oligoastrocytic tumors (OA: 2.60 ± 0.91; AOA: 2.83 ± 0.99). However, significant differences were observed between grade II tumors (DA vs. OD, P < 0.05) as well as between grade III tumors (AA vs. AOD, P < 0.05) on MET-PET. Based on these results, MET has the potential to evaluate both the grades and types of astrocytic tumors.[2]

Tumor growth potential

Tumor proliferation is generally evaluated by using the MIB-1 labeling index (LI) via immunohistochemistry. We previously examined the relationship between PET T/N ratio and MIB-1 LI, and found a significant correlation only in astrocytic tumors that included 13 cases of DAs, 14 of AAs, and 7 of GBMs; no correlation was found in oligodendroglial tumors. Correlation coefficients in astrocytic tumors between MIB-1 LI and T/N ratios using MET, FDG, and CHO were 0.64 (P < 0.001), 0.71 (P < 0.001), and 0.64 (P < 0.001), respectively.[2] Furthermore, the same relationship was examined in a limited series of grade II gliomas including 21 cases of DAs, 12 of ODs, and 16 of OAs. No significant correlation was found between the MET T/N ratio and MIB-1

LI in grade II gliomas overall; however, a significant correlation between the MET T/N ratio and the MIB-1 LI was observed in DAs. Although MET T/N ratios in ODs and OAs were higher than those in DAs, we did not detect a significant correlation between the MET T/N ratio and MIB-1 LI in either ODs or OAs.[13] On the other hand, another study revealed that MIB-1 LI correlated significantly with MET uptake in every grade of glioma.[17] Accordingly, PET can provide reliable information on proliferative activity in astrocytic tumors. It is possible that MET uptake in DAs might be more closely related to the degree of tumor viability than in ODs and OAs. It is also likely that DAs presenting with high MET uptake may develop more aggressive behavior than those presenting with lower MET uptake because amino acid transport system activity generally increases tumor proliferation. Another reason why MET T/N ratios in oligodendroglial tumors are higher than those in DAs is discussed in a later section.[13]

Tumor spread and invasion

Astrocytic tumors are strongly invasive; GBM in particular is the most malignant primary neoplasm in adults because of its highly invasive and aggressive nature.[21] However, MRI generally fails to discriminate GBM from the surrounding edema in the boundary zone adjacent to the normal brain because these regions show no Gd enhancement. MET-PET scanning appears to be more valuable for identifying the boundaries of malignant gliomas than MRI.[10,22,23] We previously determined the spread of astrocytic tumors (DA: 7 cases, AA: 11, and GBM 17) using MET-PET and CHO-PET images. We used computer software to perform planimetric measurements of the uptake area (i.e., the tumor) in each PET image. The outlines of the hot tracer lesions as well as the whole brains of the selected slices, including the lesions, were drawn manually using free hand selection (Fig. 1). The measured values in each image were defined as follows: 1) area of MET, 2) area of MET-whole brain, 3) area of CHO, and 4) area of CHO-whole brain. From these data, the following ratios were calculated as percentages: 1) area of MET/area of MET-whole brain (MET area ratio [MET-AR]), and 2) area of CHO/area of CHO-whole brain (CHO-AR). The values of CHO-AR were 0.51 ± 0.70%, 2.31 ± 2.64%, 9.25 ± 4.05% for tumor grades II, III, and IV, respectively (Fig. 2A). There were significant differences between grades II and IV ($P < 0.0001$), and between grades III and IV ($P < 0.0001$); however, there was no significant difference between grades II and III. Since CHO accumulation is associated with BBB disruption, the higher CHO-AR value in grade IV compared to grade III tumors may be attributable to the greater extent of angiogenesis in grade IV tumors, which in turn is indicative of the greater extent of tumor cell invasion. On the other hand, the fact that differences were observed in the CHO-ARs between grade II and III tumors promote the hypothesis that angiogenesis with BBB disruption in grade III tumors may not typically be different from grade II.

The MET-ARs were 4.72 ± 2.06%, 10.27 ± 3.88%, and 12.17 ± 5.44% for grades II, III, and IV tumors, respectively (Fig. 2B). There were significant differences between grades II and III ($P < 0.01$) and between grades II and IV ($P < 0.01$); however, there was no significant difference between grades III and IV. In grade II tumors, lower cell density and lower proliferation resulted in a smaller hot MET area on MET-PET. In contrast, it is extremely likely that the areas of the hot MET lesions that do not exhibit Gd enhancement in high-grade tumors are associated with the extent of tumor cell invasion, and are reflective of substantial cell density (rather than high proliferative activity) that is not necessarily correlated with a higher MET SUV given the nature of MET uptake mechanisms. Since the value of MET-AR was larger than that of CHO-AR in each tumor grade, MET-PET appears to be superior to CHO-PET in terms of evaluating the spread of astrocytic tumors.

With respect to evaluating the tumor spread in GBM cases, we compared the MET uptake area to the Gd enhancement area and to the high-intensity area on T2-weighted PET-MRI fusion images[24]; the MET uptake area completely enveloped the Gd-enhanced area. In nine GBM cases out of 10, the MET uptake area enfolded the outer side of the Gd-enhanced area and expanded it by an additional 30 mm. In contrast, the Gd-enhanced area coincided with only 58.6% of MET uptake areas on average. Based on these results, we identified three cases of possible GBM recurrences after complete resection; they presented as new Gd-enhanced lesions in the MET uptake area at the edge of the surgical removal cavity.[24] Hence, MET-PET was apparently able to detect the metabolic abnormalities in residual tumor cells before local tumor recurrence was discernible on MRI.

In only one GBM case out of 10, the MET uptake area was completely within the T2-high area; in the remaining nine cases, the MET uptake area did not coincide with the T2-high areas. We posited that the T2-high region beyond the MET uptake area was mainly peritumoral edema. However, the MET uptake area observed beyond the T2-high area likely reflected invasive tumor cells.[24] Accordingly, MET-PET appears to outline

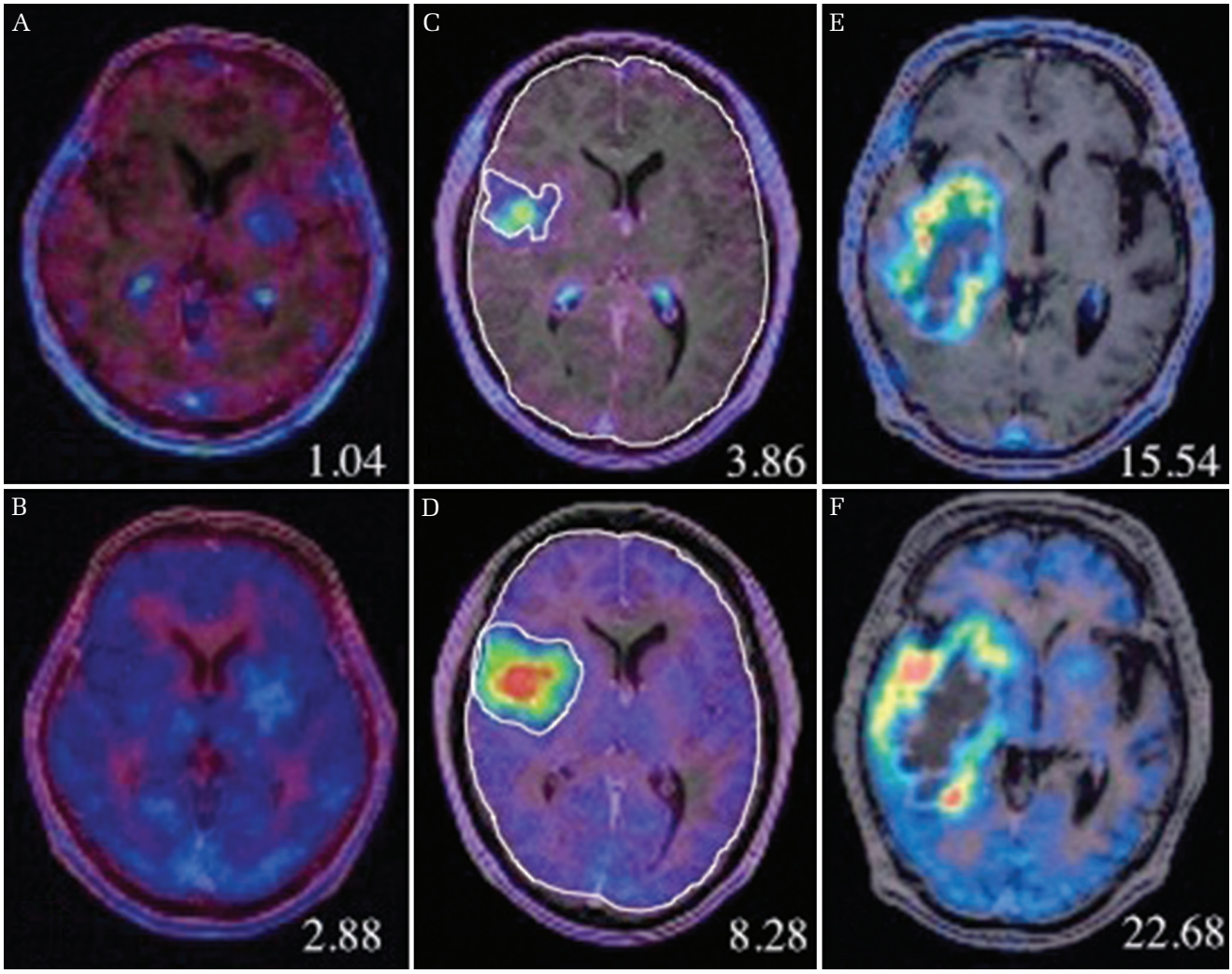

Fig. 1 Positron emission tomography and magnetic resonance imaging fusion images with gadolinium enhancement of astrocytoma (grade II according to the World Health Organization [WHO] criteria) (A and B), anaplastic astrocytoma (WHO grade III) (C and D), and glioblastoma multiforme (WHO grade IV) (E and F). The upper panels illustrate the use of ^{11}C-choline-PET (A, C, and E) while the lower panels demonstrate ^{11}C-methionine-PET (B, D, and F). The white lines in C and D were manually drawn using the Image J software to measure each hot lesion and the whole brain on the same slice. The numbers in the lower-right of each panel represent the percentages of the detected lesion areas relative to the whole brain areas (previously unpublished data from our group).

the true extent of the viable tumor tissue more precisely than MRI.[23]

With respect to planning glioma surgery using PET data, Pirotte et al.[25] performed high-grade glioma (HGG) resections under the guidance of PET (MET or FDG) combined with MRI scans in 66 consecutive patients. MET and FDG were used in 43 and 23 cases, respectively; these markers contributed to defining the target lesion in 79% and 74% of these surgeries, respectively. Furthermore, patients who underwent total PET resection exhibited a significantly longer survival than those who underwent a subtotal/partial PET resection (median survival: 32.5 vs. 17.6 months, respectively; P = 0.0001). In contrast, no significant difference in survival was observed between patients with or without residual postoperative MRI contrast enhancement (median survival: 26.4 vs. 32.8 months, respectively; P = 0.1105). The authors concluded that complete resection of the PET tracer uptake area in HGGs may contribute to longer survival, and that PET delineates HGGs more reliably than an MRI contrast enhancement.

MET-PET in oligodendroglial tumors

MET-PET shows no significant differences between grades and proliferative activities of oligodendroglial tumors; however, MET T/N ratios in ODs/AODs have

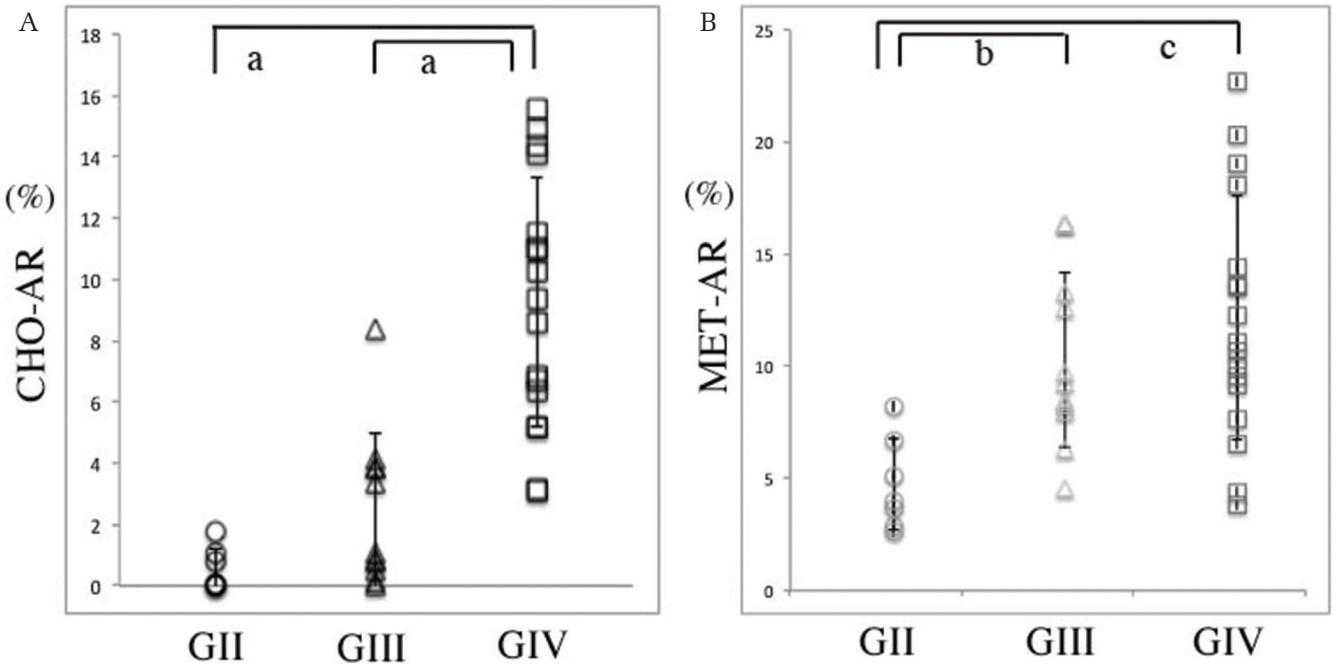

Fig. 2 Graphs showing the ^{11}C-choline (CHO)-area ratio (A) and ^{11}C-methionine (MET)-area ratio (B) for each tumor grade. (a: $P < 0.0001$, b: $P < 0.02$, and c: $P < 0.01$).

been reported to be significantly higher than those in DAs/AAs within each World Health Organization (WHO) grade.[2] In terms of the differences in MET T/N ratios, vascular proliferation and tumor angiogenesis should be taken into consideration.[2] Immunohistochemical studies of factor VIII revealed higher microvessel counts in ODs than in astrocytic tumors.[26] Furthermore, a perfusion study showed that the tumor blood volumes in ODs were significantly higher than those in DAs.[27] It was suggested that the high blood volume in ODs caused by numerous large intratumoral blood vessels was associated not only with high MET uptake but also with rapid wash-out compared to DA.[28] Therefore, we routinely performed dynamic MET-PET scanning, where image acquisition was performed in three consecutive phases (5–15, 15–25, and 25–35 min after intravenous injection of MET). Consequently, a significant dynamic decrease of MET T/N ratios was found in oligodendrocytic tumors (Fig. 3). This finding was also observed in meningiomas, although these are easier to identify clinically. A significant dynamic increase of MET T/N ratios was also observed in GBM and central nervous system lymphoma,[29] which are often indistinguishable on MRI to the extent that additional clinical data and other diagnostic modalities are required. Next, we performed dynamic MET-PET studies on GBM patients with oligodendroglial components (GBMO),[30] whose prognoses remain controversial to date. This GBMO study showed that the dynamic MET signal tended to decrease over time; these changes resembled those in the above-mentioned oligodendroglial tumors. Accordingly, GBMO may be a possible differential diagnosis when dynamic MET-PET shows a decreasing pattern.[30]

1p/19q loss of heterozygosity (LOH)

The 2016 World Health Organization Classification of Tumors of the Central Nervous System identified the 1p/19q co-deletion as one of the essential molecular diagnostic markers of OD and AOD.[31] Because analysis of the surgical specimens can validate the presence or absence of LOH, preoperative prediction of 1p/19q LOH by using a noninvasive imaging technique is of profound importance for improving the clinical management of ODs.[32] Saito et al.[33] reported that MET uptake correlated with 1p/19q LOH in ODs; the mean T/N ratios of tumors with and without 1p/19q LOH were 3.100 ± 1.163 and 2.473 ± 1.193, respectively. The former was greater than the latter in all tumors including grades II and III;[28] however, statistical significance was only observed in grade II tumors. Multivariate analyses revealed that only the threshold T/N ratio value used in the study (2.46) was an independent predictive factor with respect to the presence of 1p/19q LOH in all tumors and also within grade II tumors.[33] These findings may reflect not only a greater tumor blood volume but an increased

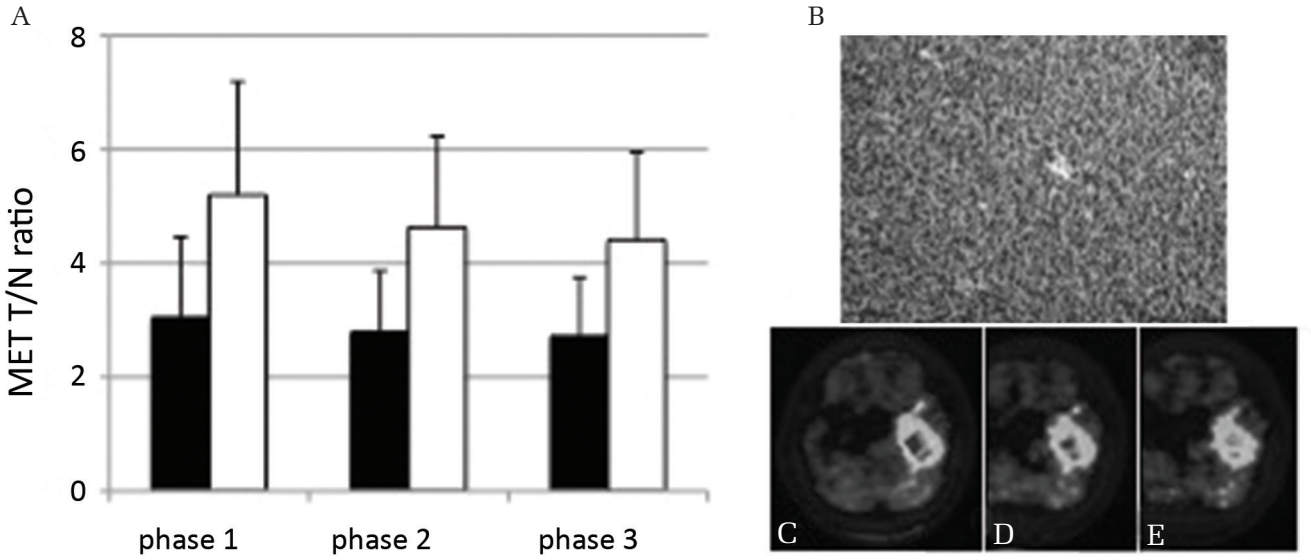

Fig. 3 (A) Graph showing the ^{11}C-methionine (MET) tumor-to-normal tissue (T/N) ratio (mean ± standard deviation) of the dynamic study in patients with oligodendroglial tumors. This graph was adapted from data published in reference number 25. Black bar: oligodendroglioma, white bar: anaplastic oligodendroglioma (B) Hematoxylin-eosin stain showing anaplastic oligodendroglioma. (C-E) MET dynamic study showing rapid washout of MET in case B. (C) phase 1, (D) phase 2, (E) phase 3.

rate of MET transport from the tumor endothelial cells, suggesting a higher metabolic demand. The T/N ratio of grade III ODs was influenced not only by 1p/19q LOH but also by further angiogenesis, increased tumor blood, and increased transport of MET from the tumor endothelial cells, which are associated with increased malignancy.[33] On the other hand, a previous study showed that the high glucose uptake demonstrated by FDG-PET is closely associated with 1p/19q LOH in WHO Grade II gliomas.[34] High FDG uptake was observed in six of eight WHO grade II gliomas with 1p/19q LOH but in none of the eight WHO grade II gliomas without 1p/19q LOH; using FDG update as a prediction method showed a sensitivity of 75% and a specificity of 100%. Hence, MET-PET and FDG-PET are considered non-invasive imaging modalities available before surgery to serve as prognostic and predictive tools.

Radiation therapy (RT) planning

MET-PET is critically useful in RT treatment planning for brain tumors, including gliomas and brain metastases, because it can precisely delineate the target volumes. The abnormal imaging areas for GBM on MET-PET, MRI with Gd, and T2-weighted images do not necessarily coincide. In terms of concordance between MET-PET and MRI, we found the sensitivity 20 mm outside of the Gd-enhanced area (86.4%) and the T2-weighted image area (96.4%) to be most significant. However, 20 mm outside of the T2-weighted image area is too wide an area when attempting to minimize radiation exposure to the normal brain tissue. Accordingly, MET-PET is better suited for precise RT planning for GBM compared MRI.[35] Next, we compared MRI and MET-PET for RT planning for brain metastases, and quantified the extent of brain metastasis growth. When the tumor volume was ≥ 0.5 mL, a 2-mm margin beyond the gross tumor volume (GTV) on MRI significantly improved the coverage of the GTV on MET-PET. Hence, MET-PET as a biologic imaging tool improves the morphologic visualization of metastasis compared to MRI. To that end, MET-PET and MRI fusion can facilitate RT planning for brain tumors through the accurate identification of the targets.

Evaluation of the effect of RT

It was reported that MET-PET could be used to evaluate the outcome of RT for metastatic brain tumors treated with stereotactic radiation therapy with intensity modulated radiation therapy (SRT-IMRT). The T/N ratios determined by MET-PET three and six months after SRT-IMRT were significantly lower than baseline (pre-SRT-IMRT). These significant decreases in MET uptake can be attributed to secondary metabolic changes, deactivation, and obliteration of the target lesion following SRT-IMRT.[36] MET-PET possesses a greater ability to detect early radiation-induced metabolic

changes than MRI; use of the latter is limited to determining the change in the size of the target several months post-RT.

Radiation necrosis (RN) following RT

RN is one of the most clinically relevant consequences of RT in brain tumors. It is often difficult to distinguish RN from tumor recurrence, since RN mimics the imaging features of malignant glioma on computed tomography or MRI. However, MET has been reported to be very useful in differentiating RN from tumor recurrence. In one study, the T/N ratios of MET in RN, grade III glioma, and grade IV glioma were 1.95 ± 0.60, 3.40 ± 1.04, and 4.29 ± 1.45, respectively. There was a significant difference in MET T/N ratios between RN and grade III glioma ($P < 0.005$) and between RN and grade IV glioma ($P < 0.001$).[37] When the cutoff value of the MET T/N ratio was set at 2.51, the sensitivity and specificity for the diagnosis of glioma recurrence were 91.2% and 87.5%, respectively. With respect to other tracers, FDG was reported to be inferior to MET in diagnosing RN.[38] Possible diagnostic tracers for differentiating RN from glioma include 3'-deoxy-3'-18F fluorothymidine (FLT)[39] and 3,4-dihydroxy-6-18F-fluoro-L-phenylalanine (FDOPA).[40] FLT reportedly shows the same level of FDG in both a semi-quantitative and qualitative manner when distinguishing between recurrent tumors and RN for moderate- and high-grade gliomas. In contrast, FDOPA PET was reported to be advantageous over perfusion-MRI in differentiating metastatic brain tumor recurrences from RN by semi-quantitative analysis. In one study, setting the cutoff value of the maximum lesion to maximum background uptake ratio to 1.59 produced a sensitivity and specificity of 90% and 92.3%, respectively.

Bevacizumab (BEV), an endothelial growth factor inhibitor, has been reported to exhibit a strong therapeutic effect against RN.[41–44] Observing the effects of BEV via MRI was demonstrated by a randomized double-blinded placebo-controlled trial.[42] We evaluated the therapeutic effect of BEV against RN using MET-PET and CHO-PET; the mean values of the MET- and CHO-based T/N ratios of nine patients before BEV administration were 2.19 and 9.24, respectively; these values dropped to 1.71 and 3.19 after BEV therapy, showing reduction rates of 24.4% and 60.7%, respectively. The decrease of CHO-PET uptake was a result of improved vascular permeability due to BEV treatment; however, MET-PET might also reflect suppressed tissue biological activity by BEV as well, because the choline/creatinine ratio as measured by magnetic resonance spectroscopy showed a significant decrease after BEV therapy.[1] These results illustrated the utility of PET in detecting the metabolic changes of RNs in addition to the morphological changes observed by MRI.

Conclusion

We reviewed the clinical utility of PET that incorporates three types of tracers (MET, CHO, and FDG) for the scanning of brain tumors. However, PET is unlikely to be used widely because of the short half-life of ^{11}C, the requirement of a cyclotron to produce positron nuclides, and the high cost of the procedure. PET is not available broadly on demand; therefore, MRI has the advantage in terms of adoption rate and cost. However, we emphasize that PET scans are very informative for tumor diagnosis, including aspects such as tumor viability, grade of malignancy, spread and invasion, and genetic mutations. Since PET can provide metabolic information in addition to the morphologic features that are also obtainable by MRI, it is critically useful in the assessment of treatment outcomes of RT, as well as for differentiating between RN and tumor recurrence. These data lead not only to devising appropriate therapeutic strategies but also to improving the prediction of prognoses of brain tumor patients. Therefore, PET appears to be an essential diagnostic tool that markedly improves brain tumor management.

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Conflicts of Interest Disclosure

Dr. H. Yano and Dr. J. Shinoda declare that they have no conflicts of interest. Dr. T. Iwama accepted research expenses from Otsuka Pharmaceutical Co. Ltd and Ogaki Tokushukai Hospital in 2013.

All authors have registered online with the Self-reported COI Disclosure Statement Forms through the website for JNS members.

Ethical Approval

All studies described in this review were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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