Amino Acid Study of Cerebral Gliomas Using Positron Emission Tomography
—Analysis of (¹¹C-methyl)-L-methionine Uptake Index—

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Abstract

Sixteen patients with gliomas (7 low grade, 9 high grade) were examined using positron emission tomography (PET) with intravenous administration of 22.2 MBq/kg (0.6 mCi/kg) of (¹¹C-methyl)-L-methionine (C-11 Met). The tracer uptake in regions of interest was calculated on PET images taken 45 minutes after injection; the uptake index was represented as a percentage of the total count in the arterial blood summed over 45 minutes. C-11 Met uptake indices in the tumors ranged from 0.020 to 0.041% with a mean of 0.032% for the low-grade gliomas and from 0.013 to 0.044% with a mean of 0.036% for the high-grade gliomas. These indices significantly increased as compared with those in the contralateral gray matter (0.008-0.032% with a mean of 0.023%; p < 0.01 vs. low-grade gliomas, p < 0.001 vs. high-grade gliomas). In the low-grade gliomas, C-11 Met PET images clearly depicted the existence and even the extent of the tumors, although x-ray computed tomography (CT) did not always distinguish tumoral lesions. In the high-grade gliomas, the areas of tracer accumulation regionally extended to peritumoral low density on CT scans, where malignant tumor cell infiltration was proved by operative and follow-up CT findings. C-11 Met may be a useful radiopharmaceutical for differential diagnosis of gliomas, and the accuracy of tumor localization will give us a better rationale in therapeutic strategies for surgery and radiation therapy of gliomas.

Key words: glioma, metabolism, amino acids, (¹¹C-methyl)-L-methionine, positron emission tomography

Introduction

With the development of such neuroradiological tools as x-ray computed tomography (CT) and magnetic resonance (MR) imaging, the location of cerebral gliomas can be more clearly identified. A contrast enhancing lesion surrounded by low density on CT scans is interpreted to be a zone of viable tumor cell accumulation and surrounding edema infiltrated by tumor cells. However, CT poorly identifies the location of non-enhancing gliomas, and even T₁- and T₂-weighted MR images with enhancement by gadolinium-diethylenetriaminepenta-acetic acid cannot always differentiate tumor tissue from edema. Infiltrating patterns and distribution of tumor cells vary widely in the peripheral margins of gliomas. Positron emission tomography (PET) with radiological enhancement by various tracers specific to tumor metabolism is expected to yield accurate localization of gliomas, although spatial resolution has been limited.

This paper presents uptake of (¹¹C-methyl)-L-methionine (C-11 Met) in cerebral gliomas according to tumor malignancy and analyzes topographic correlation with the tumor extent revealed by C-11 Met PET and CT.

Subjects and Methods

Sixteen patients with gliomas, nine males and seven females aged from 10 to 79 years with a mean age of 47, were examined (Table 1). Histological diagnoses
were six fibrillary astrocytomas, five malignant astrocytomas, and two glioblastomas. One low-grade and two high-grade gliomas were clinically diagnosed on the basis of neurological and neuroradiological findings.

The PET apparatus employed in this study was Headtome III, which provides 10 simultaneous slices with a spatial resolution of 8 mm full width at half maximum. PET was performed preoperatively in 12 cases and postoperatively in four. PET image slices were fitted to CT scan levels parallel to the orbitomeatal lines using a face mask. Forty-five minutes after intravenous administration of 22.2 MBq/kg (0.6 mCi/kg) of C-11 Met, the uptake in tumor regions (CT) was calculated on PET images. The uptake index was represented as a percentage of the total count in the arterial blood (Cp) summed over 45 minutes (t) as follows:

$$\text{C-11 Met uptake index} = \frac{C_T}{\int_0^t Cp \, dt} \times 100$$

Regions of interest, which were marked oval and in the size of $6 \times 12$ pixels ($12 \times 24$ mm) on each PET scan, were placed over the tumor region including a peak value and the corresponding contralateral gray matter. The uptake index in the tumor was analyzed for the low-grade and the high-grade gliomas, and compared with that in the contralateral gray matter. In addition, PET images of regional cerebral blood flow (rCBF) and blood volume (rCBV) were obtained with C15 02 and C15O gas inhalation. The extent of tumors visualized on C-11 Met PET images was compared with lesions detected by CT.

### Table 1 Clinical summary of gliomas studied with C-11 Met PET

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Location</th>
<th>Pre- and postcontrast CT scans</th>
<th>rCBF* (Level)</th>
<th>rCBV* (Extent)</th>
<th>C-11 Met</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>F</td>
<td>fibrillary astrocytoma</td>
<td>rt temporal</td>
<td>low/CE (−)</td>
<td>−</td>
<td>+</td>
<td>&gt;CT</td>
</tr>
<tr>
<td>2</td>
<td>35</td>
<td>F</td>
<td>fibrillary astrocytoma</td>
<td>lt parietal</td>
<td>low/CE (−)</td>
<td>−</td>
<td>=</td>
<td>&lt;CT</td>
</tr>
<tr>
<td>3</td>
<td>37</td>
<td>M</td>
<td>fibrillary astrocytoma</td>
<td>lt parietal</td>
<td>low/CE (−)</td>
<td>=/+</td>
<td>=/+</td>
<td>&gt;CT</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>F</td>
<td>fibrillary astrocytoma</td>
<td>rt temporal</td>
<td>low/CE (−)</td>
<td>−</td>
<td>+</td>
<td>&gt;CT</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>M</td>
<td>fibrillary astrocytoma</td>
<td>lt frontal</td>
<td>low/CE (−)</td>
<td>+</td>
<td>+</td>
<td>&gt;CT</td>
</tr>
<tr>
<td>6</td>
<td>58</td>
<td>F</td>
<td>fibrillary astrocytoma</td>
<td>lt parietal</td>
<td>low, calcified/CE (−)</td>
<td>−</td>
<td>−</td>
<td>&lt;CT</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>F</td>
<td>low-grade glioma*</td>
<td>rt frontobasal</td>
<td>low/CE (−)</td>
<td>+</td>
<td>+</td>
<td>&gt;CT</td>
</tr>
<tr>
<td>8</td>
<td>23</td>
<td>M</td>
<td>malignant astrocytoma**</td>
<td>rt frontal</td>
<td>high, low/CE (+)</td>
<td>−</td>
<td>−</td>
<td>&gt;CT</td>
</tr>
<tr>
<td>9</td>
<td>30</td>
<td>F</td>
<td>malignant astrocytoma</td>
<td>lt parietal</td>
<td>high, low/CE (+)</td>
<td>=/+</td>
<td>+</td>
<td>&gt;CT</td>
</tr>
<tr>
<td>10</td>
<td>46</td>
<td>F</td>
<td>malignant astrocytoma</td>
<td>rt frontal</td>
<td>high, low/CE (+)</td>
<td>−</td>
<td>−</td>
<td>&gt;CT</td>
</tr>
<tr>
<td>11††</td>
<td>57</td>
<td>M</td>
<td>malignant astrocytoma***</td>
<td>lt frontotemporal</td>
<td>high, low/CE (+)</td>
<td>−</td>
<td>=/+</td>
<td>&gt;CT</td>
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<tr>
<td>12</td>
<td>61</td>
<td>M</td>
<td>malignant astrocytoma***</td>
<td>lt temporal</td>
<td>high, low/CE (+)</td>
<td>+</td>
<td>+</td>
<td>&gt;CT</td>
</tr>
<tr>
<td>13</td>
<td>61</td>
<td>M</td>
<td>glioblastoma**</td>
<td>rt temporal</td>
<td>high, low/CE (+)</td>
<td>+</td>
<td>+</td>
<td>&gt;CT</td>
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<tr>
<td>14</td>
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<td>M</td>
<td>glioblastoma</td>
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<td>+</td>
<td>+</td>
<td>&gt;CT</td>
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<tr>
<td>15</td>
<td>57</td>
<td>M</td>
<td>high-grade glioma*</td>
<td>lt thalamus</td>
<td>high, low/CE (+)</td>
<td>+</td>
<td>+</td>
<td>&gt;CT</td>
</tr>
<tr>
<td>16</td>
<td>65</td>
<td>M</td>
<td>high-grade glioma*</td>
<td>tegmentum</td>
<td>high, low/CE (+)</td>
<td>+</td>
<td>=/+</td>
<td>&gt;CT</td>
</tr>
</tbody>
</table>

*Judged by rCBF, rCBV, and C-11 Met uptake index as compared with the contralateral gray matter: +, more than 10% increase; =, within 10% increase or decrease; −, more than 10% decrease. ††Harbored tumor recurrence at the PET study. *Not verified histologically. **Postoperative PET case. CE: contrast enhancement.

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### Results

The means and standard deviations of C-11 Met uptake indices in the tumors were $0.032 \pm 0.008\%$ (range, 0.020–0.041%) for the low-grade gliomas ($n = 7$) and $0.036 \pm 0.010\%$ (0.013–0.044%) for the high-grade gliomas ($n = 9$). These values significantly increased as compared with those in the contralateral gray matter (0.008–0.032% with a mean of 0.023%; $p < 0.01$ vs. low-grade gliomas, $p < 0.001$ vs. high-grade gliomas) (Fig. 1). Tumor/gray matter ratios ranged from 0.86 to 1.91 with a mean of 1.39 for the low-grade gliomas and from 1.21 to 2.73 with a mean of 1.67 for the high-grade gliomas.

In 14 (88%) of 16 glioma cases, C-11 Met PET images clearly depicted the tumor as a tracer-accumulating ("hot") lesion with more than 10% increase in the uptake index as compared with the con-
The remaining two cases without appreciable accumulation of C-11 Met in the tumor had low-grade gliomas, which were cystic astrocytoma (Case 2) and minute calcified tumor (Case 6, 0.5 cm² size at maximum). The failure to detect these tumors was mainly due to the limited spatial resolution of PET. rCBF or rCBV decreased in the tumor as compared with the contralateral gray matter, representing "cold" lesions, in 12 cases (Table 1).

In seven low-grade gliomas (Cases 1-7), the tumor was mostly hypodense without contrast enhancement on CT scans. The location of the tumor or the interface between the tumor and the normal brain parenchyma was fuzzy, especially in the white matter. On the contrary, C-11 Met PET images clearly delineated the existence and extent of the tumor by tracer accumulation in five cases (71%). In nine high-grade gliomas (Cases 8-16), the areas with increased tracer uptake on C-11 Met PET images extended more widely than hypo- and hyperdensity areas on CT scans. The tumor extent defined by C-11 Met accumulation correlated well with the area of tumor cell infiltration confirmed by histological and follow-up CT findings.

Two representative cases are presented.

**Case 8:** Malignant astrocytoma in a 23-year-old male. Preoperative CT scans disclosed a cystic tumor with ring-like enhancement in the right frontal region (Fig. 2A). Following extensive resection of the tumor, focal irradiation at a total dose of 60 Gy was given. Postradiation CT scans revealed a linear enhancement, uncertain as to whether tumor residues or postoperative glial proliferation, adjacent to the incised surface of the brain (Fig. 2B). C-11 Met PET images showed tracer accumulation beyond the enhancing lesion on CT scans (Fig. 3). Reoperation proved the lesion to be the residual tumor.

**Case 13:** Glioblastoma in a 61-year-old male. Biopsy specimens of the right temporal tumor illustrated high cellularity of atypical tumor cells, vascular proliferation, and numerous aggregations of small necroses. Postoperative CT scans showed a multilocular enhancing tumor with peripheral hypodensity, which compressed the ventricles and shifted the
midline structures (Fig. 4). The tumor had high rCBF and rCBV in part and was clearly depicted by the extensive tracer accumulation on PET images (Fig. 5).

**Fig. 3** Case 8. PET images, showing C-11 Met accumulation (C, arrows), low rCBF (A), and low rCBV (B) in the lesion.

**Fig. 4** Case 13. Pre- (left) and postcontrast (right) CT scans after biopsy and external decompression, showing a multilocular enhancing tumor with surrounding low density in the right temporal region. Compression of the lateral ventricle and displacement of the midline structure are also seen.

midline structures (Fig. 4). The tumor had high rCBF and rCBV in part and was clearly depicted by the extensive tracer accumulation on PET images (Fig. 5).

**Discussion**

Methionine is an essential amino acid, which yields methyl bases in the cellular metabolism. Demethylated methionine is a precursor of the other amino acids and incorporates into protein synthesis. C-11 Met might accumulate in brain tumors by passive diffusion due to the blood-brain barrier (BBB) disruption or by active transport through cell membranes. The result that C-11 Met accumulated even in the low-grade gliomas without contrast enhancement, indicating intact BBB, (Cases 1, 3–5, and 7) suggests tracer accumulation by active transport. The common, competitive membrane transport of amino acids was evident in the brain tumors as well as the normal brain tissue because pretreatment of leucine, valine, or isoleucine reduced uptake of C-11 Met by 35%.

The present study showed that the C-11 Met uptake index in the tumors significantly increased as compared with that in the contralateral gray matter and that C-11 Met accumulated in the tumors except for one cystic and one minute lesions. C-11 Met PET images are superior for tumor imaging, because the tumor was illustrated as a "hot" lesion by increased accumulation and was delineated differently from the non-tumor lesion.

There was no significant difference in the uptake index between the low-grade and high-grade gliomas in the present study. Some authors contend that C-11 Met uptake in the tumor increases with malignancy. In Derlon's report, a significant difference was observed between grades II and III or grades II and IV but not between grades III and IV. This less definite difference was partly due to the tissue heterogeneity, i.e., necroses, cysts, hemorrhages, and calcifications. Further study, including kinetic analysis of C-11 Met, is required to reach clinically informative conclusions in relation to tumor malignancy.

Ericson et al. have previously reported on C-11 Met PET images of supratentorial tumors in comparison with 11C-D-glucose and 68Ga-ethylenediaminetetra-acetic acid (EDTA) PET images. C-11 Met accumulated in six (67%) of nine low-grade astrocytomas, in all three oligoastrocytomas, and
more intensely in the two anaplastic astrocytomas. The degree of C-11 Met uptake in the tumor was relatively higher than that of C-D-glucose uptake. Marked accumulation of C-11 Met was noted in seven low-grade gliomas and in the two anaplastic astrocytomas with surrounding edema. C-11 Met PET images better reflected the extent of the low-grade gliomas as compared with C-D-glucose PET images, which had limitations in delineating the tumors because of low uptake. C-11 Met uptake often increased in normal areas on CT scans, although the areas with high uptake of 68Ga-EDTA corresponded to the contrast enhancing lesion on CT scans. The areas detected only by C-11 Met accumulation were histologically found to contain tumor cells with numerous mitoses, less necrosis, and less vascular proliferation.1)

Topographic correlation between C-11 Met PET and the histological findings using a stereotactic technique has been studied.10) The tumor cell distribution was consistent with the areas of high uptake of C-11 Met in 22 (71%) of 31 cases with brain tumors, and C-11 Met PET was more accurate in imaging tumors than CT.

In the present study, the lesion detected by high C-11 Met uptake was more obvious and wider than that by CT; the tracer often extended even into the brain parenchyma, which seemed normal on CT scans. C-11 Met accumulation was well correlated with tumor extent confirmed by operative and follow-up CT findings. In an infiltrative glioma (Case 9), CT scans showed a tiny enhancing lesion with surrounding low density, but the entire tumor extent was equivocal.10) C-11 Met PET images revealed intense and extensive tracer accumulation in the lesion and could detect the contralateral lesion sooner than CT did. The growth pattern of gliomas divided into two major categories, infiltrative and expansive.12) PET is especially powerful in imaging such an infiltrative type of glioma.

An important role of surgery in the treatment of gliomas is to lessen the tumor volume as extensively as possible in order to enhance the efficacy of radiochemotherapy, although the resection is limited by the site of the tumor and the vulnerable anatomical structures adjacent to the tumor. In Case 8, postoperative PET images detected the region with the C-11 Met accumulation, which was diagnosed as a residual tumor. Reoperation proved a regrowing tumor at the site of high C-11 Met uptake. PET is therefore useful to detect the existence of postoperatively residual tumors and to select effectively concessive treatment.

Definition of the tumor extent is mandatory in planning an appropriate surgical approach to and the pertinent radiation therapy of gliomas. C-11 Met is a promising positron tracer in imaging gliomas and their spatial configuration.

Addendum

This work was presented in part at the 46th Annual Meeting of the Japan Neurosurgical Society, October, 1987, Tokyo, Japan.

References


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