Clinical Positron Emission Tomography for Brain Tumors: Comparison of Fludeoxyglucose F 18 and \( \text{L-}^{\text{\text{\textsuperscript{11}}}\text{C-}} \text{methionine} \)

Toshihide Ogawa, Atsushi Inugami, Jun Hatazawa, Iwao Kanno, Matsutaro Murakami, Nobuyuki Yasui, Katsuyoshi Mineura, and Kazuo Uemura

PURPOSE: To evaluate the differences between fludeoxyglucose F 18 (FDG) and \( \text{L-}^{\text{\text{\textsuperscript{11}}}\text{C-}} \text{methionine} \) as tracers for positron emission tomography (PET) in the evaluation of brain tumors. METHODS: We analyzed 10 patients with histologically verified cerebral glioma or meningoima and 1 patient with a neuroradiologic diagnosis of low-grade glioma by using FDG, \( \text{L-}^{\text{\text{\textsuperscript{11}}}\text{C-}} \text{methionine} \), and PET. We qualitatively and quantitatively evaluated the extent and degree of accumulation of FDG and \( \text{L-}^{\text{\text{\textsuperscript{11}}}\text{C-}} \text{methionine} \) in the tumor tissue. RESULTS: Although PET with FDG depicted malignant tumors as a hot spot in all cases, it was not able to delineate the extent of the tumor. Conversely, PET with \( \text{L-}^{\text{\text{\textsuperscript{11}}}\text{C-}} \text{methionine} \) outlined the tumors as areas of increased accumulation of \( \text{L-}^{\text{\text{\textsuperscript{11}}}\text{C-}} \text{methionine} \), regardless of the degree of malignancy. CONCLUSION: PET with FDG and with \( \text{L-}^{\text{\text{\textsuperscript{11}}}\text{C-}} \text{methionine} \) can play complementary roles in the evaluation of brain tumors.

Index terms: Brain neoplasms, radionuclide studies; Positron emission tomography

Positron emission tomography (PET) has provided valuable biophysiological information on various central nervous system disorders. In brain tumors, various radiotracers have been applied with PET to evaluate tumor blood flow and metabolism, as well as to detect tumors and to assess the degree of malignancy (1–4). Among the various radiotracers, fludeoxyglucose F 18 (FDG) has been the most frequently used for the evaluation of glucose metabolism in brain tumors. In addition, the assessment of tumor protein synthesis has been attempted with various amino acid tracers, and the most experience has been obtained with \( \text{L-}^{\text{\text{\textsuperscript{11}}}\text{C-}} \text{methionine} \) (3, 5–7). In a few studies both FDG and \( \text{L-}^{\text{\text{\textsuperscript{11}}}\text{C-}} \text{methionine} \) have been applied to tumors (8–10). In the present study, we applied both tracers to patients with glioma or meningoima to evaluate the differences of FDG and \( \text{L-}^{\text{\text{\textsuperscript{11}}}\text{C-}} \text{methionine} \) as radiotracers for brain tumors.

Subjects and Methods

Subjects

We used PET with FDG and \( \text{L-}^{\text{\text{\textsuperscript{11}}}\text{C-}} \text{methionine} \) to examine 16 patients who were clinically thought to have brain tumors. Five of them were confirmed to have radiation injury, and, as in our previous report on this group (11), we excluded these 5 from the present analysis and assessed the other 11 patients (6 men and 5 women) (Table 1). The patients ranged in age from 29 to 67 years (mean, 48 years). Pathologic verification was obtained in 10 patients (5 had low-grade glioma, 4 had high-grade glioma, and 1 had meningoima), and in the remaining patient, low-grade glioma was diagnosed from the neuroradiologic data.

Methods

PET was carried out with Headtome IV PET scanners (Shimadzu, Kyoto, Japan). The Headtome IV scanner provides 14 images with 6.5-mm intervals and a spatial resolution of 4.5-mm full width at half maximum in the imaging plane (12). PET was performed parallel to the orbitomeatal line.
After a transmission scan was obtained, a dose of 185 to 333 MBq (5 to 9 mCi) of FDG or 740 to 2220 MBq (30 to 60 mCi) of \(^{11}\text{C}\)-methionine was intravenously injected into the cubital vein within 1 minute. Static scanning was performed for a 12-minute period at 60 minutes after the FDG injection. Arterial blood samples were obtained periodically after the injection of FDG. For PET with \(^{11}\text{C}\)-methionine, a 12-minute static scan using the Headtome IV was begun 30 minutes after \(^{11}\text{C}\)-methionine injection. No arterial blood samples were obtained for PET with \(^{11}\text{C}\)-methionine. The interval between PET with FDG and PET with \(^{11}\text{C}\)-methionine was less than 1 week (mean, 4.5 days).

Before the first PET scan, a CT/T 9800 scanner (GE Medical Systems, Milwaukee, Wis) was used to obtain computed tomographic (CT) scans both before and after the injection of iopamidol. Scans were obtained parallel to the orbitomeatal line with a 10-mm section thickness and 6.5-mm section interval. The method of achieving accurate alignment between CT and PET studies has been previously reported in detail (13, 14). Magnetic resonance (MR) imaging was also performed before and after injection of gadopentetate dimeglumin with a 0.5-T superconducting MR unit (Magnex 50, Shimadzu) in six patients before the second PET examination. Informed consent for the PET studies was obtained from the patients or their relatives. This project was approved by the Committee for Clinical PET Study of the Research Institute of Brain and Blood Vessels—Akita.

### Data Analysis

We evaluated the accumulation of FDG and \(^{11}\text{C}\)-methionine in tumor tissue both qualitatively and quantitatively. Tracer accumulation was divided into three grades (lower, similar, and higher) by comparison with the accumulation in the contralateral gray matter. For a quantitative analysis of FDG uptake, the metabolic rate for glucose (MRGlu) was assessed by the FDG method of Phelps et al (15). The MRGlu was calculated by using fixed-rate constants from healthy volunteers and a lumped constant of 0.52 (16). To assess \(^{11}\text{C}\)-methionine uptake, we evaluated the concentration of \(^{11}\text{C}\)-methionine at 36 minutes after injection on the basis of the differential absorption ratio (DAR) (17) of tumor tissue. The DAR was calculated as follows: DAR = [(pixel count/pixel volume)/(injected radioisotope activity/bodyweight)] \times calibration factor, where the calibration factor denotes the ratio of the counts recorded by the PET camera to those of a well counter. By superimposing a CT scan on the corresponding PET image, we defined a region of interest (ROI) in the tumor tissue and calculated the MRGlu and DAR of \(^{11}\text{C}\)-methionine in the same location. A round ROI 16 to 24 mm in diameter was located in the tumor, depending on the tumor’s size. When the tumor showed enhancement on CT scans, we set the ROI on the enhanced region. When the tumor showed no enhancement on CT scans, we set the ROI on the homogeneous solid component but avoided areas of calcification. We compared the MRGlu and the DAR of \(^{11}\text{C}\)-methionine in the tumors by using linear regression analysis.

### TABLE 1: Clinical data of patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y/ Sex</th>
<th>Location of Tumor</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29/M</td>
<td>L frontal</td>
<td>Astrocytoma grade 2</td>
</tr>
<tr>
<td>2</td>
<td>40/F</td>
<td>R frontal</td>
<td>Astrocytoma grade 2</td>
</tr>
<tr>
<td>3</td>
<td>67/M</td>
<td>R frontotemporoparietal</td>
<td>Astrocytoma grade 2</td>
</tr>
<tr>
<td>4</td>
<td>33/M</td>
<td>R frontal, basal ganglia</td>
<td>Oligodendroglioma grade 2</td>
</tr>
<tr>
<td>5</td>
<td>53/M</td>
<td>R lateral ventricle</td>
<td>Central neurocytoma (low-grade glioma)*</td>
</tr>
<tr>
<td>6</td>
<td>41/F</td>
<td>Brain stem</td>
<td>Meningioma</td>
</tr>
<tr>
<td>7</td>
<td>61/F</td>
<td>Bilateral frontal</td>
<td>Malignant astrocytoma grade 3</td>
</tr>
<tr>
<td>8</td>
<td>57/M</td>
<td>R temporoparietal</td>
<td>Malignant astrocytoma grade 3</td>
</tr>
<tr>
<td>9</td>
<td>31/F</td>
<td>L frontal</td>
<td>Glioblastoma multiforme</td>
</tr>
<tr>
<td>10</td>
<td>54/M</td>
<td>L frontal</td>
<td>Glioblastoma multiforme</td>
</tr>
<tr>
<td>11</td>
<td>67/F</td>
<td>R frontal</td>
<td>Glioblastoma multiforme</td>
</tr>
</tbody>
</table>

* Histology not available. This case was neuroradiologically diagnosed as low-grade glioma.

### TABLE 2: Qualitative and quantitative data from positron emission tomographic studies

<table>
<thead>
<tr>
<th>Patient</th>
<th>Degree of Accumulation in Tumor Tissue</th>
<th>Area of Accumulation in Tumor Tissue</th>
<th>Quantitative Evaluation of Accumulation in Tumor Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FDG Met</td>
<td>MRGlu (mg/100 mL/min) DAR of Met</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>– ++</td>
<td>3.04 2.16</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>– ++</td>
<td>1.81 1.49</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>– +</td>
<td>3.20 1.97</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>– +</td>
<td>2.75 2.24</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>+ +</td>
<td>3.89 1.80</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>– +</td>
<td>3.99 3.29</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>– +</td>
<td>1.97 1.61</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>++ ++</td>
<td>5.84 4.17</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>++ +</td>
<td>3.80 2.22</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>++ +</td>
<td>5.78 3.29</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>++ +</td>
<td>10.40 5.71</td>
<td></td>
</tr>
</tbody>
</table>

Note.—FDG indicates fludeoxyglucose F 18; Met, L-methyl-\(^{11}\text{C}\)-methionine; MRGlu, metabolic rate of glucose; DAR, differential absorption ratio; –, uptake less than in gray matter; +, uptake almost the same as in gray matter; ++, uptake greater than in gray matter; <, markedly less than.
Fig 1. Patient 1. Astrocytoma, grade 2.

A, Unenhanced CT scans (upper) show a round area of low attenuation (short arrows) with a small nodule of calcification (long arrow) in the medial frontal region. Contrast-enhanced CT scans (lower) show faint ringlike enhancement (open arrows) around the mass.

B, PET with FDG scans (upper) show a hypometabolic area in the left medial frontal region (arrows). PET with $^{11}$C-methionine scans (lower) show markedly increased accumulation of $^{11}$C-methionine in the left frontal lobe tumor (arrows).
Fig 2. Patient 8. Malignant astrocytoma, grade 3.

A. Contrast-enhanced T1-weighted gradient-echo MR images (420/10 [repetition time/echo time], 90° flip angle) (upper) show ringlike enhancement around the round mass (long arrow) in the right parietal lobe. T2-weighted spin-echo MR images (3000/90) (lower) show an extensive hyperintense area mainly involving the white matter in the right temporoparietooccipital region (short arrows).

B. PET scans with FDG (upper) show a hypermetabolic focus (long arrow) that corresponds to the enhancing lesion on MR images and a surrounding hypometabolic area. PET scans with 11C-methionine (lower) show an area of 11C-methionine accumulation in the right temporoparietooccipital region (short arrows) extending to the right basal ganglia. Figure continues.
Results

Table 2 summarizes the qualitative and quantitative data for PET with FDG and for PET with $^{11}$C-methionine. PET with FDG showed FDG hypometabolism in tumor tissue as compared with the contralateral gray matter in all patients with low-grade glioma or meningioma except one (patient 5). In patients with high-grade glioma, PET with FDG showed FDG hypermetabolism in the tumors of all patients. Conversely, PET with $^{11}$C-methionine showed equal or increased accumulation in the tumors of all patients regardless of the grade of malignancy (Figs 1–3). The degree of accumulation in the tumor tissue was greater than in the adjacent and contralateral gray matter in nine patients. In the remaining two patients (who had low-grade glioma and meningioma, respectively), the accumulation in the tumor tissue was almost the same as that in the gray matter. In one patient with meningioma, PET with $^{11}$C-methionine showed an increased accumulation in the enhancing part of the tumor but no increase of accumulation in the surrounding edema. In one patient with a low-grade glioma and four patients with high-grade gliomas, PET showed increased tumor accumulation of both tracers, but the area of increased accumulation of $^{11}$C-methionine was larger than that for FDG (Figs 2 and 3).

Quantification of FDG accumulation showed that the MRGlu of high-grade gliomas was significantly higher than that of low-grade tumors ($P < .02$, Student’s $t$ test) (Table 3). The DAR of $^{11}$C-methionine was also significantly higher for high-grade gliomas than for low-grade tumors ($P < .02$, Student’s $t$ test) (Table 3). A good correlation was found between the MRGlu and DAR values of tumor tissue by linear regression ($P < .001$) (Fig 4).

Discussion

PET with FDG has been widely used for the evaluation of many different types of tumor. Since Di Chiro et al (1) used PET with FDG to show that the glucose utilization of tumor tissue was correlated with the degree of malignancy, the clinical usefulness of this technique for brain tumors has been generally accepted. Clinical studies of brain tumors with PET and FDG have shown that it is useful for evaluating tumor grade, selecting a site for stereotaxic biopsy, evaluating the prognosis and the response to treatment, and distinguishing between recurrence and radiation necrosis (18–26).

In this study, PET with FDG showed hypometabolic foci in all but one patient with low-grade glioma and meningioma, and it showed a visible focus of FDG hypermetabolism in four patients with high-grade glioma. PET with FDG was thus helpful for distinguishing between low-grade and high-grade tumors, except in one patient. Malignant glioma, especially glioblastoma multiforme, usually shows regional histologic heterogeneity. Whole-brain sections con-

---

**Fig 2, continued.**

C, Histology of the enhancing lesion in the right parietal lobe on MR imaging revealed grade 3 malignant astrocytoma from the findings of increased cellularity, polymorphism of the tumor cells (short arrows), mitotic figures (long arrow), and proliferation of the blood vessels with glomeruloid appearance (open arrows) (hematoxylin-eosin, magnification $\times200$).

D, Histology of the temporal and occipital lobes gave a diagnosis of low-grade astrocytoma from the presence of tumor cells with nuclear atypism (arrow) (hematoxylin-eosin, magnification $\times200$).
Fig 3. Patient 11. Glioblastoma multiforme.
A, Unenhanced CT scans (upper) show a poorly defined area of low attenuation (closed arrows) with many tiny calcified foci in the right frontal lobe and basal ganglia extending to the corpus callosum. Contrast-enhanced CT scans (lower) show irregular enhancement in the right frontal lobe (open arrows) extending to the left frontal lobe through the corpus callosum.
B, PET with FDG images (upper) show marked FDG hypermetabolism in the right frontal lobe tumor (arrows) extending to the left frontal lobe. The area of increased accumulation of $^{11}$C-methionine (arrows) (lower) is slightly larger than that of FDG, hypermetabolism.
tain a mixture of well-differentiated and poorly
differentiated cells within the same glioblas-
tomamultiforme lesion (27). Although the prin-
cipal features that distinguish low-grade astro-
cytomas from high-grade astrocytomas are
cellularity and pleomorphism (28), Herholz et al
(29) found that tumor cell density was a major
determinant of astrocytoma glucose consump-
tion. As we showed in the present study, meta-
bolic imaging with FDG was useful for detecting
malignant foci in highly heterogeneous tumors.
However, it was difficult to evaluate tumor ex-
tent on PET scans with FDG.

Most reports have stressed that PET with 11C-
methionine can achieve better delineation of
tumor tissue than CT scanning can (4, 5, 30–
32). In this study, PET with 11C-methionine
clearly delineated the tumor extent regardless of

<table>
<thead>
<tr>
<th>Tumor Grade</th>
<th>MRGlu (mg/100 mL/min)</th>
<th>DAR of L-Methyl-11C-methionine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade (n = 7)</td>
<td>3.0 ± 0.9</td>
<td>2.1 ± 0.6</td>
</tr>
<tr>
<td>High grade (n = 4)</td>
<td>6.5 ± 2.8</td>
<td>3.8 ± 1.5</td>
</tr>
</tbody>
</table>

Note.—MRGlu indicates metabolic rate for glucose; DAR, differential absorption rate of L-methyl-11C-methionine. Values are expressed as mean ± standard deviation. The difference between the values for low-grade tumors and the values for high-grade tumors is statistically significant (P < .02, according to Student's t test).

In conclusion, PET with FDG is useful for
detecting malignant tumor foci, and PET with
11C-methionine is useful for the delineation of
tumor extent. Therefore, PET with FDG and PET
with 11C-methionine play a complementary role
in the evaluation of brain tumors, particularly

Fig 4. Correlation between metabolic rate for glucose (MRGlu) and differential absorption ratio (DAR) of L-methyl-11C-
methionine (11C-Met) in tumor tissue.
malignant gliomas and their heterogeneous histology.

Acknowledgments

We thank Yoshitaka Tozawa, BS, for photographic assistance.

References

35. Busch H, Davis JR, Honig GR, Anderson DC, Nair PV, Nyhan WL. The uptake of a variety of amino acids into nuclear proteins of tumors and other tissues. *Cancer Res* 1959;19:1030–1039

