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Correlation of amino-acid uptake using methionine PET and histological classifications in various gliomas

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Objective: The uptake of L-methyl-^{11}C-methionine (MET) by gliomas is greater than that by intact tissue, making methionine very useful for evaluation of tumor extent. If the degree of malignancy of brain tumors can be evaluated by MET-PET, the usefulness of MET-PET as a means of diagnosing brain tumors will increase. ***Methods:*** We performed this study on 67 glioma patients between 3 and 69 years of age (36 males and 31 females). Tumors included diffuse astrocytoma, anaplastic astrocytoma, glioblastoma, ependymoma, oligodendroglioma, medulloblastoma, dysembryoplastic neuroepithelial tumor, choroid plexus papilloma, central neurocytoma, optic glioma, gliomatosis cerebri, pleomorphic xanthoastrocytoma, and ganglioglioma. Tumor activity and degree of malignancy were evaluated using Ki-67LI (LI: labeling index) and Kaplan-Meier survival curves. The correlations between methionine uptake and tumor proliferation (tumor versus contralateral gray matter ratio (T/N) and Ki-67LI) were determined for the group of all subjects. The existence of significant correlations between T/N and Ki-67LI and between SUV and Ki-67LI was determined for astrocytic tumors. Receiver operating characteristics (ROC) analysis of T/N and standardized uptake value (SUV) was performed for the group of astrocytic tumors. We also determined the ROC cut-off levels to ensure high accuracy of the analysis. ***Results:*** For the 67 cases of glioma, the degree of accumulation was variable. Ki-67LI differed significantly between the high-grade group and low-grade group at T/N levels between 1.5 and 1.8 on analysis using tumor proliferative potential ($p = 0.019–0.031$). The prognosis differed significantly between the high-grade and low-grade groups when T/N was in the range of 1.6–1.8 ($p = 0.028–0.032$). The accuracy thus calculated was highest (85.7%) when T/N was 1.5 as determined by ROC analysis. ***Conclusions:*** When analysis was confined to cases of astrocytic tumor, a correlation was noted between methionine accumulation and Ki-67LI. For the astrocytic tumors, T/N ratio seemed to be more useful as a diagnostic indicator than SUV. The cut-off level of T/N ratio for distinction between high-grade and low-grade astrocytoma appears to lie between 1.5 and 1.6.

Key words: ^{11}C-methionine-PET, Ki-67LI, glioma

INTRODUCTION

POSITRON EMISSION TOMOGRAPHY (PET) allows noninvasive evaluation of regional brain metabolism using positron tracers. For this reason, PET has been used for pathophysiological investigation of brain tumors and distinguishing given types of brain tumors from others. PET yields functional images different from the anatomical images yielded by computerized tomography (CT), magnetic resonance imaging (MRI), etc. Early and accurate diagnosis of glioma is most important for formulating the treatment strategy and determining the prognosis. Cells take up ^{18}F-fluorodeoxy-glucose (FDG) depending on the rate of intracellular glucose metabolism. Since FDG accumulates in cells without degradation, it can be used for calculation of glucose metabolism. Since it has already

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been demonstrated that glucose metabolism in the presence of glioma increases with the degree of tumor malignancy, degree of FDG accumulation is used as an indicator of the malignancy of glioma.[1] The uptake of L-methyl-^{11}C-methionine (MET) by glioma is greater than that by intact tissue, making methionine very useful in evaluation of tumor extent. For investigating the extent of brain tumor invasion, methionine is more useful than FDG.[2] If the degree of malignancy of brain tumors can be evaluated by MET-PET, the usefulness of MET-PET as a means of diagnosing brain tumors will increase. However, while some investigators have reported that degree of methionine accumulation correlated with degree of tumor malignancy,[3] others have indicated that intense methionine accumulation was observed even in patients with benign tumors.[4–10] No consensus has yet been reached concerning this relationship. The present study was undertaken to evaluate the degree of methionine accumulation in patients with various types of glioma using MET-PET to determine its relationship to degree of tumor malignancy. We also performed a similar evaluation limited to astrocytic tumors.

MATERIALS AND METHODS

Patients

We performed this study on 67 glioma patients between 3 and 69 years of age (36 males and 31 females). The classification of the gliomas of the 67 cases was based on the World Health Organization (WHO) system.[11] Subject details are shown in Table 1. Histological examination of surgical specimens of tumor was performed for all patients. MET-PET was performed on all patients prior to treatment. Their informed consent was a prerequisite for participation in this study. This PET study is approved by the ethics committee of our department.

PET studies

A HEADTOME IV (Shimadzu Co., Japan), a four-ring fourteen-slice positron emission tomography apparatus, was employed with a transaxial resolution of 4.5 mm in full width at half maximum (FWHM) and slice thickness of 6.5 mm in FWHM. Patients were injected intravenously with 7.4 MBq (0.2 mCi)/kg MET in a fasting state. PET scanning was started 20 min after injection. Viable tumor tissue was determined using MRI equivalent in scanning level with PET. The portion of the lesion with the highest MET accumulation was selected as the region of interest (ROI), and ROI was set in the region that was drawn with the border of the tumor region on one slice of the PET image. If no abnormality could be detected, ROI was located over the area corresponding to the MR abnormality. Several circular ROIs with a diameter of 10 mm were located over the gray matter of the contralateral frontal lobe (Fig. 1). When a tumor is present in the central portion of the brain, several control ROIs were set in both frontal lobes. The average radioactivity concentration was determined for these ROIs. Tumor-to-normal gray matter ratio (T/N) was defined as the ratio of average radioisotope counts per pixel in the lesion or tumor (T) ROI, divided by average counts per pixel in several normal gray matter (N) ROIs. The standardized uptake value (SUV) of methionine was calculated as follows: SUV = RI count/(MET dose/BW), (RI count: activity concentration, BW: body weight).

Table 1 Subject details of 67 glioma cases

Tumors	n
Diffuse astrocytoma	10
Anaplastic astrocytoma	12
Glioblastoma	21
Ependymoma	5
Oligodendroglioma	4
Medulloblastoma	3
Dysembryoplastic neuroepithelial tumor	2
Choroid plexus papilloma	2
Central neurocytoma	2
Optic glioma	2
Gliomatosis cerebri	2
Pleomorphic xanthoastrocytoma	1
Ganglioglioma	1

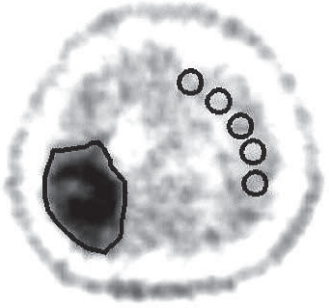

Fig. 1 This figure shows regions of interest (ROIs). The tumor ROI is set at the border of the high methionine accumulated area. The contralateral normal ROIs are set as several circles with a diameter of 10 mm in the frontal cortex.

Immunohistochemical analysis for Ki-67

The DAKO EPS (enhanced polymer one-step staining) method was applied to detect Ki-67. After deparaffinization, hydrated autoclave pretreatment (121°C 10 min) was performed. Then the sections were incubated with anti-Ki-67 polyclonal antibody (DAKO; A047) overnight at 4°C. The slides obtained were examined by light microscopy. At least 1000 cells of each specimen were counted to determine Ki-67 labeling index (LI), the percentage of Ki-67-positive cells, in five to eight viable areas. High Ki-67LI indicated high tumor proliferation.[12,13]

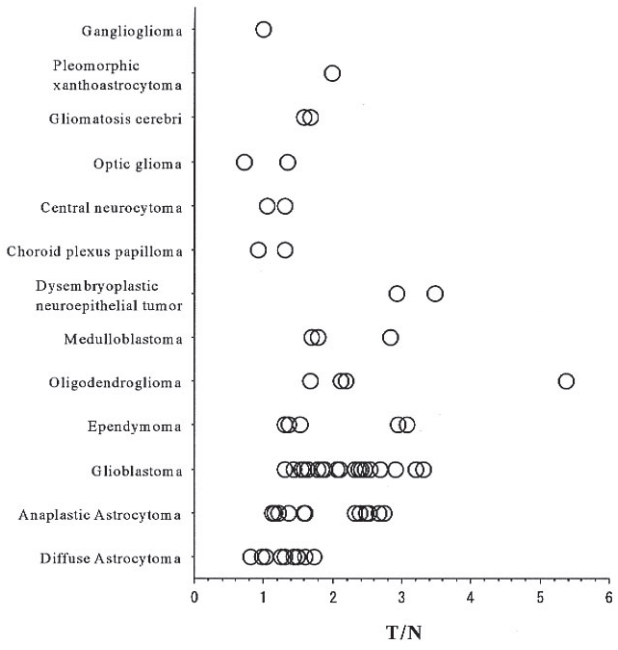

Fig. 2 The degree of accmulation of 67 cases of glioma. The degree of accumulation was found to vary.

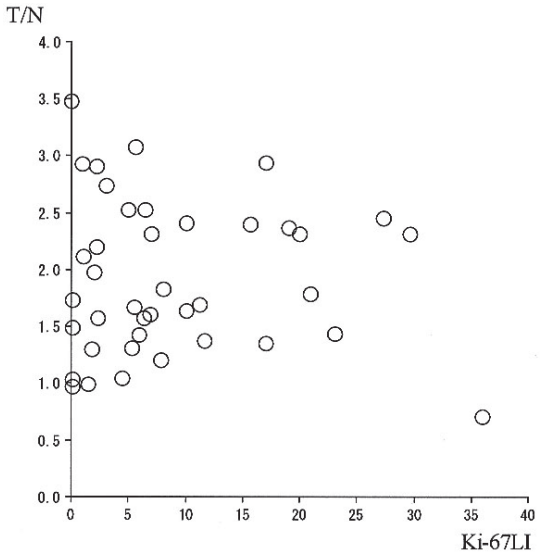

Fig. 3 Correlation between T/N and Ki-67LI for the 67 cases of glioma. No strong correlation was observed between T/N and Ki-67LI ($r = -0.35$, $p = 0.832$).

Table 2 Characteristics of 28 cases of astrocytic tumors

Case	Age/Sex	Tumor location	Tumor histology	T/N	SUV	Ki-67
1	22/F	Lt temporal	diffuse astrocytoma	1.60	1.68	6.83
2	31/F	Lt frontal	diffuse astrocytoma	1.32	1.99	0.46
3	31/M	Rt frontal	diffuse astrocytoma	1.49	1.69	0.10
4	34/F	Lt temporal	diffuse astrocytoma	1.04	1.98	0.10
5	35/M	Rt parietal	diffuse astrocytoma	1.43	2.41	5.88
6	39/M	Lt temporal	diffuse astrocytoma	1.30	1.37	2.00
7	40/F	Rt temporal	diffuse astrocytoma	0.97	1.54	0.10
8	46/F	Rt frontal	diffuse astrocytoma	0.67	1.15	1.00
9	47/M	Rt frontal	diffuse astrocytoma	2.11	3.47	0.10
10	52/F	Lt insula	diffuse astrocytoma	1.52	1.80	0.90
11	8/M	Rt frontal	anaplastic astrocytoma	2.53	1.54	5.00
12	29/M	Rt frontal	anaplastic astrocytoma	1.58	1.97	6.40
13	36/F	Rt parietal	anaplastic astrocytoma	2.36	2.19	7.80
14	40/M	Rt caudate	anaplastic astrocytoma	2.32	4.35	20.00
15	67/M	Lt parietal	anaplastic astrocytoma	1.37	1.59	11.60
16	24/M	Lt thalamus	glioblastoma	2.41	3.03	10.00
17	25/F	Lt parietal	glioblastoma	1.10	1.93	16.80
18	40/F	Rt temporal	glioblastoma	1.64	2.11	10.00
19	44/M	Rt parietal	glioblastoma	1.81	2.20	10.00
20	45/F	Lt frontal	glioblastoma	1.84	2.70	8.00
21	53/M	Lt thalamus	glioblastoma	2.46	2.64	27.30
22	56/M	Rt thalamus	glioblastoma	2.53	3.21	6.50
23	58/F	Rt frontal	glioblastoma	1.56	2.39	16.60
24	58/F	Rt temporal	glioblastoma	2.32	3.80	7.00
25	61/M	Lt thalamus	glioblastoma	2.32	2.84	29.60
26	62/M	Rt temporal	glioblastoma	2.91	4.57	7.20
27	63/F	Lt occipital	glioblastoma	2.37	3.51	19.00
28	70/M	Rt thalamus-frontal	glioblastoma	2.43	3.23	10.00

Statistical analysis

SUV and T/N were used as indicators of the degree of methionine accumulation. Tumor activity and malignancy level were evaluated using Ki-67LI [14–19] and Kaplan-Meier survival curves. The correlation between T/N and Ki-67LI was analyzed for the group of all subjects. The existence of correlations between T/N and Ki-67LI and between SUV and Ki-67LI was determined for the astrocytic tumor group. Receiver operating characteristics (ROC) analysis of T/N and SUV was performed for the subjects with astrocytic tumors. ROC analysis was performed by calculating the sensitivity and specificity of every predicated probability and by plotting sensitivity against 1-specificity. We also determined the ROC cut-off levels to ensure high accuracy of the analysis. ROC analysis evaluates the relationship between sensitivity and specificity at given cut-off levels. Subjects were divided by T/N into two groups. Those with T/N below the cut-off level were assigned to the low-grade group and those with higher T/N levels to the high-grade group. For astrocytic tumor subjects, the cut-off level of T/N between the low-grade group and the high-grade group was determined for each evaluation of Ki-67LI and the cumulative survival rate. The T/N level between 1.3 and 2.0 that produced a significant difference in Ki-67LI between the

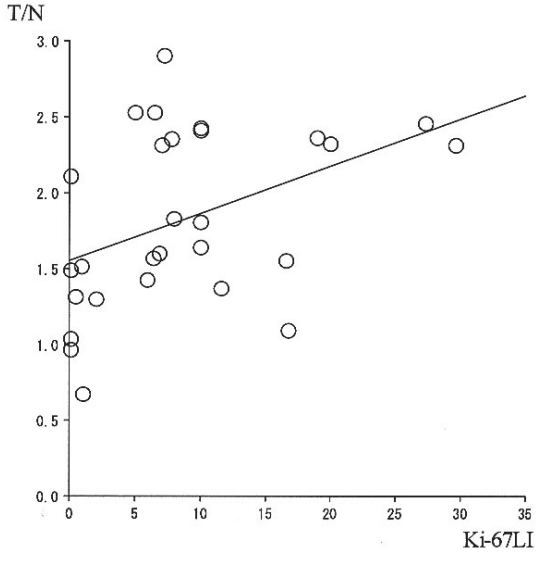

Fig. 4 Correlation between T/N and Ki-67LI for the 28 cases of astrocytic tumors. A significant correlation between T/N and Ki-67LI was observed for this subgroup of subjects (r = 0.426, p = 0.023).

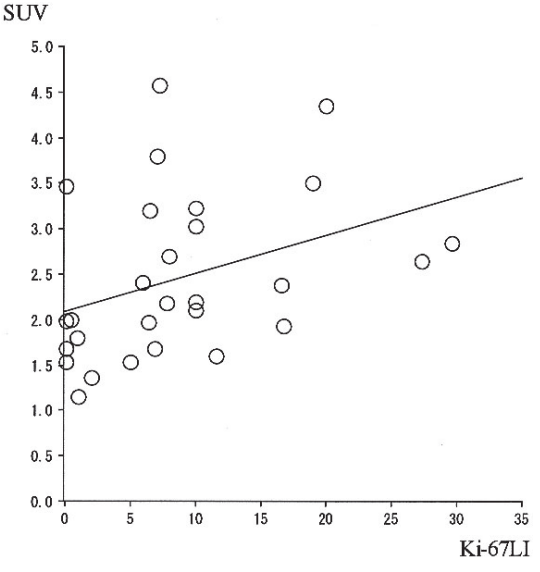

Fig. 5 Correlation between SUV and Ki-67LI for the 28 cases of astrocytic tumors. A significant correlation was also noted between SUV and Ki-67LI for them (r = 0.374, p = 0.05).

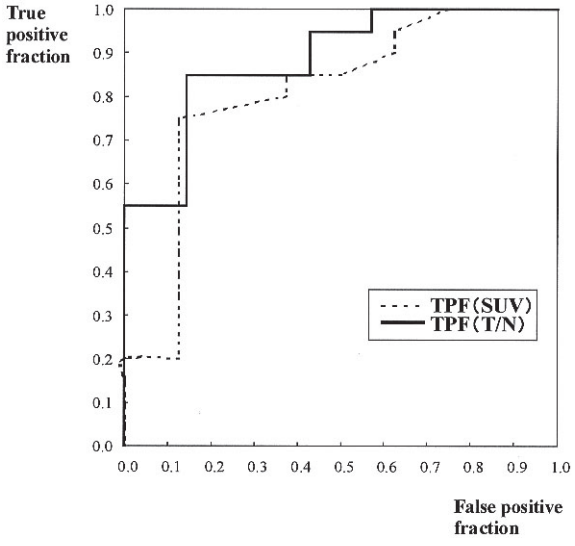

Fig. 6 ROC curves of T/N and SUV. To determine which of T/N and SUV is more useful for diagnosis, ROC curves were created and the areas under the curves obtained. Area was greater for T/N (0.894) than for SUV (0.794).

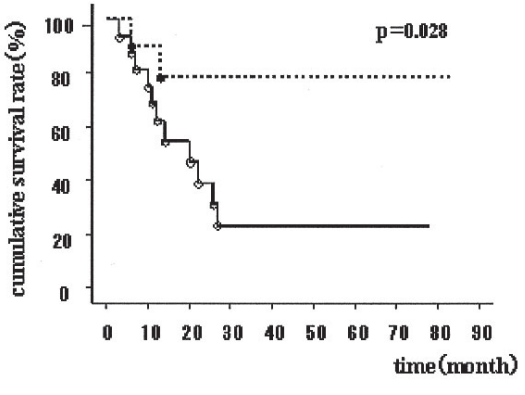

Fig. 7 Prognosis, as evaluated using survival period as an indicator, differed significantly between the high-grade and low-grade groups when T/N was 1.6 (p = 0.028).

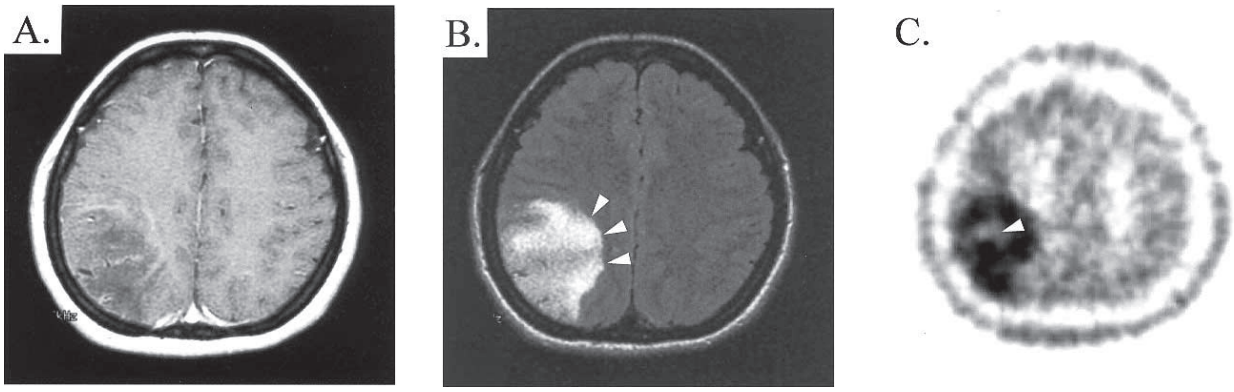

Fig. 8 MRI revealed abnormal mass lesion of the right parietal lobe. (A) Gadolinium enhancement image showed low signal and a poorly enhanced lesion. (B) FLAIR image showed high signal in the lesion and slight edema adjacent to the tumor (*white triangles*). (C) Met-PET showed increased uptake by the tumor, but there was slight low uptake area in the tumor (*white triangle*).

two groups was determined by Mann-Whitney U test. T/N levels giving rise to significant inter-group differences in cumulative survival rate (calculated by the Kaplan-Meier method) when the T/N level was between 1.3 and 2.0 were determined by log-rank test. In all tests, $p < 0.05$ was regarded as statistically significant.

RESULTS

When the degree of methionine accumulation was analyzed for the 67 cases of glioma divided by disease type, it was found to vary (Fig. 2). The mean T/N was 1.92 ± 0.67 (range: 0.71–3.48). For the 67 cases of glioma, no strong correlation was observed between T/N and Ki-67LI ($r = -0.35$, $p = 0.832$) (Fig. 3). Of these 67 cases, the 28 cases with astrocytic tumor (which was relatively frequent) were analyzed separately (Table 2). A significant correlation between T/N and Ki-67LI was observed for this subgroup of subjects ($r = 0.426$, $p = 0.023$) (Fig. 4). A significant correlation was also noted between SUV and Ki-67LI for them ($r = 0.374$, $p = 0.049$) (Fig. 5). To determine which of T/N and SUV is more useful for the diagnosis, ROC curves were created and the areas under the curves obtained. Area was greater for T/N (0.894) than for SUV (0.794), as shown in Figure 6. Analyzed from the viewpoint of tumor proliferative potential, Ki-67LI was found to differ significantly between the high-grade group and the low-grade group at T/N levels between 1.5 and 1.8 ($p = 0.019$–0.031). Prognosis, as evaluated using survival period as an indicator, differed significantly between the high-grade and low-grade groups when T/N was in the range of 1.6–1.8 ($p = 0.028$–0.032) (Fig. 7). ROC analysis of T/N was performed to divide the subjects with astrocytic tumor into two groups (high-grade and low-grade) according to degree of MET accumulation. The accuracy thus calculated was highest (85.71%) when T/N was 1.5.

Representative Case

Case #13 (Fig. 8)

A 36-year-old female had general convulsions. MRI revealed an abnormal mass lesion of the right parietal lobe. Gadolinium (Gd) enhanced image showed low signal and poorly enhanced lesion. FLAIR image showed high signal in the lesion and slight edema adjacent to the tumor. MET-PET showed increased uptake by the tumor, but there was a slightly low uptake area in the tumor. T/N volume was high (2.36) and SUV was moderately low (2.19). The lesion was totally removed. Histological finding showed anaplastic astrocytoma (grade 3) and Ki-67LI was moderately high (7.8).

DISCUSSION

Gliomas (neuroepithelial tumors) develop from the glial cells that compose the supportive tissue of the brain. Gliomas are classified by cell of origin and histological features, while their degree of malignancy is rated on a four-grade scale on the basis of the histological features. Grade 1 and 2 gliomas grow slowly, and relatively high rates of survival are expected for patients following surgery and/or radiotherapy. At grades 3 and 4, high rates of survival are not expected even when surgery is combined with radiotherapy and/or chemotherapy. For this reason, determination of the degree of malignancy is important when predicting prognosis or planning therapeutic strategies for patients with glioma. It will be more useful for treatment if patients can be checked for recurrence, or if the possibility of increase in malignancy of glioma cells can be evaluated. Glioma usually spreads in an infiltrative manner through normal brain tissue, making it difficult to demarcate glioma-affected areas from intact brain tissue. The blood-brain barrier (BBB) is sometimes preserved within this tumor, and contrast material for imaging is not taken up by it. For this reason, it is not easy to determine

the extent of glioma invasion by conventional diagnostic imaging techniques such as CT and MRI, and evaluation of the degree of malignancy on the basis of the distribution of contrast material is difficult. PET is in some cases useful for the diagnosis of this brain tumor and the evaluation of its response to treatment. Measurement of brain glucose metabolism using FDG is useful for diagnosing brain tumors. It is known that brain glucose metabolism as evaluated using FDG correlates with the degree of malignancy or prognosis of brain tumors.[1] However, since the rate of glucose metabolism in brain parenchyma is usually high, brain tumors tend to be depicted as cold lesions unless they are very malignant. Furthermore, since FDG also accumulates in abscess tissue or inflamed areas after radiotherapy, it is difficult to distinguish these areas from those affected by tumor when determining the extent of tumor invasion or following the course of patients after treatment. If methionine is used as an indicator of amino acid metabolism in the brain, the tumor-affected area can be distinguished from the area of radiation necrosis.[20] Since the background methionine level in brain parenchyma is low, areas exhibiting methionine accumulation can be presented in good contrast to other areas. This is useful for localizing tumors and identifying regions of invasion. Some investigators have reported that it was not possible to distinguish low- and high-grade malignancy glioma with FDG,[1] while others have reported a correlation between the degree of FDG accumulation and patient prognosis.[21,22] Some studies of methionine have shown it to be useful for distinguishing low-grade from high-grade glioma.[23] It has also been reported that methionine accumulation is higher in low-grade than in high-grade glioma and is useful for diagnosis.[2,24] In the present study, the degree of methionine accumulation was analyzed for the group of all 67 cases of glioma divided by disease type according to the WHO classification.[11] The types of glioma in these subjects were diverse, as was the degree of methionine accumulation. Even benign tumors sometimes exhibit high methionine accumulation.[4–10] It seems unlikely that the degree of methionine uptake simply reflects the proliferative potential of glioma in general. Pylocystic astrocytoma, optic glioma, choroid plexus papilloma, and oligodendroglioma exhibited high methionine accumulation, suggesting that factors other than proliferative potential (e.g. passage through the BBB and vascular bed) are closely related to the accumulation of methionine in glioma. Subsequent to these findings, we excluded specific types of glioma (including grade 1 cases) and separately analyzed astrocytic tumors, which are relatively common and have been reported to exhibit a strong correlation between FDG accumulation and degree of malignancy. This analysis revealed that amino acid accumulation reflected the degree of tumor malignancy. These findings show that MET-PET can serve as an indicator of the degree of malignancy of astrocytic tumors but does not necessarily reflect the degree of malignancy of other types of glioma. In addition to T/N, SUV is available as an indicator of methionine accumulation in tumors. In the present study, we examined which of these indicators is more suitable for clinical diagnosis. Significant differences between T/N and Ki-67LI and between SUV and Ki-67LI were found ($p = 0.023$, $p = 0.049$, respectively). This suggests that although both T/N and SUV are useful for diagnosis, T/N is more closely correlated with Ki-67LI than SUV. ROC analysis of T/N and SUV showed that the area under the curve was greater for T/N than for SUV. This result together with the above findings indicates that T/N provides a better means of evaluating methionine accumulation than SUV. There are some cases that show a discrepancy between T/N and SUV. Concretely, Case #4, which had a benign tumor, showed low T/N and high SUV. On the other hand, Case #11, which was anaplastic type, showed high T/N and low SUV. One reason for this finding is that the tendency for methionine to accumulate in intact gray matter varies greatly among individuals, and T/N is based on the assumption of a constantly normal denominator. Finally, we attempted to identify the cut-off level (border level) of T/N that would permit distinction between the high-grade and low-grade astrocytic tumor groups. To this end, we checked for significant differences between the two groups at varying T/N levels. Significant inter-group differences in Ki-67LI were explored when T/N was varied between 1.3 and 2.0. This analysis revealed significant inter-group differences ($p < 0.005$) when T/N was between 1.5 and 1.8. The correlation with prognosis was analyzed while T/N was varied between 1.3 and 2.0. Cumulative survival rate, analyzed as an indicator of prognosis, differed significantly between the two groups when T/N was between 1.6 and 1.8. ROC analysis revealed an accuracy of 85% when T/N was 1.5. Taken together, these findings indicate that it is appropriate to set the cut-off T/N at 1.5–1.6 when distinguishing high-grade from low-grade astrocytic tumor.

In this way, MET-PET is a very useful tool for evaluating the degree of malignancy of astrocytic tumor. But we must take the limitations of this study into consideration. There are many tumors in the gray zone, whose T/Ns show around 1.5–1.6, and we cannot often make a differential diagnosis before treatment. Because MET accumulation depend on not only tumor proliferation itself but also other various factors, additional examinations are needed to determine the mechanism.

CONCLUSION

In this study, the degree of MET accumulation varied greatly among individual cases of glioma and was not significantly correlated with Ki-67LI on analysis performed for the entire glioma group. When analysis was confined to cases of astrocytic tumor, a correlation was noted between methionine accumulation and Ki-67LI.

For the astrocytic tumors, T/N ratio seemed to be more useful as a diagnostic indicator than SUV. The cut-off level of T/N ratio for distinction between high-grade and low-grade astrocytoma appears to lie between 1.5 and 1.6.

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