Discrepancy between lesion distributions on methionine PET and MR images in patients with glioblastoma multiforme: insight from a PET and MR fusion image study

K Miwa, J Shinoda, H Yano, A Okumura, T Iwama, T Nakashima, N Sakai

Objective: To examine 11C-methyl methionine (MET) accumulation on positron emission tomographic (PET) imaging of glioblastoma multiforme to determine the distribution of metabolic abnormality compared with magnetic resonance imaging (MRI).

Methods: Contemporaneous MRI was superimposed on corresponding MET-PET images in 10 patients with newly diagnosed glioblastoma multiforme before treatment. Differences between the extended area of MET accumulation on PET imaging (MET area), the gadolinium (Gd) enhanced area on T1 weighted images (Gd area), and the abnormal high signal intensity area on T2 weighted images (T2-high area) were assessed.

Results: The MET area was larger than the Gd area and included the entire Gd area. The discrepancy in volume between the MET and Gd areas became greater with increasing tumour diameter. On average, 58.6% of the MET area was located within the Gd area, 90.1% within 10 mm outside the Gd area, 98.1% within 20 mm, and 99.8% within 30 mm. A newly developed Gd area had emerged in five of the 10 cases up to the time of study. In three of the five cases this was in the MET area even after complete surgical resection of the Gd area on the initial MRI; in the remaining two it originated in the residual Gd area after surgery. In all cases, the T2-high area was larger than the MET area. The MET area extended partly beyond the T2-high area in nine cases, and was completely within it in one.

Conclusions: Glioblastoma multiforme cells may extend over the Gd area and more widely with increasing tumour size on Gd-MRI. The T2-high area includes the greater part of the tumour but not its entire area. The methods reported may be useful in planning surgical resection, biopsy, or radiosurgery.

METHODS

Patient population
Ten patients with newly diagnosed glioblastoma multiforme were studied. Metabolic activity was examined using MET-PET before treatment. In all cases, MRI was carried out at the time of PET imaging, and a pathological diagnosis was made from a tumour specimen obtained during surgery. The investigation was approved by the clinical research committee of our university, and informed consent was obtained from each patient.

PET methods
PET was undertaken with an Advance NXi imaging system (General Electric Medical Systems, Hino-shi, Tokyo, Japan), which provides 35 transaxial images with 5.0 mm intervals. The in-plane spatial resolution (full width at half maximum) was 4.0 mm. Patients were placed in the PET scanner so that slices were parallel to the canthomeatal line. Immobility was checked by alignment of three laser beams with lines drawn on the patient’s face. After a seven minute transmission scan had been obtained, a dose of 370 to 550 MBq (10–15 mCi) of MET was injected intravenously into the cubital vein within one minute. A 10 minute static PET scan was begun 20 minutes after the MET injection. No arterial blood samples were obtained.

MRI methods
A 1.5 T MRI system (Signa Horizon LX; General Electric, Waukesha, Wisconsin, USA) was used to obtain transaxial T1 weighted fast spin echo images (repetition time (ms)/echo time (ms)/number of excitations = 700/10/2) and T2 weighted fast spin echo images (4000/102/2) (FOV 24×24 cm, matrix...
Slice thickness was 6 mm, with a 3 mm slice gap. For contrast enhancement studies, 0.1 mmol/kg body weight of Gd was injected intravenously.

Data analysis
The maximum tumour diameter was defined as the maximum diameter of the area of Gd enhancement on a T1 weighted image (Gd area). The area of increased MET accumulation on PET (the MET area) was defined as the region of an accumulation of MET apparently higher than that of normal grey matter in the occipital lobe, assessed by qualitative visual analysis. The PET and MRI datasets were transferred to a SUN workstation (SPARC MP20; SUN Microsystems, Mountain View, California, USA). Co-registration of MET-PET and MRI was undertaken on the SUN workstation with a commercial software package (Dr View; Asahi Kasei Joho System, Tokyo, Japan), using a method described by Kapouleas and colleagues. Co-registered images provide 35 transaxial slices at 5.0 mm intervals. The size of the area in each slice was automatically calculated using the same software package.

Over the co-registered images, we drew seven lines which outlined the Gd area and 5 mm, 10 mm, 15 mm, 20 mm, 25 mm, and 30 mm beyond the Gd area (fig 1). In each slice, we measured the size of the MET area involved within each outline. Measurements were made by manually outlining the margins of the MET area. The sum of the size of the MET area in each slice was counted, and the size occupation ratio (SOR), accounting for all of the MET area within each outline, was calculated. The SOR was determined using the following equation:

$$\text{SOR} = \frac{\text{MET area}}{\text{total area}}$$

Figure 1  Co-registered $^{11}$C-methyl methionine–positron emission tomography (MET-PET) images and gadolinium (Gd) enhanced T1 weighted magnetic resonance images. Red indicates the MET areas. Upper panel: all transaxial images in which the Gd area was demonstrated. Lower panel: a representative transaxial image with white lines which outline the Gd area, and 5 mm, 10 mm, 15 mm, 20 mm, 25 mm, and 30 mm beyond the Gd area.
SOR (%) of MET area within x mm outside the Gd area = sum of the size of the MET area within x mm outside the Gd area in each slice/sum of the size of the MET area in each slice.

In addition, the distance beyond the Gd area (the MET distance) at which more than 98% of the MET area was occupied was assessed in all cases. We compared the maximum tumour diameter and the MET distance using linear regression analysis.

Subsequently, we estimated the difference in the location and extent between the MET area and the area of high signal intensity on T2 weighted images (T2-high area). The cases were divided into the following two types, based on the relation between the MET area and the T2-high area: type 1,
the MET area partly extended beyond the T2-high area (fig 2); type 2, the MET area was completely within the T2-high area (fig 3).

RESULTS

The results are summarised in table 1. Representative transaxial slices of the cases are illustrated in figs 2 and 3.

Table 1  The relation between the tumour size and the extent of $^{11}$C-methyl methionine (MET) area of the patients with glioblastoma multiforme

<table>
<thead>
<tr>
<th>Case No</th>
<th>Age (years)/sex</th>
<th>Location of tumour</th>
<th>Max tumour diameter (mm)</th>
<th>SOR (%) of MET area within x mm outside Gd area*</th>
<th>Type of relation between MET area and T2-high area†</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0 mm 5 mm 10 mm 15 mm 20 mm 25 mm 30 mm</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>76/M</td>
<td>R frontal</td>
<td>28</td>
<td>70.9 98.4 100 100 100 100 100 100</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>59/F</td>
<td>R temporal</td>
<td>34</td>
<td>63.4 95.6 100 100 100 100 100 100</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>70/F</td>
<td>L frontal</td>
<td>35</td>
<td>75.2 96.1 100 100 100 100 100 100</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>78/F</td>
<td>R frontal</td>
<td>43</td>
<td>59.2 76.5 87.3 98.0 100 100 100 100</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>60/M</td>
<td>L temporal</td>
<td>47</td>
<td>68.6 82.9 93.1 98.3 100 100 100 100</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>69/M</td>
<td>R temporal</td>
<td>57</td>
<td>45.0 69.6 85.9 93.1 100 100 100 100</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>59/M</td>
<td>R frontal</td>
<td>60</td>
<td>54.3 71.5 84.7 92.4 97.3 100 100 100</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>41/M</td>
<td>L temporal</td>
<td>60</td>
<td>54.6 80.0 91.8 96.6 98.5 100 100 100</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>59/M</td>
<td>L frontal</td>
<td>65</td>
<td>47.8 67.1 81.5 89.0 95.9 99.0 100 100</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>66/F</td>
<td>R temporal</td>
<td>73</td>
<td>47.3 65.1 77.5 87.0 92.3 95.6 98.0 100</td>
<td>1</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td></td>
<td></td>
<td>50.2 58.6 80.3 90.1 95.4 98.1 99.4 99.8</td>
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</tbody>
</table>

*SOR (%) of MET area within x mm outside the Gd area = sum of the size of the MET area within x mm outside the Gd area in each slice/sum of the size of the MET area in each slice.

†Type 1, the MET area and T2-high area were not coincident; type 2, the MET area was completely within the T2-high area.

In all cases, the MET area was larger than the Gd area, encompassing it completely. In all but case 10, the MET area was completely located within 30 mm of the Gd area. On average, 58.6% of the MET area was located within the Gd area, 90.1% within 10 mm outside the Gd area, 98.1% within 20 mm, and 99.8% within 30 mm (table 1). The MET distance...

Discrepancy between MET area and Gd area

In all cases, the MET area was larger than the Gd area, encompassing it completely. On average, 58.6% of the MET area was located within the Gd area, 90.1% within 10 mm outside the Gd area, 98.1% within 20 mm, and 99.8% within 30 mm (table 1). The MET distance...
increased with an increase in the maximum tumour diameter, and a significant correlation was found between these variables by linear regression. ($y = 0.535x - 8.865$, $x = \text{maximum tumour diameter (mm)}$, $x > 16.6$, $y = \text{MET distance (mm)}$, $y > 0$) (regression coefficient: $r = 0.975$, $p < 0.001$).

**DISCREPANCY BETWEEN MET AREA AND T2-HIGH AREA**

In all cases, the T2-high area was larger than the MET area. The MET area partly extended beyond the T2-high area (type 1) in nine cases (fig 2), and was completely within the T2-high area (type 2) in one case (fig 3).

**MET AREA AND LOCATION OF TUMOUR RECURRENTNESS**

A newly developed Gd area emerged in five of the 10 cases during their clinical course up to the time of the study. These areas were demonstrated in the MET area even after complete surgical resection of Gd area on the initial MRI in three of the five cases (6, 8, and 9) (fig 2), and originated in the residual Gd area after surgery in the remaining two cases. These newly developed Gd areas were verified as tumour recurrences pathologically at the time of a second operation or at necropsy.

**DISCUSSION**

The use of PET, an imaging technique providing metabolic data, may play an important role in improving diagnostic procedures for determining the extent of malignant gliomas. PET is a radiopharmaceutical that can be used for PET scanning, and accumulation of MET in tissues seems to reflect transmembrane transport, which is influenced by requirements of the cells for protein synthesis precursors; it therefore correlates with tissue proliferation and malignancy.17–19 Because the metabolism of proteins is much greater in tumour cells than in the surrounding brain tissue, PET scanning appears to be a more valuable tool for defining the boundaries of malignant gliomas than abnormal signal intensity on MRI.20–22 However, an accurate assessment of the relationship between the distribution of the metabolic abnormality and that of the signal abnormality on MRI in patients with glioblastoma multiforme has not been reported. Our study addressed these issues by recording tumour margins from PET scanning.

**Figure 4** Correlation between the maximum tumour diameter (MTD) and the distance outside the Gd area (MET distance), at which more than 98% of the MET area was occupied. The hatched line represents a regression line with the equation $y = 0.535x - 8.865$, $x = \text{maximum tumour diameter (mm)}$, $x > 16.6$, $y = \text{MET distance (mm)}$, $y > 0$ (regression coefficient: $r = 0.975$, $p < 0.001$).

Conclusions

Previous PET studies on glioblastoma multiforme have reported that the MET area corresponds well with the area of tumour extension. The results of our study show that glioblastoma multiforme cells may extend beyond the Gd area and more widely with increasing tumour size on Gd-MRI. The T2-high area includes the greater part of glioblastoma multiforme, but does not show the entire area involved, and the evidence that tumour cells extend beyond the T2-high area is strong. The T2-high area beyond the MET area is probably mainly a reflection of peritumoral oedema. The methods discussed in this report could be useful in planning surgical resection, biopsy, or radiosurgery for glioblastoma multiforme.

**Authors’ affiliations**

K Miwa, J Shinoda, H Yano, T Iwama, N Sakai, Department of Neurosurgery, Gifu University School of Medicine, Gifu, Japan
A Okumura, T Nakashima, Chubu Medical Centre for Prolonged Traumatic Brain Dysfunction, Minokamo, Japan

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REFERENCES