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Proliferative Activity**

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Analysis of ¹¹C-methionine Uptake in Low-Grade Gliomas and Correlation with Proliferative Activity

BACKGROUND AND PURPOSE: The relationship of ¹¹C-methionine (MET) uptake and tumor activity in low-grade gliomas (those meeting the criteria for World Health Organization [WHO] grade II gliomas) remains uncertain. The aim of this study was to compare MET uptake in low-grade gliomas and to analyze whether MET positron-emission tomography (PET) can estimate tumor viability and provide evidence of malignant transformation.

MATERIALS AND METHODS: We studied glioma metabolic activity in 49 consecutive patients with newly diagnosed grade II gliomas by using MET PET before surgical resection. On MET PET, we measured tumor/normal brain uptake ratio (T/N ratio) in 21 diffuse astrocytomas (DAs), 12 oligodendrogliomas (ODs), and 16 oligoastrocytomas (OAs). We compared MET T/N ratio among these 3 tumors and investigated possible correlation with proliferative activity, as measured by Mib-1 labeling index (LI).

RESULTS: MET T/N ratios of DA, OD, and OA were 2.11 ± 0.87 , 3.75 ± 1.43 , and 2.76 ± 1.27 , respectively. The MET T/N ratio of OD was significantly higher than that of DA ($P < .005$). In comparison of MET T/N ratios with the Mib-1 LI, a significant correlation was shown in DA ($r = 0.63$; $P < .005$) but not in OD and OA.

CONCLUSION: MET uptake in DAs may be closely associated with tumor viability, which depends on increased amino acid transport by an activated carrier-mediated system. DAs with lower MET uptake were considered more quiescent lesions, whereas DA with higher MET uptake may act more aggressively.

World Health Organization (WHO) grade II brain tumors, such as diffuse astrocytomas (DAs) and oligodendrogliomas (ODs), are classified by low proliferation rates and the lack of malignant histologic features, such as necrosis and vascular proliferation. However, these tumors frequently recur, even after intervals of more than 10 years, and commonly progress to higher-grade lesions.¹ In most studies, the median survival of grade II glioma is 5 to 10 years with a varying clinical course. The initial treatment of grade II gliomas is usually surgical resection, but many of these tumors diffusely infiltrate into healthy brain tissue, making complete resection difficult. Early radiation therapy after surgery has been shown to prolong the time to progression but not overall survival.² Chemotherapy for ODs is increasingly used as primary treatment³; however, long-term advantages including improvement in quality of life are uncertain. Currently, it is not possible to predict the course of grade II gliomas in individual patients, and thus treatment strategies remain controversial.^{4,5}

It has been shown that positron-emission tomography (PET), a noninvasive imaging technique, is helpful in numerous clinical situations.⁶ A relationship has previously been demonstrated between [¹⁸F] fluorodeoxyglucose (FDG) uptake and glioma grade.⁷⁻¹⁰ However, FDG uptake in grade II

glioma is infrequently seen. Previous studies also have shown a significant correlation between ¹¹C-methionine (MET) uptake and glioma grade.¹⁰⁻¹⁵ In addition, MET uptake has been correlated with Mib-1 labeling index (LI), proliferating cell nuclear antigen, microvessel attenuation, and survival.¹⁴⁻¹⁸ Mib-1 LI is a good marker to determine proliferative activity and has an important role in determining both malignant neoplasm and a patient's prognosis. To our knowledge, no study has been published regarding MET uptake and proliferative activity for patients with grade II glioma only. It is generally believed that for most patients with grade II gliomas, the tumor will at some point transform into a more malignant form.¹⁹ We hypothesized that MET uptake correlates significantly with proliferative activity and may thus be a predictor of malignant transformation in low-grade gliomas. We therefore compared MET uptake in DAs, ODs, and oligoastrocytomas (OAs) and investigated correlation with proliferative activity, as measured by Mib-1 LI.

Materials and Methods

Patient Population

Within the 5-year period of 2002 to 2006, we studied the metabolic activity in 49 consecutive patients with newly diagnosed WHO grade II gliomas at the Chubu Medical Center for Prolonged Traumatic Brain Dysfunction, Kizawa Memorial Hospital. All patients had space-occupying supratentorial lesions that, on CT and MR imaging, appeared highly suspicious for gliomas. We included cases of resectable hot lesions demonstrated preoperatively on MET PET. Patients with brain stem, thalamic, and hypothalamic tumors were excluded. Presurgical radiologic evaluation was performed with MET PET and MR imaging in all patients, and all patients underwent open surgical

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Clinical data and histopathologic results*

Histologic Diagnosis	Number of Patients (M/F)	Age	Location			
			F	P	T	I
Diffuse astrocytoma	21 (14/7)	40.9 ± 15.2	8	3	4	6
Oligodendroglioma	12 (8/4)	38.0 ± 13.5	10	2	0	0
Oligoastrocytoma	16 (10/6)	39.3 ± 13.8	8	3	2	3
Total	49 (32/17)	39.6 ± 14.1	26	8	6	9

Note:—F indicates frontal; P, parietal; T, temporal; I, insular.
* Data are expressed as mean ± SD.

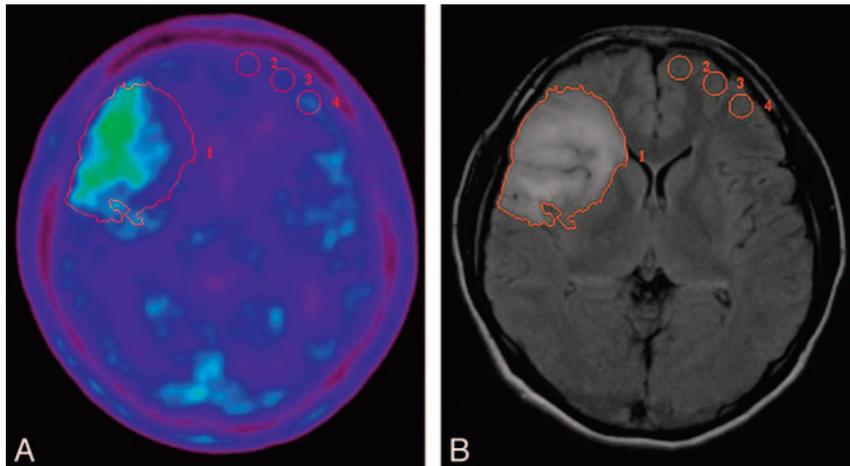


Fig 1. Standard ROI placement. Co-registration of PET and MR imaging was attempted in all cases. The tumor maximal SUV was selected as the highest accumulation in the entire tumor. Also, the mean SUV of the contralateral normal frontal cortex was drawn in 3 circular ROIs with a diameter of 10 mm on each of the 3 axial planes. Left: MET PET. Right: FLAIR image.

procedures within 4 weeks after PET scanning. Tumors were classified on histologic examination with use of the WHO classification system.²⁰ There were 21 DAs, 12 ODs, and 16 OAs (Table). All patients gave written informed consent, and the protocol was approved by the research committee of Kizawa Memorial Hospital Foundation.

PET Scan Procedure

PET scan was performed as previously described.²¹ The PET study was carried out according to the standardized procedure used in our institution. The PET scanner was an ADVANCE NXi Imaging System (GE Yokokawa Medical System, Hino-shi, Tokyo, Japan), which provides 35 transaxial images at 4.25-mm intervals. The in-plane spatial resolution (full width at half maximum) was 4.8 mm, and the scan mode was the standard 2D mode. Before the emission scan was performed, a 3-minute transmission scan was performed to correct photon attenuation with a ring source containing ⁶⁸Ge. A dose of 7.0 MBq/kg of MET was injected intravenously, depending on the examination. The emission scan was acquired for 30 minutes, beginning 5 minutes after MET injection. During PET data acquisition, head motion was continuously monitored with laser beams projected onto ink markers drawn over the forehead skin and corrected manually as necessary. The images were reconstructed with the ordered-subsets expectation maximization algorithm.

MR Imaging Procedure

MR imaging was performed on a 1.5T system (Signa; GE Healthcare, Milwaukee, Wis). T1-weighted images, T2-weighted images, and fluid-attenuated inversion recovery (FLAIR) images were acquired with use of our standard protocol. For co-registration of metabolic and anatomic data, we also acquired 3D spoiled gradient-echo images after administration of 0.2 mL/kg of gadopentetate dimeglumine

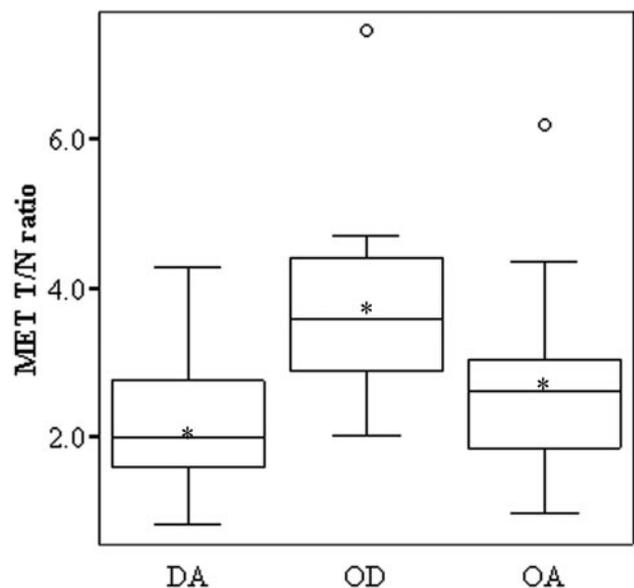


Fig 2. Box plots comparing MET T/N ratio in grade II gliomas. Circles above bars represent outliers ($1.5 \times$ the interquartile range). Asterisks represent the mean value. There was a significant difference between the MET T/N ratios of DA and OD ($P < .005$).

(Magnevist; Nihon Shering, Osaka, Japan) using the following parameters: no gap; 1.0-mm thickness; TR, 20 ms; TE, 1.6 ms; flip angle, 15°; NEX, 1; and axial views.

Data Analysis

Tracer accumulation in the region of interest (ROI) was analyzed as the standardized uptake value (SUV), which is the activity concentration in the ROI at a fixed time point divided by the injected dose

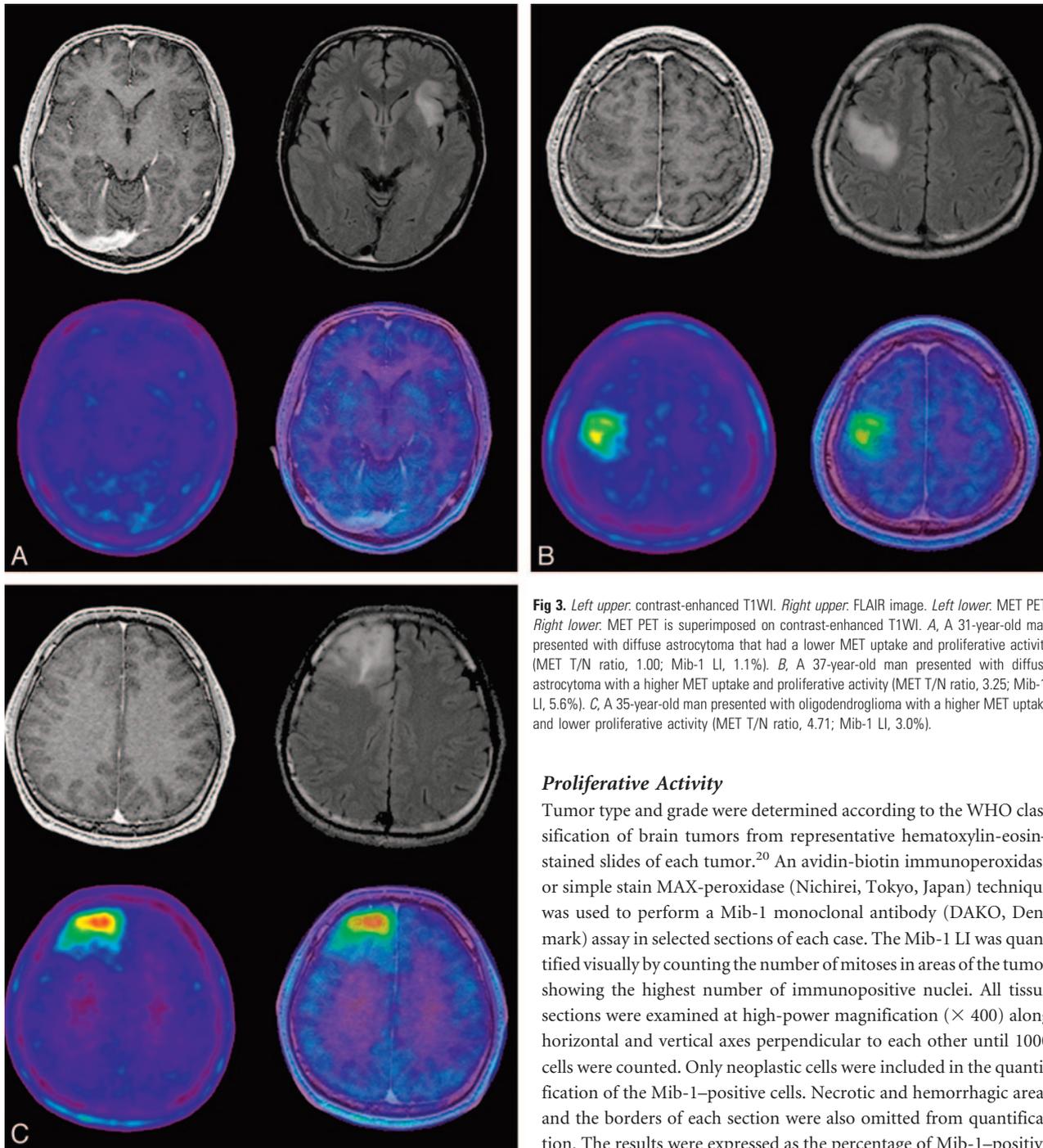


Fig 3. Left upper: contrast-enhanced T1WI. Right upper: FLAIR image. Left lower: MET PET. Right lower: MET PET is superimposed on contrast-enhanced T1WI. A, A 31-year-old man presented with diffuse astrocytoma that had a lower MET uptake and proliferative activity (MET T/N ratio, 1.00; Mib-1 LI, 1.1%). B, A 37-year-old man presented with diffuse astrocytoma with a higher MET uptake and proliferative activity (MET T/N ratio, 3.25; Mib-1, LI, 5.6%). C, A 35-year-old man presented with oligodendroglioma with a higher MET uptake and lower proliferative activity (MET T/N ratio, 4.71; Mib-1 LI, 3.0%).

normalized to the patient's measured weight. The MET SUV ratios (T/N ratios) were calculated by dividing the maximum SUV for the tumor by the mean SUV of the contralateral normal frontal cortex. The tumor maximum SUVs were selected as the highest accumulation, and the reference ROIs were drawn in 3 circular ROIs with a diameter of 10 mm on each of the 3 axial planes (Fig 1). Co-registration of PET and MR imaging was undertaken in all cases with the Dr. View, an image analysis software package (AJS, Tokyo, Japan). If increased accumulation was absent or was not clear, a ROI was selected in consultation with the fusion image. We used the T/N ratio instead of absolute SUV because of the high, unexplained intersubject variability of SUV. We used tumor maximal SUV instead of tumor mean SUV to minimize the effect of tumor heterogeneity.

Proliferative Activity

Tumor type and grade were determined according to the WHO classification of brain tumors from representative hematoxylin-eosin-stained slides of each tumor.²⁰ An avidin-biotin immunoperoxidase or simple stain MAX-peroxidase (Nichirei, Tokyo, Japan) technique was used to perform a Mib-1 monoclonal antibody (DAKO, Denmark) assay in selected sections of each case. The Mib-1 LI was quantified visually by counting the number of mitoses in areas of the tumor showing the highest number of immunopositive nuclei. All tissue sections were examined at high-power magnification ($\times 400$) along horizontal and vertical axes perpendicular to each other until 1000 cells were counted. Only neoplastic cells were included in the quantification of the Mib-1-positive cells. Necrotic and hemorrhagic areas and the borders of each section were also omitted from quantification. The results were expressed as the percentage of Mib-1-positive cells per 1000 tumor cells.

Statistical Methods

Data are presented as mean \pm SD. To compare the T/N ratios among the different tumors, we performed statistical analyses with analysis of variance and a Tukey post hoc test. To determine if the MET T/N ratio was related to proliferative activity, we calculated Spearman correlation coefficients. *P* values less than .05 were considered statistically significant.

Results

Results of MET T/N Ratio

The mean MET SUV of the contralateral normal frontal cortex was 1.22 ± 0.37 . The mean MET T/N ratio of all

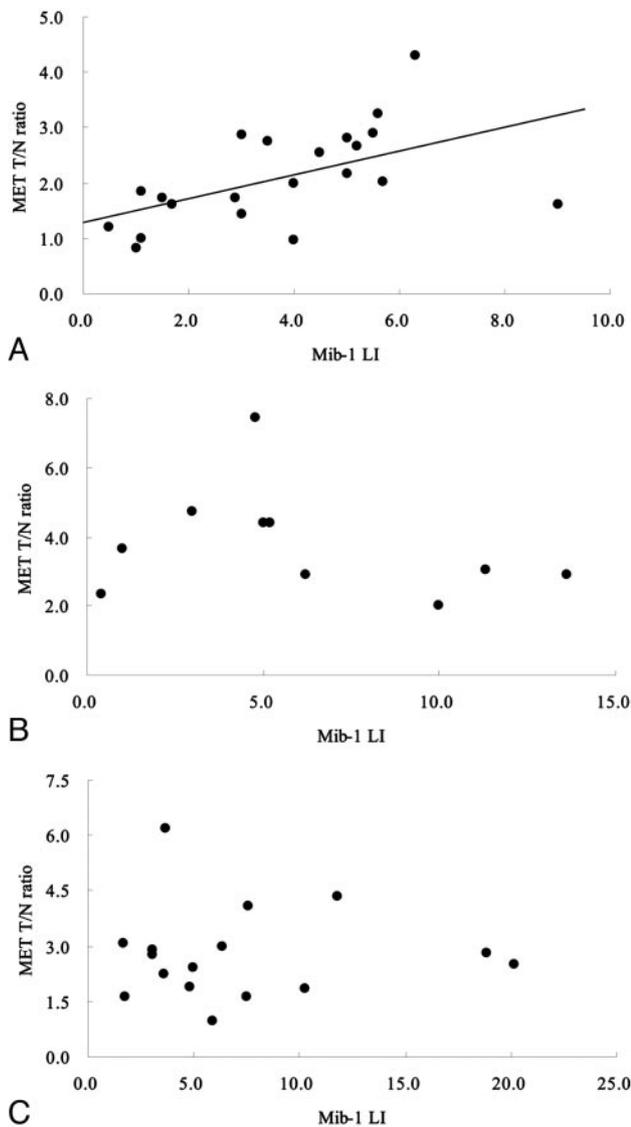


Fig 4. Graph showing the correlation between MET T/N ratio and Mib-1 LI. A significant correlation was shown in diffuse astrocytoma (A; $r = 0.63$; $P < .005$). A correlation could not be demonstrated in oligodendroglioma (B) and oligoastrocytoma (C).

gliomas was 2.72 ± 1.31 . The mean MET T/N ratios of DA, OD, and OA were 2.11 ± 0.87 , 3.75 ± 1.43 , and 2.76 ± 1.27 , respectively, and there was a significant difference between the average MET T/N ratios of DA and OD (DA/OD, $P < .005$; DA/OA, $P = .21$; OD/OA, $P = .08$, Fig 2). Representative cases are shown in Fig 3.

Correlation between MET T/N Ratio and Proliferative Activity

We evaluated the proliferative activity measured by Mib-1 LI from 47 gliomas. The mean Mib-1 LI of 21 DAs, 10 ODs, and 16 OAs was $3.8 \pm 2.2\%$, $6.1 \pm 4.4\%$, and $7.2 \pm 5.6\%$, respectively, and there was no significant difference between the mean Mib-1 LI in each glioma. The mean Mib-1 LI of all 47 gliomas was $5.6 \pm 4.4\%$, and there was no significant correlation between MET T/N ratio and the Mib-1 LI in all grade II gliomas. When comparing MET T/N ratios and Mib-1 LI in the different tumor classes, we

could demonstrate a significant correlation in DA ($r = 0.63$, $P < .005$; Fig 4).

Discussion

In this study, the MET T/N ratio of OD was the highest when compared with DA and OA, which is in agreement with previous reports.^{10,17,22} We detected a significant difference between the average MET T/N ratios of DA and OD ($P < .005$). One of the reasons for the higher MET T/N ratio in OD is the difference in microvessel attenuation in each glioma. As measured by immunostaining with factor VIII, OD demonstrates high microvessel counts and high MET uptake compared with malignant astrocytomas.¹⁸ In addition, tumor blood volume in OD was revealed to be significantly higher than that of DA on the basis of a perfusion MR imaging study.²³ These differences of the tumor vascular bed may be one of the reasons why MET uptake of OD is higher than that of DA. The MET T/N ratio of OA fell between that of DA and OD, suggesting that OA may have mixed metabolic features of both astrocytic and oligodendroglial tumors.

One half to more than 90% of patients with WHO grade II astrocytoma experience malignant transformation.^{24,25} Glioblastoma multiforme (GBM) may develop from either primary or secondary pathways; thus, these subtypes of GBM may constitute distinct disease entities.²⁶ The mean time to progression from anaplastic glioma to GBM was approximately 2 years, and that from low-grade glioma to GBM was approximately 5 years.²⁷ Kim et al¹⁵ reported that Mib-1 LI correlated significantly with MET uptake in every grade of glioma. We were able to demonstrate a significant correlation in DA between MET T/N ratio and Mib-1 LI; to the best of our knowledge, this is the first clinical study to demonstrate a significant correlation between MET uptake ratio and Mib-1 LI in DAs only.

MET is a natural amino acid taken up by glioma cells, usually found at a very low concentration in normal brain tissue. The main mechanism of MET uptake is from an increase of MET transport into the tumor. In gliomas, MET uptake may be attributed to the activation of a carrier-mediated transport system at the normal blood-brain barrier (BBB). This uptake does not directly reflect protein synthesis, but it represents cell avidity for amino acids.^{11,12} Langen et al²⁸ reported that the amino acid transport system was dependent on the proliferative activity of the human glioma cells. Increased uptake of MET is present in most low-grade gliomas despite the absence of damage to the BBB.^{13,29-31} In malignant gliomas with BBB damage, passive diffusion also contributes to total uptake of MET.³² We hypothesize that the MET uptake, especially in DAs without BBB disruption, may be closely associated with tumor viability, which itself is dependent on increased amino acid transport. There was no correlation between MET uptake and Mib-1 LI in ODs and OAs, which may be because of the different mechanisms of MET uptake in these tumors compared with DA. We considered that even if the MET uptake is high, ODs will not always be transformed malignantly because a tumor vascular bed often causes a high MET. The case is not the same regarding ODs with a high MET compared to DAs.

Previous reports have shown that grade III/IV gliomas demonstrate higher MET uptake than grade II gliomas.¹⁰⁻¹⁵ In grade II glioma (DA, 33; OD, 39; OA, 17), tumor resection had

a clear effect in patients with high MET uptake; however, no effect from surgery was found in the group of patients with low MET uptake.¹⁷ Smits et al¹⁹ analyzed DAs and oligodendrocytic tumors (OD and OA) separately in the reevaluation of the prognostic impact of the European Organisation for Research and Treatment of Cancer (EORTC) factors after adding the MET uptake as an extra prognostic factor. The MET uptake was the most important prognostic factor in DA, and the presence of contrast enhancement on CT or MR imaging did not influence survival in both groups.¹⁹ These findings demonstrate that DA with higher MET uptake may be more likely to undergo malignant transformation. On conventional MR imaging, local enhancement or peripheral edema suggests malignant transformation; however, these changes may not always be evident in the biologic history of a grade II glioma. We considered that MET PET seems to be useful in assessing tumor histologic processes in grade II glioma and evaluating tumor viability, especially in DAs. Cases of DA with higher MET uptake will require careful therapeutic decision making because these tumors may be more prone to malignant transformation.

The limitation of this study was the lack of long-term follow-up in patients with grade II glioma. Future studies will need to examine possible correlations between MET uptake and proliferative activity in patients with both DA and secondary anaplastic astrocytoma/GBM.

Conclusions

The MET T/N ratio of OD was significantly higher than that of DA and OA. A significant correlation between MET T/N ratio and Mib-1 LI was shown in DAs. MET uptake in DAs may be closely associated with tumor viability, which depends on increased amino acid transport by an activated carrier-mediated system. DAs with higher MET uptake may be more aggressive tumors than their counterparts with lower MET uptake.

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