The Accumulation of 11C-Methionine and Histological Grade in Cerebral Glioma Studied with PET

IV. 2. The Accumulation of ^{11}C-Methionine and Histological Grade in Cerebral Glioma Studied with PET

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Introduction

The appearance of positron emission tomography (PET) has opened the new filed in medicine. Different from the CT scan or magnetic resonance imaging (MRI), which give us mainly the anatomical information in detail, PET provides various physiological characteristics of human body. We sometimes feel difficulty to know the extent of glioma or to differentiate biological malignancy of glioma based on the information from the conventional three-dimensional diagnostic tools. Believing that the information of amino acid metabolism in glioma will give us an important clue to elucidate the biological characteristics of glioma, which will be of great value in establishing the treatment strategy for this disease, we undertook the PET study of glioma patients using ^{11}C labeled essential amino acid.

Materials and Method

Patients

Fourteen cases of histologically defined glioma patients were studied with PET using L-[methyl-^{11}C]methionine (^{11}C-MET); 12 males and 2 females, mean age was 42.4 years-old, ranging from 28 to 63 years-old (Table 1). All of the patients underwent PET examination before radical surgery. Histological diagnoses were made from CT-guided stereotaxic biopsy (9 cases) or operative specimen (5 cases). There were 4 cases of grade IV (4 glioblastoma), 3 cases of grade III (2 anaplastic astrocytoma and 1 anaplastic ganglioglioma), and 7 cases of grade II (6 fibrillary astrocytoma and 1 gemistocytic astrocytoma). The tumor tissue for histological diagnosis was obtained within 1 months from the PET study in 13 cases and 3 months in one. Informed consent was obtained from the patients and/or

relatives. The present project was approved by the Committee for Clinical PET Study of Tohoku University.

Scanner and Procedure

The ECAT II (EG&G, Ortec)[20] and PT-931(CTI, Knoxville, Tennessee)[22] were employed. The spatial resolutions of the images are 17 and 8 mm, and slice thickness are 18 and 7 mm in FWHM for the ECAT II and PT-931 respectively. Following the intravenous administration of 6 to 25 mCi of ^{11}C-MET, sequential scanning (each scan being of 5 minutes duration) was performed for 45 minutes, after which additional images in other positions were obtained. Usually three images were obtained with the ECAT II at 1 cm center to center spacing and 7 images were obtained simultaneously with PT-931 at 7 mm spacing. The PET images were reconstructed using a measured attenuation correction.

Tissue uptake of ^{11}C-MET was also calculated and expressed as the differential absorption ratio (DAR)[16] that is related to % injected dose and expressed as:

$$DAR=C_{pet}*W/D$$

where Cpet is tissue concentration of ^{11}C expressed in mCi/g, W and D are body weight in g and injected dose in mCi respectively. Ovale region of interest were located on the brain tumor and the contralateral gray matter in the sequential images, using CT images as an anatomical guide, and the DAR was calculated. Statistical analysis was done by Welch's t test.

Results

In all 16 cases of glioma showed positive images of brain tumor regardless of their histological grades (Fig. 1, 2).

The results of DAR at 45-50 minutes after the administration of ^{11}C-MET are summarized in Table 1, the mean DAR and the standard deviation in the 4 grade IV glioma was 3.13±0.86 and 3.33±1.34 in the 3 grade III glioma, and when these two groups are mixed it was 3.21±1.10. Whereas the value of 1.87±0.40 was obtained in 7 grade II glioma. The significant difference was observed between high grade glioma and low grade glioma($p<0.05$).

The value of DAR of the contralateral gray matter was 1.43±0.22, and the ratio of tumor/gray matter was 2.22±0.48 in gradeIV, 2.4±0.49 in grade III and 1.5±0.49 in grade II glioma(Fig. 3). The statistical difference was also observed between high grade gliomas and low grade gliomas.

Discussion

PET provides a unique opportunity to investigate three-dimensional information of biological properties in a noninvasive manner. Accordingly, there have been various reports concerning the metabolic observation of brain tumor.[1-9,11-15, 17-19, 21,23] Di Chiro et al.[6,7] reported that ^{18}F-fluorodeoxyglucose (FDG) was useful in differentiating high and low grade gliomas, and Patronas et al.[18] suggested that glucose metabolism significantly correlates with the prognosis of the patients. On the other hand, as they themselves stated the visual appearance of the tumor with FDG depends on its location, since FDG images of the normal brain show a biphasic uptake, with high activity in gray-matter and low activity in white-matter[6,7,9]. Therefore, a low grade tumor within a white-matter region will not stand out and a high grade tumors that invade the cortex or other gray matter may easily be confused with normal structure. Moreover, according to the recent report of Tyler et al.[23], even the glucose utilization rate of high grade glioma is sometimes lower than the contralateral gray matter. The results obtained through the present study with ^{11}C-MET was in good contrast to the FDG study; all of the glioma showed positive image compared with the surrounding brain tissue regardless of the tumor grade and DAR ratio of tumor/contralateral gray-matter exceeds 1.0.

Recently the authors have investigated the metabolism of nucleic acid of glioma using ^{18}F-fluorodeoxyuridine (FdUrd) and found that there was a clear difference between the high and low grade gliomas[13]; clear positive images were seen in high grade gliomas, whereas low grade glioma failed to show definite accumulation of FdUrd. This finding was also in good contrast with the present results of ^{11}C-MET study.

In the present study decreased accumulation of ^{11}C-MET was not observed in any cases. On the contrary, however, Mosskin et al.[17] reported the result of PET study of brain tumor using ^{11}C-MET and they stated that 3 cases of low grade glioma out of 36 showed decreased or ordinary accumulation of ^{11}C-MET compared with normal brain tissue. Lilja et al.[14] also observed that the accumulation of ^{11}C-MET in two cases of low grade glioma was 0.8 to 1.0 of that in surrounding brain, and Bustany et al.[5] reported that ^{11}C-MET incorporation rate between tumor and normal parenchyma was 78 and 80% in two cases of low grade glioma respectively among their 13 cases of glioma patients. These may be due to the unavoidable partial volume effect of this kind PET study. In spite of the improved resolution of the recent PET with X-ray CT and MRI, it still has a much less spatial resolution compared with X-ray CT and MRI. Therefore, if the tumor is very small or tumor cell is scattered around the brain

tissue, or the tumor has cavitation component surrounded by a thin rim of solid tumor, false negative results can be obtained in ^{11}C-MET study.

^{11}C-MET accumulation ratio of tumor/contralateral gray matter showed significant difference between low and high grade gliomas. However, no significant difference was observed between grade III and IV. There are several reasons to be considered.
1) Relatively small number of patients were examined in this study. 2) The heterogeneity of high grade gliomas, with the mixture of necrotic tissue and actively growing cells, and different tumor cell density, all of which can cause the wide variation of ^{11}C-MET accumulation in the tumor. 3) Treatment effect may not be overlooked. As Bustany et al. reported that protein synthesis rate in high grade glioma showed definite decrease after radiation therapy[5], care must be taken in analyzing the clinical data. 4) And finally, as reported by Hoshino et al[10], the cell proliferative potential of gliomas determined by the bromodeoxyuridine labeling technique showed wide variation even in the same graded glioma. These may support the large deviation of DAR in high grade gliomas in the present study.

Little is known about the exact mechanism of increased ^{11}C-MET accumulation in glioma. In the present PET study with ^{11}C-MET, however, it was succeeded to reveal positive images of glioma even in the cases without contrast enhancement effect on conventional X-ray CT scan, and to differentiate low and high grade gliomas by comparing the accumulating ratio. We conclude that PET study with ^{11}C-MET will give us an important information to manage glioma patients.

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Table 1. Patients list

case	age	sex	histological grade	CT enhancement	DAR tumor	DAR gray	DAR ratio
1	38	M	II	-	1.3	1.1	1.2
2	34	M	II	-	2.4	1.4	1.7
3	45	M	II	-	0.9	0.9	2.1
4	38	M	II	-	2.1	1.4	1.5
5	43	F	II	-	1.3	1.2	1.1
6	49	M	II	-	1.9	0.9	2.1
7	35	M	II	-	2.2	1.2	1.8
8	73	F	III	+	5.2	1.9	3.0
9	49	M	III	+	2.1	1.2	1.8
10	63	M	III	+	2.7	1.2	1.8
11	52	M	IV	+	3.4	1.4	2.4
12	60	M	IV	+	2.2	1.3	1.8
13	45	M	IV	+	2.5	1.5	1.7
14	59	M	IV	+	4.4	1.5	2.9

DAR: differential absorption ratio,

ratio: DAR ratio of tumor/contralateral grey matter

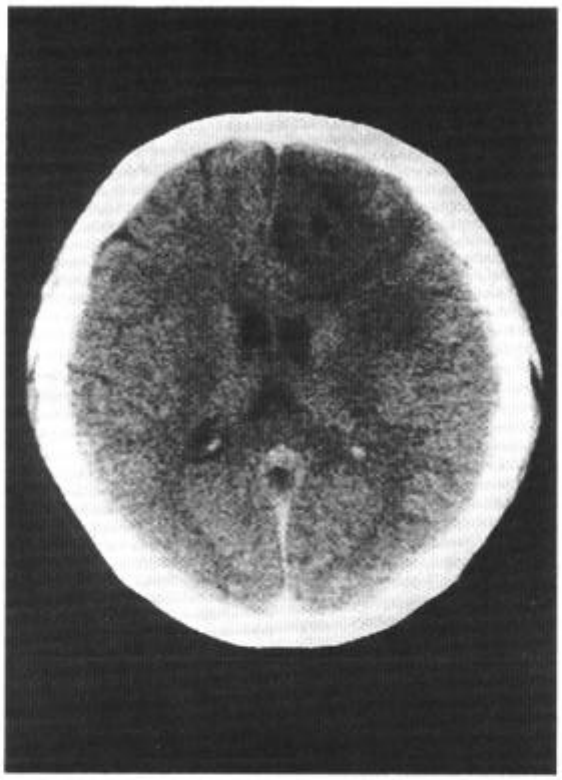

Fig. 1A. A CT scan of case 7 revealed a low density lesion in the right frontal region.

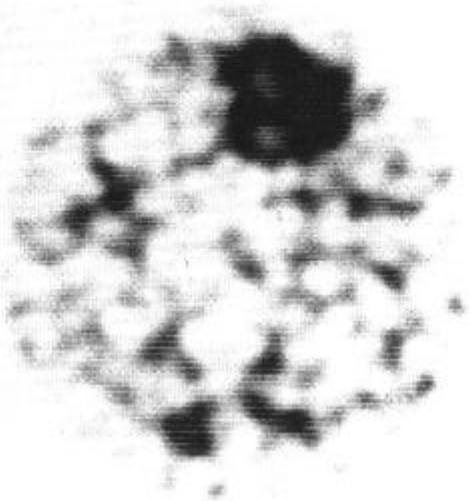

Fig. 1B. A PET scan with ^{11}C-MET showed a lesion with high accumulation.

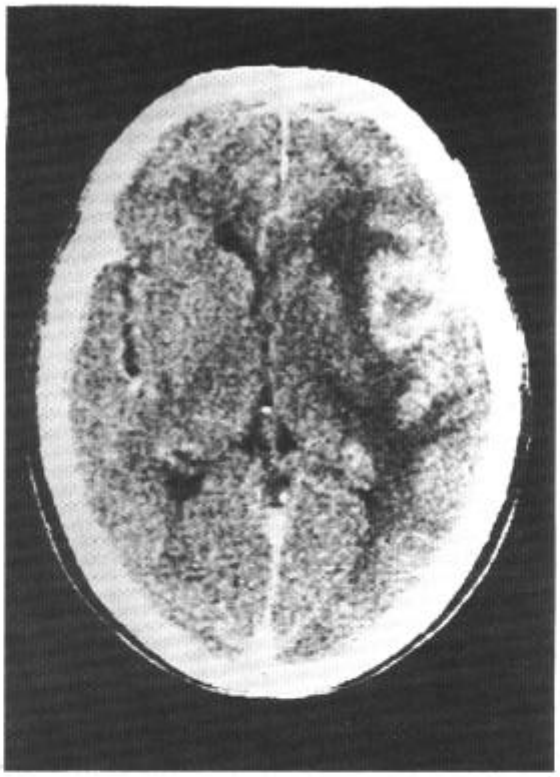

Fig. 2A. A CT scan of case 10 revealed an enhanced tumor with a surrounding low density area in the right fronto-temporal region.

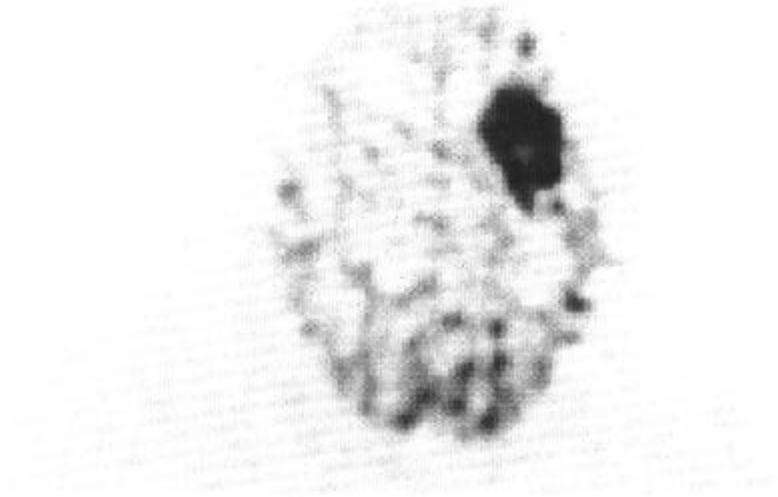

Fig. 2B A PET scan with ^{11}C-MET showed a high accumulating lesion.

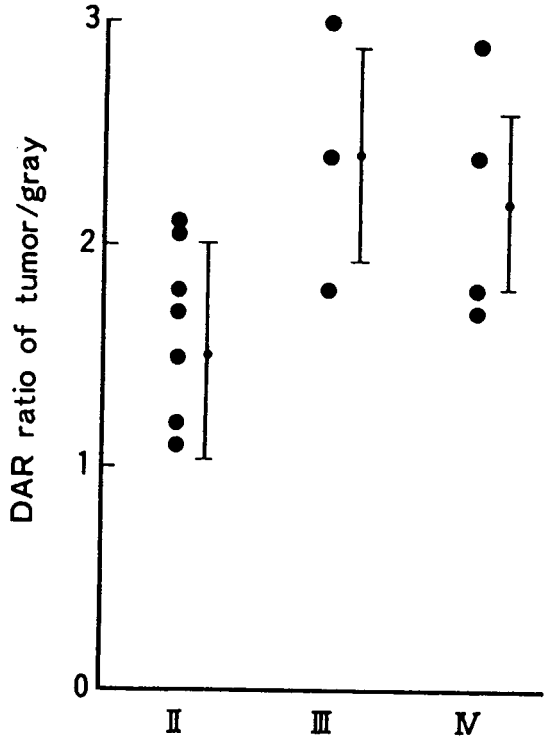

Fig. 3. DAR ratio of tumor/contralateral gray-matter.