Delayed Radiation Necrosis of Brain Evaluated Positron Emission Tomography

TOSHIHIDE OGAWA, KAZUO UEMURA, IWAO KANNO, FUMIO SHISHIDO, ATSUSHI INUGAMI, TATSUO YAMAGUCHI, MATSUTARO MURAKAMI, KENJI HIRATA, TOSHIO KATO, KATSUYOSHI MINEURA† and MASAYOSHI KOWADA†

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OGAWA, T., UEMURA, K., KANNO, I., SHISHIDO, F., INUGAMI, A., YAMAGUCHI, T., MURAKAMI, M., HIRATA, K., KATO, T., MINEURA, K. and KOWADA, M. Delayed Radiation Necrosis of Brain Evaluated Positron Emission Tomography. Tohoku J. exp. Med., 1988, 155 (3), 247-260 — In four patients highly suspected of having delayed radiation necrosis of the brain, regional cerebral blood flow and metabolism were studied by using positron emission tomography (PET) with the 15O-labelled gases, 18F-fluorodeoxyglucose (18FDG). All four patients showed marked decreases in glucose and oxygen consumption in the lesion with that suspected pathology in comparison with those in normal brain parenchyma. Two of them were histologically proved to have radiation injuries (one was radiation necrosis and another was early delayed reactions). But one patient was histologically proved to have a recurrent tumor. Although metabolic study with PET using 18FDG is generally an excellent procedure for differentiation between radiation injuries and recurrent brain tumor, these results imply that in some cases the differential diagnosis is difficult even with 18FDG. The present study demonstrated considerably more pronounced reduction in the metabolism than the decrease of the blood flow in the lesion with radiation necrosis. This result would indicate that the primary effect causing the radiation necrosis is a direct effect of irradiation on neural tissue rather than the capillary damage. —— radiation necrosis; brain; positron emission tomography

x-Ray CT (XCT) offers useful information not only for diagnosis of brain tumors, but also for evaluation of the effect of therapy on malignant brain tumors (Marks and Gado 1977). However, it is often difficult to differentiate radiation
necrosis from a recurrent brain tumor even with XCT. Accordingly, exploratory craniotomy and biopsy have usually been required for correct diagnosis (Brismar et al. 1976; Martins et al. 1977). Patronas et al. (1982) and Di Chiro et al. (1987) reported that positron emission tomography (PET) with $^{18}$F-fluorodeoxyglucose ($^{18}$FDG) is a useful technique for differentiation between radiation necrosis and recurrent brain tumors. Recently, we obtained the same result in regard to radiation necrosis of the brain by using PET with the $^{15}$O-labelled gas steady state inhalation method ($^{15}$O-steady state method) and $^{18}$FDG (Ogawa et al. 1986).

In this study, we examined four patients who were suspected of having radiation necrosis of the brain, by using PET.

We discuss two main subjects. One is differentiation between radiation necrosis and recurrent brain tumors, and the other is the observation of the pathogenesis of radiation necrosis of the brain by analysis using PET. The present study is the first that analyzes functionally the mechanism of radiation necrosis of the brain using PET.

**MATERIALS AND METHODS**

Four patients suspected of having radiation necrosis from clinical information and neuroradiological examinations were included in the study (Table 1). They had been given radiation therapy for malignant brain tumors.

PET was performed parallel to the orbito-meatal (OM) line using Headtome III (Kanno et al. 1985) which gives a transaxial resolution of 9 mm full width at half maximum (FWHM) and the axial resolution of 12 mm FWHM. The Headtome III system has three rings of 160 bismuth germanate oxide detectors and provides five images 15 mm apart with a single scanning. We obtained 10 images 7.5 mm apart by two scanings to image the entire brain.

XCT was also carried out on the same plane as the corresponding PET study with a GE CT/T 9800 scanner. To achieve accurate agreement of the section slices between PET and

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/Sex</th>
<th>Primary tumor</th>
<th>Calculated dose to the enhanced lesion on XCT (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39/M</td>
<td>Astrocytoma grade III (Rt. Front-Parietal)</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>27/F</td>
<td>Medulloblastoma (Rt. Cerebellum)</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>38/M</td>
<td>Olfactory neuroblastoma</td>
<td>110</td>
</tr>
<tr>
<td>4</td>
<td>45/F</td>
<td>Astrocytoma grade III (Rt. Frontal)</td>
<td>70</td>
</tr>
</tbody>
</table>

M, male; F, female.
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XCT, we routinely used a moulded plastic face mask with landmarks (Ogawa et al. 1985). The detailed methodology of the examination is reported elsewhere (Sasaki et al. 1986; Shishido et al. 1987).

By using the $^{15}$O-steady state method (Frackowiak et al. 1980), blood flow (BF), oxygen extraction fraction (OEF), oxygen consumption ($\text{MRO}_2$) and blood volume (BV) were measured quantitatively. OEF was corrected by BV by the method of Lammertsma and Jones (1983). Glucose consumption ($\text{MRGI}$) was calculated by using the $^{15}$FDG method with the Sokoloff model modified by Phelps et al. (1979) neglecting the critical problems of lumped constant and rate constants. The glucose extraction fraction (GEF) was calculated by using the relationship $\text{MRGI} = \text{BF} \times \text{GEF} \times \text{Cp}$. Cp is the measured plasma concentration of the stable glucose (Rhodes et al. 1983).

Functional images by PET in each patient were analyzed by defining the regions of interest (ROIs) for the enhanced lesions on XCT which are thought to be radiation necrosis, for regions of the contralateral hemisphere comparable to the enhanced lesions and for the bilateral insular cortex. By using XCT images as an anatomic guide, ROIs were defined and each of the above values was obtained from the ROIs. The size of the ROIs was 2.56 ~8 cm$^2$ according to the size of the analyzed area.

**RESULTS**

The clinical and XCT findings and quantitative values of tissue BF and metabolism by PET are summarized in Tables 1 and 2. Three of the patients (Cases 1, 3 and 4) presented clinical symptoms 37 months or more after the start of radiation therapy, while one patient (Case 2) showed abnormal findings on XCT without clinical symptoms such as hemiparesis and disturbance of visual field earlier after cessation of radiation therapy. As shown in Table 1, in all of the subjects, XCT revealed an enhanced lesion with a surrounding low attenuation area following infusion of contrast medium. Calcification was found in one case (Case 1). Those XCT findings are not specific to radiation necrosis of the brain. However, high dose areas on dose reconstruction plans of radiation therapy were

<table>
<thead>
<tr>
<th>Elapsed time from completion (start) of radiation</th>
<th>CT findings</th>
<th>Final diagnosis from histological examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 months (82 months)</td>
<td>Contrast enhancement, low attenuation area, calcification</td>
<td>Radiation necrosis</td>
</tr>
<tr>
<td>4.5 months (5.5 months) Low attenuation area</td>
<td>Contrast enhancement</td>
<td>Early delayed reactions</td>
</tr>
<tr>
<td>22 months (37 months)</td>
<td>Contrast enhancement, low attenuation area</td>
<td>Not examined</td>
</tr>
<tr>
<td>93 months (94 months)</td>
<td>Contrast enhancement, low attenuation area</td>
<td>Recurrent tumor (Astrocytoma grade III)</td>
</tr>
<tr>
<td>Case 1</td>
<td>BF (ml/100 ml/min)</td>
<td>MRO₂ (ml/100 ml/min)</td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Enhanced lesion*</td>
<td>17.2</td>
<td>0.79</td>
</tr>
<tr>
<td>Comparable region of C.H.</td>
<td>26.9</td>
<td>1.42</td>
</tr>
<tr>
<td>Insular cortex of I.H.</td>
<td>29.9</td>
<td>1.83</td>
</tr>
<tr>
<td>Insular cortex of C.H.</td>
<td>47.5</td>
<td>2.80</td>
</tr>
<tr>
<td>Case 2</td>
<td></td>
<td></td>
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<tr>
<td>Enhanced lesion</td>
<td>36.9</td>
<td>1.85</td>
</tr>
<tr>
<td>Comparable region of C.H.</td>
<td>45.6</td>
<td>2.89</td>
</tr>
<tr>
<td>Insular cortex of I.H.</td>
<td>46.5</td>
<td>3.49</td>
</tr>
<tr>
<td>Insular cortex of C.H.</td>
<td>50.0</td>
<td>3.53</td>
</tr>
<tr>
<td>Case 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enhanced lesion</td>
<td>31.8</td>
<td>1.44</td>
</tr>
<tr>
<td>Insular cortex of R.H.</td>
<td>52.6</td>
<td>3.64</td>
</tr>
<tr>
<td>Insular cortex of L.H.</td>
<td>51.1</td>
<td>3.42</td>
</tr>
<tr>
<td>Case 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enhanced lesion</td>
<td>55.5</td>
<td>1.17</td>
</tr>
<tr>
<td>Comparable region of C.H.</td>
<td>40.9</td>
<td>2.26</td>
</tr>
<tr>
<td>Insular cortex of I.H.</td>
<td>36.0</td>
<td>2.26</td>
</tr>
<tr>
<td>Insular cortex of C.H.</td>
<td>36.8</td>
<td>2.37</td>
</tr>
</tbody>
</table>

C.H., contralateral hemisphere to the enhanced lesion; I.H., ipsilateral hemisphere to the enhanced lesion; R.H., right cerebral hemisphere; L.H., left cerebral hemisphere; * region of delayed radiation necrosis or suspected delayed radiation necrosis.
Fig. 1. Case 2: A 27 year-old woman with medulloblastoma of the right cerebellar hemisphere. She received post-operative radiation therapy to a total dose of 53 Gy of 10 MV linear accelerator x-ray.  
a: XCT. A pre-contrast XCT performed about 5 months after termination of the radiation therapy (left) shows low attenuation area in the right occipital lobe. The post-contrast XCT (right) shows enhanced nodular lesion in the cuneus of the right occipital lobe.  
b: Isodose curve. Isodose curves show the right occipital lobe irradiated 50 to 55 Gy. The high dose area corresponds to the enhanced lesion with surrounding low attenuation area on XCT.
c: PET. MRO$_2$ and MRGI in the enhanced lesion on XCT are much low in comparison with those of the comparable region of the contralateral cortex. On the other hand, the decrease of BF of the lesion is slight and OEF and GEF are reduced.

d: Histology. Microscopic section of the enhanced lesion shows no tumor cells and mainly moderate demyelination with decrease of oligodendroglia and proliferation of astrocyte. Vascular damage is not prominent. These findings are compatible with early delayed effect. (Elastica Masson stain $\times 100$)
Fig. 2. Case 4: A 45 year-old woman with astrocytoma grade III of the right frontal lobe. She was treated with surgical extirpation and radiation therapy to a total dose of 67.5 Gy using $^{60}$Co $\gamma$-ray about 9 years ago.

a: XCT. A pre-contrast XCT performed about 9 years after termination of radiation therapy (left) shows a low attenuation area of the right fronto-temporal lobe adjacent to the previous tumor bed. The post-contrast XCT (right) shows the enhanced lesion in the right putamen and in the temporopolar region.

b: Isodose curve. Isodose curves show the right putamen and right temporopolar region that received a radiation dose of 70 Gy and correspond to the enhanced lesion on XCT.
consistent with the enhanced lesions with surrounding low attenuation areas on XCT in all of the subjects.

From the quantitative assessment of the PET studies (Table 2), MRO$_2$ (0.79 ~ 1.85 ml/100 ml/min) and MRGl (2.76 ~ 4.55 mg/100 ml/min) of the enhanced lesions on XCT were markedly decrease in comparison with those of the region (MRO$_2$, 1.42 ~ 2.89 ml/100 ml/min; MRGl, 5.14 ~ 6.62 mg/100 ml/min) of the contralateral hemisphere comparable to the enhanced lesion and those of structurally normal gray matter (MRO$_2$, 1.83 ~ 3.64 ml/100 ml/min; MRGl, 5.16 ~ 8.99 mg/100 ml/min). BF (17.2 ~ 36.9 ml/100 ml/min) of the lesions also decreased except in one case (Case 4; BF, 55.5 ml/100 ml/min), while BV (3.39 ~ 7.51 ml/100 ml) was not different from the region (BF, 26.9 ~ 45.6 ml/100 ml/min; BV, 3.61 ~ 6.11 ml/100 ml) of the contralateral hemisphere comparable to the enhanced lesion and structurally normal gray matter (BF, 29.9 ~ 52.6 ml/100 ml/min; BV, 3.55 ~ 8.15 ml/100 ml). On each patient, OEF (0.14 ~ 0.33) and GEF (0.07 ~ 0.19) of the lesions showed lower values than those of the region (OEF, 0.33 ~ 0.42; GEF, 0.15 ~ 0.23) of the contralateral hemisphere comparable to the enhanced lesion and those of structurally normal gray matter (OEF, 0.36 ~ 0.50; GEF, 0.14
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As compared with the values in gray matter of normal volunteers (Mineura et al. 1986) (OEF, 0.42±0.07 (n=21); GEF, 0.22±0.03 (n=14); mean±s.d., GEF, unpublished data), these values of the lesions were remarkably low. This decrease of OEF and GEF in the lesions can be interpreted as pronounced reduction of metabolism in comparison with decrease of BF. This tendency of marked impairment of metabolism with a slight decrease in BF was marked in Case 2 (Fig. 1). Case 1 and Case 2 were proved histologically to be of radiation necrosis and early delayed reaction respectively. In Case 3 surgical intervention was not performed, but follow up CT performed 49 months after start of radiation therapy showed no interval changes in comparison with that of 37 months. That lesion was compatible with radiation necrosis. Case 4 (Fig. 2) showed high BF with low MRO₂ and MRGl in the lesion compared with structurally normal gray matter. Surgical intervention disclosed that the lesion was a recurrent tumor (astrocytoma grade III).

DISCUSSION

In general, the adverse effects of irradiation on the human brain have been divided in three groups according to time of appearance: 1) acute reactions that can occur during a course of irradiation; 2) early delayed reactions that appear a few weeks to months after irradiation; 3) late delayed reactions (radiation necrosis) that typically appear from several months to many years later (Sheline 1980). Among them, radiation necrosis is the major hazard to the central nervous system and is generally irreversible and frequently progressive.

Since Fischer and Hohlfelder (1930) first described a case of radiation necrosis of the human brain in 1930, many clinical and experimental studies on this subject have been presented (Davidoff et al. 1938; Pennybacker and Russell 1948; Crompton and Layton 1961; Zeman 1963; Lampert and Davis 1964; McDonald and Hayes 1967; Rubinstein 1972; Kramer and Lee 1974; Nakazaki et al. 1976; Martins et al. 1977; Mikhail 1978; Reinhold and Hopewell 1980; Sundaresan et al. 1981; Safdari et al. 1985; Dooms et al. 1986; Jellinger 1986). The incidence of delayed radiation necrosis of the brain reported from clinical-materials varies from 1.5 to 25% (Sundaresan et al. 1981; Safdari et al. 1985; Jellinger 1986). This wide variation would be related to the limit of tolerance of normal brain tissue for any variation in radiation therapy schedule including total radiation dose, fractionation, dose per fraction and so on. Practically, it is hard to determine the exact incidence of the radiation induced lesion, because many patients die of their primary brain tumor before the development of post-radiation damage in the brain. However, radiation necrosis is now becoming a more serious problem, in accordance with improvement in performance by advances in radiation therapy, such as heavy particle beams, fast neutron therapy and so on.
Differential diagnosis

It has been generally accepted that differentiation between radiation necrosis including early delayed effect and recurrent or residual brain tumors is very difficult, because of nonspecific findings of this lesion provided by various neuro-radiological procedures inducing XCT (Crompton and Layton 1961; Kramer and Lee 1974; Brismar et al. 1976; Marks and Gado 1977; Martins et al. 1977; Mikhael 1978; Sundaresan et al. 1981). For the differential diagnosis of the lesion, Mikhail (1978) emphasized the importance of the correlation between the XCT findings and zones of high radiation dose shown by dose reconstruction plans. Dooms et al. (1986) reported that a recurrent of residual brain tumor could not be distinguished from radiation necrosis even by magnetic resonance imaging.

Energy metabolism of neural tissue, such as MRO$_2$ and MRGl studied by PET, reflect the activity of the tissue. In this respect, necrosis of neural tissue should cause a marked decrease in tissue metabolism, while it has been shown by Di Chiro et al. (1982) and by Ogawa et al. (1984) and Mineura et al. (1986) using PET that MRGl of tumor tissue increases according to the malignancy of the tumor. Moreover, on the basis of the results of a pretreatment tumor study, we have simultaneously analyzed the effect of radio-chemotherapy on the tumor tissue and structurally normal brain tissue (Ogawa et al. 1988). In that study, MRGl of tumor tissue was reduced significantly following radio-chemotherapy. Using PET and $^{18}$FDG, Patronas et al. (1982) showed that MRGl in recurrent tumors was accelerated, while that in the tissue with radiation necrosis was less than that in the normal brain parenchyma. Di Chiro et al. (1987) stress, from the analysis of PET with $^{18}$FDG in 95 patients referred for the purpose of differentiating recurrent tumor from radiation necrosis, they have not yet been confronted with a false-positive or a false-negative diagnosis of radiation necrosis. In the present series, all of the four subjects who were suspected of having radiation necrosis showed a marked decrease in MRO$_2$ and MRGl in the suspected lesion compared to those of normal brain tissue on XCT. Two of them (Cases 1 and 2) were later histologically proved to have radiation necrosis and early delayed effects respectively, but one patient (Case 4) was histologically proved to have a recurrent tumor. Generally, PET with $^{18}$FDG is an excellent procedure for differentiation between radiation necrosis including early delayed effects and a recurrent tumor. However, these results can be interpreted as follows. When we look at the increased MRGl in the lesion -hot spot-, concerning differentiation between a recurrent tumor and radiation necrosis, we can easily understand it to be a recurrent tumor. But when we look at the decreased MRGl-in the lesion -cold spot-, we cannot deny the possibility of a recurrent tumor such as relatively slow growing tumor. We stress that even with $^{18}$FDG the differential diagnosis would be hard in some case (Case 4).
Mechanism producing delayed radiation necrosis

In spite of abundant literature in the radiation induced lesions in the brain tissue, the mechanism producing this pathology has not been fully understood. Some authors believe that the basic mechanism of this necrosis is direct damage to the neural parenchyma caused by radiation (Davidoff et al. 1938), but many more investigators emphasize that the primary site of radiation damage is capillary endothelial cells and that vascular destruction plays the principal role in the development of the necrosis (Pennybacker and Russell 1948; McDonald and Hayes 1967; Rubinstein 1972). Since clinical manifestation of radiation necrosis usually requires several months or years after the cessation of radiation therapy, some investigators have suggested that the basic mechanism of that necrosis is based on an autoimmune mechanism (Crompton and Layton 1961). Most of the hypotheses mentioned above are based on histopathological observation; however, functional change of neural tissue, which may precede the morphological change, have not been studied.

In the present study, regional MRO$_2$ and MRGl were measured in combination with regional BF study. In our observations, the lesions with radiation necrosis (Case 1) and probable radiation necrosis (Case 3) showed not only marked decrease in MRO$_2$ and MRGl but relatively mild reduction of BF. This was obvious from decrease of OEF and GEF in the lesions. Especially, in Patient 2, who suffered from radiation injury relatively early (4 months) after the radiation therapy, reduction of the BF of the lesion was slight compared with the decrease in MRO$_2$ and MRGl. If one considers that vascular damage plays a significant role in developing radiation necrosis, the regional BF of the lesion should decrease initially. We have studied the early effects of radio-chemotherapy on tissue BF and metabolism in structurally normal brain tissue irradiated with more than 30 Gy (Ogawa et al. 1988). The BF of structurally normal brain tissue did not show significant changes compared with the pretreatment study, while its MRGl significantly decreased within a month after the completion of the therapy. This result implies that radio-chemotherapy initially affect tissue metabolism rather than tissue circulation. This tendency of marked impairment of metabolism with relatively slight decrease of BF was also preserved in early delayed reactions (Case 2) and radiation necrosis (Cases 1 and 3). Though acute reactions and early delayed reactions are generally transient, they can be severe and in some fatal. Matsutani (1987) questions from the observation of clinical symptoms and CT findings whether early delayed reactions are essentially differentiated pathological entity from radiation necrosis. We can easily expect that some patients suffered from acute and early delayed reactions lead to radiation necrosis. The results obtained by the present study would indicate that radiation effects on the neural tissue rather than the capillary endothelial cells primarily play an important as pathogenesis of radiation necrosis. In patients whose PET study for examination
for radiation necrosis was carried out considerably after the cessation of the radiation therapy, the BF of the lesion was also reduced markedly (Cases 1 and 3). Vascular damage would be manifested after the neural tissue injury and would play an important role in progression of radiation necrosis. Our speculation described above could be confirmed by the observation of BF and metabolism of brain normal tissue in patients followed up for a long time after radiation therapy. These observations may be useful not only for the early diagnosis of this pathological condition but for considering how to prevent radiation necrosis.

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References


