Methionine positron emission tomography of recurrent metastatic brain tumor and radiation necrosis after stereotactic radiosurgery: is a differential diagnosis possible?

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**Object.** In this study the authors examined how to differentiate radiation necrosis from recurrent metastatic brain tumor following stereotactic radiosurgery by using positron emission tomography (PET) with \( \text{L-[methyl-}^{11}\text{C}] \)methionine (MET).

**Methods.** In 21 adult patients with suspected recurrent metastatic brain tumor or radiation injury, MET-PET scans were obtained. These patients had previously undergone stereotactic radiosurgery and subsequent contrast-enhanced magnetic resonance (MR) examinations before nuclear medicine imaging. Positron emission tomography images were obtained as a static scan of 10 minutes performed 20 minutes after injection of 370 MBq of MET. On MET-PET scans, the portion of the tumor with the highest accumulation of MET was selected as the region of interest (ROI), and the ratio of tumor tissue to normal tissue (T/N) was defined as the mean counts of radioisotope per pixel in the tumor divided by the mean counts per pixel in normal gray matter. The standardized uptake value (SUV) was calculated using the same ROI in the tumor. The accuracy of the MET-PET scan was evaluated by correlating findings with results of subsequent histological analysis (11 cases) or, in cases in which surgery or biopsy was not performed, with subsequent clinical course and MR imaging findings (10 cases).

Histological examinations performed in 11 cases showed viable tumor cells with necrosis in nine and necrosis with no viable tumor cells in two. Another 10 cases were characterized as radiation necrosis because the patients exhibited stable neurological symptoms with no sign of massive enlargement of the lesion on follow-up MR images after 5 months. The mean T/N was 1.15 in the radiation necrosis group (12 cases) and 1.62 in the tumor recurrence group (nine cases). The mean SUV was 1.78 in the necrosis group and 2.5 in the recurrence group. There were statistically significant differences between the recurrence and necrosis groups in T/N and SUV. Furthermore, the borderline T/N value was 1.42 according to a \( 2 \times 2 \) factorial table (high T/N or low T/N, recurrence or necrosis). From this result, the sensitivity and specificity of MET-PET scanning in detecting tumor recurrence were determined to be 77.8 and 100%, respectively.

**Conclusions.** The use of MET-PET scanning is a sensitive and accurate technique for differentiating between metastatic brain tumor recurrence and radiation necrosis following stereotactic radiosurgery. This study reveals important information for creating strategies to treat postradiation reactions.

**Key Words • metastasis • tumor recurrence • positron emission tomography • stereotactic radiosurgery • radiation necrosis**

**Abbreviations used in this paper:** BBB = blood–brain barrier; FDG = \([^{18}\text{F}]\)fluorodeoxyglucose; GFAP = glial fibrillary acidic protein; GKS = gamma knife surgery; HMPAO = hexamethylpropyleneamine oxime; LCA = leukocyte common antigen; MET = \( \text{L-[methyl-}^{11}\text{C}] \)methionine; MR = magnetic resonance; PET = positron emission tomography; ROI = region of interest; SPECT = single-photon emission computerized tomography; SUV = standardized uptake value; T/N = tumor/normal tissue.

COMPUTERIZED tomography, MR imaging, and SPECT scanning are essential in the evaluation of metastatic brain tumors. Nevertheless, a differential diagnosis between tumor recurrence and radiation necrosis is difficult after radiotherapeutic treatment of brain tumors by using these modalities. Authors of some published reports have shown that PET scanning with the aid of MET is effective in differentiating recurrent glioma from radiation-induced changes and can provide early detection of a recurrence. The purpose of this study was to evaluate the clinical usefulness of MET-PET scanning for the differentiation of recurrent metastatic brain tumor from radiation necrosis.

**Clinical Material and Methods**

**Patient Population**

Twenty-nine patients, ranging in age from 41 to 70 years (mean 58.6 years), each with a metastatic brain tumor, were included in this study. Twenty-one patients who had undergone stereotactic radiosurgery (gamma knife or X-knife) were at high risk of tumor recurrence based on MR imaging findings (Table 1). The dose applied to the tumor mar-
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**TABLE 1**
Characteristics of 21 patients harboring brain tumors

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Tumor Location</th>
<th>Max Tumor Diameter (mm)</th>
<th>201Tl-SPECT Tumor Uptake</th>
<th>Follow Up (mos)</th>
<th>Tumor Origin</th>
<th>Histological Dx</th>
<th>Op or Biopsy After PET</th>
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* Adeno = adenocarcinoma; BG = basal ganglia; cer = cerebellar; Dx = diagnosis; N = necrosis; ND = not done; occip = occipital; R = recurrence; RCC = renal cell carcinoma; SCC = squamous cell carcinoma; SMCC = small cell carcinoma; SRS = stereotactic radiosurgery; temp = temporal; + = high uptake.

**TABLE 2**
Characteristics of eight patients who underwent MET-PET scanning before treatment

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Tumor Location</th>
<th>Max Tumor Diameter (mm)</th>
<th>SUV</th>
<th>T/N</th>
<th>Histological Dx</th>
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* HCC = hepatocellular carcinoma.
mean (SEM). The T/N value was 1.15 ± 0.22 (SEM 0.06) in the radiation necrosis group (12 patients), and 1.62 ± 0.28 (SEM 0.09) in tumor recurrence group (nine patients).

Transverse, coronal, and sagittal scans were assessed qualitatively for areas of abnormal tracer uptake. Such areas were graded as either positive or negative for abnormality on the basis of visual analysis. In addition, an ROI was located over the area of maximal 201 Tl activity demonstrated on transaxial scans as well as the same size ROI over the contralateral portion. The 201 Tl index was defined as the ratio between the mean counts of radioisotope per pixel in the tumor ROI and the mean counts in the contralateral ROI. Interpretations of the scans were performed by two experienced nuclear medicine radiologists.

**Histological Analysis**

For histological studies, all sections were stained with hematoxylin and eosin. In Cases 10 and 11, sections were immunostained for GFAP and LCA.

**Statistical Analysis**

The T/N and SUV in both the pretreatment group and the recurrence group were compared using the Mann–Whitney U-test. Furthermore, T/N and SUV in the tumor recurrence and necrosis groups were compared using the Mann–Whitney U-test.

We chose arbitrary values of T/N and SUV and divided patients into two groups of above or below the value (high and low groups). We constructed a 2 × 2 factorial table and calculated the probability value by using the Fisher exact test. We found that the lowest probability values corresponded with the borderline values of T/N and SUV for recurrence and necrosis.

Values are expressed as the means ± standard deviation, unless noted otherwise. The level of significance was defined as a probability value less than 0.05.

**Results**

Clinical summaries and PET scanning results are shown in Tables 1 and 2. The uptake of MET in the frontal lobe in the 20 healthy volunteers showed no laterality, and the mean SUV was 1.36 ± 0.29. In the 29 patients with tumor, the SUV in the contralateral (side without tumor) frontal lobe gray matter was 1.46 ± 0.39. There was no significant difference between the healthy volunteers and patients harboring tumor with regard to the SUV in the frontal lobe.

The results of the 21 patients who underwent stereotactic radiosurgery are shown in Table 1. Eleven patients (Cases 1–11) underwent biopsy or surgical resection after radiosurgery. Nine (Cases 1–9) of them were histologically proven to have tumor recurrence. In the patients in Cases 1 and 7, there were few tumor islands within the necrotic tissue. The patients in two cases (10 and 11) were histologically proven to have radiation necrosis with no viable tumor cells, and there was no sign of recurrence at the MR imaging and clinical follow up after more than 5 months post-PET scanning. In these two cases, samples stained negative for GFAP. Samples stained positive for LCA only in Case 10. Ten other patients (Cases 12–21) not subjected to histological analysis were determined to have radiation necrosis; these patients had stable neurological symptoms and no massive enlargement of the lesion on MR images more than 5 months after PET scanning (mean follow-up period 8.8 months). The T/N ranged from 0.61 to 1.41 (mean 1.15 ± 0.22) in the radiation necrosis group (Cases 10–21) and from 1.29 to 2.05 (mean 1.62 ± 0.28) in the tumor recurrence group (Cases 1–9). The SUV ranged from 0.97 to 2.71 (mean 1.78 ± 0.47) in the necrosis group and from 1.91 to 4.34 (mean 2.5 ± 0.74) in the recurrence group.

In the eight patients who underwent pretreatment MET-PET scanning (Cases 22–29) the T/N ranged from 1.74 to 3.58 (mean 2.24 ± 0.64) and the SUV from 1.58 to 4.99 (mean 2.64 ± 1.08). The degree of MET uptake was not dependent on the histological type of tumor.

There was a significant difference in the T/N (p = 0.027) between the pretreatment group (Cases 22–29) and the recurrence group (Cases 1–9), but none in the SUV. In contrast, there were more significant differences between the recurrence and necrosis groups in both the T/N (p = 0.0006; Fig. 1) and SUV (p = 0.0095).

In terms of visible accumulation of MET, results of MET-PET studies did not demonstrate high accumulation in two cases (1 and 7) in the recurrence group, but showed visible accumulation in two cases (10 and 19) in the necrosis group. The lowest probability value was 0.0003, which related to the borderline T/N value of 1.42 in comparing the recurrence and necrosis groups (Table 3). For SUV, the lowest probability value was 0.03 and the borderline SUV was 2.03 (Table 3). The sensitivity of both the T/N and SUV was found to be 77.8%, and the specificity of T/N and SUV was 100 and 75%, respectively.
In 17 of the 21 patients who had undergone stereotactic radiosurgery, $^{201}$TI-SPECT scanning results demonstrated visible accumulation in lesions and there was no significant difference between recurrence and necrosis groups.

**Illustrative Cases**

**Case 1**

This 70-year-old woman had been treated for metastatic tumor around the left basal ganglion (adenocarcinoma originating in the lung) by using GKS. Thirty-seven months after that treatment, follow-up MR images revealed an enlarging enhanced lesion (Fig. 2 left). A $^{201}$TI-SPECT scanning demonstrated this lesion to be a high-uptake area. An MET-PET study revealed slight visible accumulation and a somewhat elevated T/N of 1.29 (Fig. 2 center). From PET images we were unable to distinguish necrosis from recurrence, and the tumor was removed. After resection, histological analysis revealed a small tumorous lesion within the necrosis (Fig. 3). This case was classified as a tumor recurrence.

**Case 2**

This 67-year-old woman had been treated for a left parietal metastatic tumor (adenocarcinoma originating in the lung) by using GKS. By 12.5 months after treatment, follow-up MR images revealed an enlarging enhanced lesion (Fig. 4 left). Results of $^{201}$TI-SPECT scanning demonstrated this lesion as a slight-uptake area ($^{201}$TI index 1.46; Fig. 4 right), and MET-PET studies confirmed increased uptake and a T/N of 1.41 (Fig. 4 right). According to PET findings, the lesion was a tumor recurrence and thus it was removed. Histological analysis showed necrosis with vascular proliferation and no viable tumor cells (Fig. 7 left). Staining with LCA showed positive findings (Fig. 7 right). This suggests a visually false-positive case. This patient had no recurrence at follow-up MR imaging more than 5 months after PET scanning.

**Case 10**

This 66-year-old woman had been treated for a right frontal lobe metastatic tumor (adenocarcinoma originating in the lung) by using GKS. Sixteen months after treatment, follow-up MR images revealed an enlarging enhanced lesion (Fig. 6 left), and her left motor weakness was worsening. A $^{201}$TI-SPECT scan demonstrated this lesion as a high-uptake area (Fig. 6 center), and MET-PET studies confirmed increased uptake and a T/N of 1.41 (Fig. 6 right). According to PET findings, the lesion was a tumor recurrence and thus it was removed. Histological analysis revealed necrosis with vascular proliferation and no viable tumor cells (Fig. 7 left). Staining with LCA showed positive findings (Fig. 7 right). This suggests a visually false-positive case. This patient had no recurrence at follow-up MR imaging more than 5 months after PET scanning.

**Case 12**

This 65-year-old man noticed right hemiparesis during treatment for lung cancer (adenocarcinoma), and a left parietal metastatic tumor was observed. He was treated with...
gamma knife radiation. Thirteen months after the radiation treatment, follow-up MR images revealed an enlarging enhanced lesion (Fig. 8 left). A $^{201}$Tl-SPECT scan demonstrated this lesion to be a high-uptake area ($^{201}$Tl index 5.2; Fig. 8 right); however, MET-PET studies revealed the same area as having decreased uptake and a low T/N ratio (0.98; Fig. 8 center). Results of PET scanning indicated that the lesion was radiation necrosis. After 16 months of follow up, MR images revealed no extensive enhanced lesions and neurological findings were improved. This case was defined as radiation necrosis.

**Discussion**

Postradiation reactions in the central nervous system are well described in conventional radiotherapy literature; they can be classified as acute, early-delayed, and late-delayed reactions. Following radiosurgery, acute reactions occur in the same manner as those described following conventional radiotherapy. These reactions include a transient swelling phenomenon caused by vasogenic edema that occurs 12 to 48 hours after therapy; this is fully reversible and not associated with long-term neurological damage. Early-delayed reactions occur from a few weeks to several months later than the subacute reactions following conventional fractionated radiotherapy or radiosurgery. This is probably due to temporary demyelination and vascular damage and may prove fully or partially reversible, or it may progress to permanent sequelae. Tumor swelling sometimes occurs in the early-delayed phase and is associated with edema in

![Fig. 4. Case 2. Left: An MR image demonstrating an abnormal enhanced lesion in the left parietal lobe. Center: A $^{201}$Tl-SPECT scan exhibiting accumulation in the lesion (T/N 1.95). Right: A $^{201}$Tl-SPECT scan revealing slight accumulation in the lesion ($^{201}$Tl index 1.46).](image1)

![Fig. 5. Case 2. Photomicrograph of a tissue section showing viable tumor cells. H & E, original magnification × 125.](image2)
the surrounding normal brain. Tumor shrinkage occurs later, with subsidence of the surrounding edema. Similarly, contrast enhancement at this time, particularly in the tumor perimeter, reflects a host reactive response and not tumor activity. Sometimes, it is not easy to distinguish this phenomenon and tumor recurrence. Persistent clinical neurological signs and MR imaging changes (best demonstrated on T2-weighted sequences) beyond 2 years indicate late damage or reaction. In the first stages, it is difficult to determine whether this response is tumor recurrence or radiation necrosis based on MR imaging, computerized tomography scanning, and other clinical studies. Late-delayed reactions that typically appear from several months to many years posttreatment are irreversible and frequently progressive. Regardless, the development of reactions is uncommon, because stereotactic radiosurgery involves the use of high doses of radiation administered in one or two fractions to very limited volumes of brain tissue.

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Fig. 6. Case 10. Left: An MR image revealing an enhanced lesion in the right frontal lobe. Center: An MET-PET scan revealing increased uptake in the lesion and a high T/N ratio (1.41). Right: A 201 Tl-SPECT scan demonstrating this lesion to be a high-uptake area.

Fig. 7. Case 10. Photomicrographs of tissue sections demonstrating necrosis with vascular proliferation and no viable tumor cells (left) and many LCA-positive cells (right, arrows). H & E, original magnification × 100 (left); LCA, original magnification × 100 (right).
jury, a differential diagnosis is difficult in some cases of recurrent brain tumor with FDG hypometabolism.

In contrast to FDG, background uptake of amino acids in normal brain tissue is low, providing good contrast with tumor uptake. Most amino acid studies have been performed on brain tumors, usually with MET-PET scanning. Note that MET-PET scanning has been reported to be a useful technique in differentiating tumors from nontumorous tissue, detecting recurrent or residual tumors, distinguishing tumors from treatment-induced lesions, and correlating with the tumor’s histological grade in glioma. The MET-PET images can demonstrate the existence of tumorous cells, even in a small tumor, with the lesion being characterized by a marked uptake of MET; however, an increased uptake of MET has occasionally occurred in brain hematoma and in necrotic areas caused by radiation therapy performed to treat brain tumors. Ogawa, et al. reported that the combined use of MET- and FDG-PET scanning can improve the accuracy in diagnosis of recurrent brain tumor and radiation injury. They showed that lesions characterized by hypometabolism of FDG and a high uptake of MET were recurrent tumors, and that lesions with hypometabolism of FDG and the same degree of MET uptake as that in contralateral cortical tissue were indicative of radiation injury. Nonetheless, it is actually difficult to obtain both FDG- and MET-PET images during the same period. On the other hand, Sonoda, et al. reported that the ratio of tumor tissue to contralateral gray matter on MET-PET scans of recurrent glioma was significantly higher than that of radiation necrosis.

In our study, first, there was no significant difference between healthy and tumor groups in MET uptake (SUV) in the frontal lobe cortex (nonlesion side). This may indicate that metabolism of contralateral cortex is not affected by tumor invasion and radiosurgery. If the SUV of cortex on the nonlesional side is changeable, the T/N value may not make sense. Second, the significant difference in the T/N ratio between the pretreatment group and the recurrence group may suggest that MET uptake into recurrent tumor region is lower than that in the primary region, because of a recurrent tumor growing in a radiation-injured region. Finally, our results demonstrated that there were significant differences between recurrence and necrosis groups in T/N ratio and SUV. From these results, we can assert that MET-PET scanning is useful in differentiating metastatic brain tumor from radiation necrosis.

Based on MET-PET scanning results, we thought that two cases (1 and 7) were visually false negative, and another two (10 and 19) were visually false positive. It may be difficult to distinguish high or low uptake of MET, however, because visual evaluation is subjectively analyzed. On the other hand, the T/N ratio or SUV is objectively analyzed. We were able to estimate the borderline T/N ratio and SUV value between recurrence and necrosis groups by constructing a 2 × 2 cross table and calculating the probability value by using the Fisher exact test. We found that the lowest probability value corresponded to a borderline T/N ratio of 1.42 and an SUV of 2.03. Table 3 shows two false-negative and no false-positive cases with regard to T/N, and two false-negative and three false-positive cases with regard to SUV. We believe that T/N ratio is superior to SUV as useful objective analysis. Given the high specificity of MET-PET scanning, if PET studies display high uptake (> 1.42 T/N) of MET in postradiation reactions in some cases, we may be able to perform a second stereotactic radiosurgery and consider the lesion as a tumor recurrence without surgical procedures.

The mechanism of the accumulation of MET remains unclear. The causes for its accumulation are thought to be increased protein synthesis by proliferative cells, active carrier-mediated transport across the cell membrane, disruption of the BBB, and high vascular density. On the basis of their results in an experimental study, Kubota, et al., have reported that MET-PET studies were used to differentiate inflammation from tumor. On the other hand, Ishii, et al., have speculated that the mechanism of MET uptake in brain abscess was due to increased metabolism and active amino acid transport due to the increased density of inflammatory cells as well as the disruption of the BBB arising from the discrepancy between the area of MET uptake and the Gd-enhanced lesion as revealed on MR images. Disruption of the BBB may not be necessary for increased MET uptake.
uptake, especially given that high uptake of MET has been observed in low-grade glioma in which the BBB is intact. In the late phase of radiation injury, vascular changes are well characterized. There is proliferation of endothelial cells and fibroblasts, as well as a perivascular inflammatory response characterized by the presence of lymphocytes, plasma cells, and macrophages. Inflammation occurs during the latent period up to the onset of late radiation-induced injury. Furthermore, the radiation-induced astrocytic and microglial responses that follow brain radiation are indicative of reactive gliosis. Iwai, et al., reported on a case microglial responses that follow brain radiation are indicative of reactive gliosis. MET-PET studies did not show high accumulation because tissue in two false-negative cases (1 and 7). We surmise that the accumulation of MET in tissue with the mechanism of uptake was reactive gliosis, and LCA as the marker of inflammation (reacting macrophages and histiocytes) in two cases of necrosis (10 and 11). In the patient with false-positive results (Case 10), we detected many LCA-positive cells in the necrotic lesion, but no positive finding of GFAP in those lesions. The accumulation of MET in tissue with radiation injury is certainly thought to be related to disruption of the BBB and vascular proliferation. Given our findings, however, we think that the cause can be attributed to not only the disrupted BBB and vascularity, but also an inflammatory response. On the other hand, we observed viable tumor cells forming a small tumor island in necrotic tissue in two false-negative cases (1 and 7). We surmise that MET-PET studies did not show high accumulation because of the low density of tumor cells.

Note that 201Tl-SPECT scanning is reported to be as effective as PET scanning in distinguishing radiation necrosis from brain tumor recurrence. Kline, et al., showed that its sensitivity and specificity in cases in which gamma knife therapy was used were 92 and 67%, respectively. In fact, increased 201Tl uptake has been observed in radiation necrosis and inflammatory infectious processes. The use of thallium-201 in brain SPECT studies has been shown to be a sensitive, but relatively nonspecific, imaging modality in the evaluation of brain tumors. Nonneoplastic lesions with BBB disruption, including radiation necrosis, postsurgical inflammatory changes, hematomas, infarcts, and abscesses can also show increased 201Tl uptake. Sonoda, et al., reported that there was no significant difference between radiation necrosis and tumor recurrence in 201Tl-SPECT index. Schwartz, et al., however, reported that dual-isotope (201Tl and 99mTc-HMPAO) SPECT scanning is useful to distinguish between recurrent glioma and radiation necrosis. High 201Tl uptake in the treated tumor bed indicated local tumor recurrence, and low 201Tl uptake indicated radiation necrosis. In cases of an intermediate level of 201Tl uptake, HMPAO uptake differentiated between cases with active tumor and those without; increased perfusion showed local recurrence, and decreased perfusion showed no recurrence. In our study, 201Tl-SPECT scanning tended to demonstrate both radiation necrosis and tumor recurrence as lesions with increased accumulation.

Conclusions

We demonstrated that there were significant differences between the recurrence and necrosis groups on MET-PET scanning. Furthermore, the sensitivity and specificity were 77.8 and 100%, respectively, when the borderline T/N ratio was 1.42. Results of MET-PET studies matched the clinical diagnoses and is useful in differentiating metastatic brain tumor from radiation necrosis. In this study we presented important information for creating strategies to treat postradiation reactions.

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