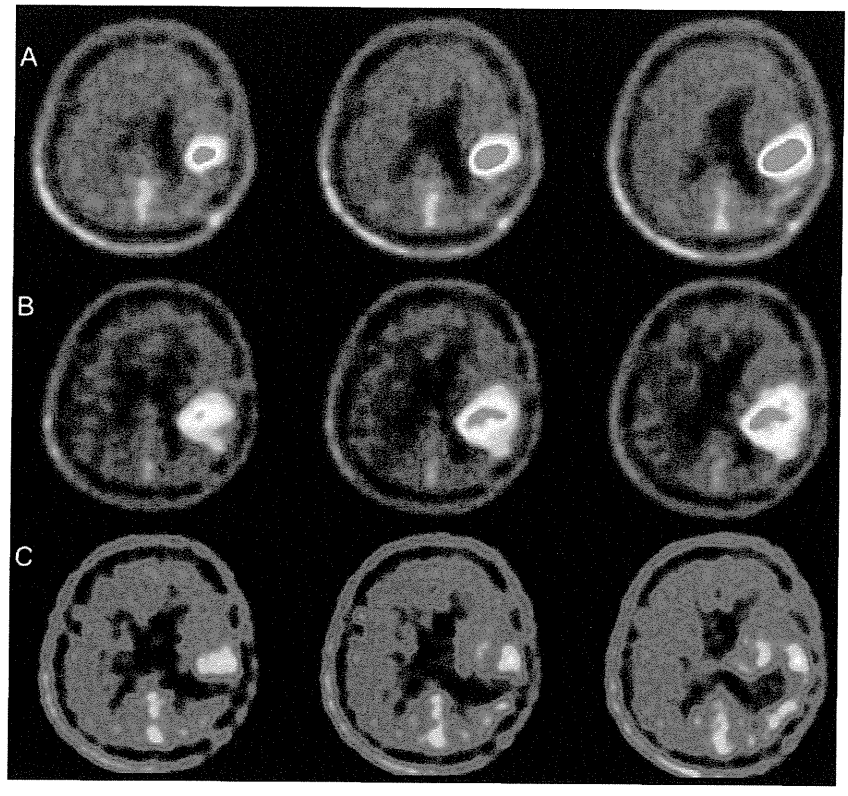

Fig. 2. F-BPA-PET in case 1, prior to BNCT and at aggravation as well as in follow-up with the patient in good condition. (A) Prior to BNCT; (B) 4 months after BNCT (at aggravation); (C) 8 months after BNCT.

tumors and on the normal brain. The dose estimation method was described previously.[8]

One week after BNCT, anticoagulant and vitamin E were administered. This was for the prevention of RN, as we reported previously.[9] Right hemiparesis and aphasia occurred and became aggravated gradually after BNCT, even with an escalated dose of corticosteroids. Then, 4 months after BNCT, follow-up MRI and F-BPA-PET were applied simultaneously. In MRI, the Gd-enhanced lesion and the high-intensity area in FLAIR increased markedly (Fig. 1B and E). The second F-BPA-PET, taken 4 months after BNCT, showed decreased uptake of the tracer, as shown in Fig. 2B (L/N ratio, 4.7). Thereafter, the aggravation of clinical symptoms and MRIs was attributed not to tumor progression but to psPD.

We proposed bevacizumab treatment to the patient, his family, and the physician in charge. Thereafter, he was administered 5 mg/kg bevacizumab biweekly with 6 cycles. MRI taken after 3 cycles showed marked improvement in both Gd-enhanced and FLAIR images, as shown in Fig. 1C and F. The patient's speech disturbance and hemiparesis improved markedly by the treatment. The third F-BPA-PET, undertaken 8 months after BNCT with the patient in a stable state, showed a further decrease of tracer uptake, with an L/N ratio of 1.8, as shown in Fig. 2C. This finding suggests no tumor progression and good control of the tumor so far. The follow-up MRI showed no tumor progression (data not shown).

Case 2

A 27-year-old female developed left hemiparesis. A right frontal enhanced mass was removed gross totally in May 2005. The histological diagnosis was anaplastic oligoastrocytoma. She received fractionated X-ray treatment (total 72 Gy) and repetitive chemotherapy with nitrosourea. The lesion recurred and re-craniotomy was applied in November 2009 with the same pathological diagnosis. This was followed by successive TMZ chemotherapy. Unfortunately, the recurrence was confirmed by MRI and C-Met-PET, and the patient retired from her job as a nurse due to progression of left hemiparesis and seizures. She was referred to us for BNCT. Upon referral, MRI showed a Gd-enhanced lesion in the right frontal lobe with moderate perifocal edema, as shown in Fig. 3A and D.

For this case, BNCT was applied using the same protocol described in case 1. In BNCT, the maximum brain dose, maximum tumor dose, and minimum tumor dose were 11.5, 71.6, and 30.1 Gy-Eq, respectively. In this case, anticoagulant and vitamin E were also administered 1 week after BNCT to prevent RN. After BNCT, her hemiparesis became aggravated gradually even with an increasing dose of corticosteroids. MRI taken 2 months after BNCT showed an enlarged enhanced lesion with increased perilesional edema (Fig. 3B and E). The patient had no chance to receive further amino acid PET, but we considered this aggravation as symptomatic of psPD based on the duration of aggravation after

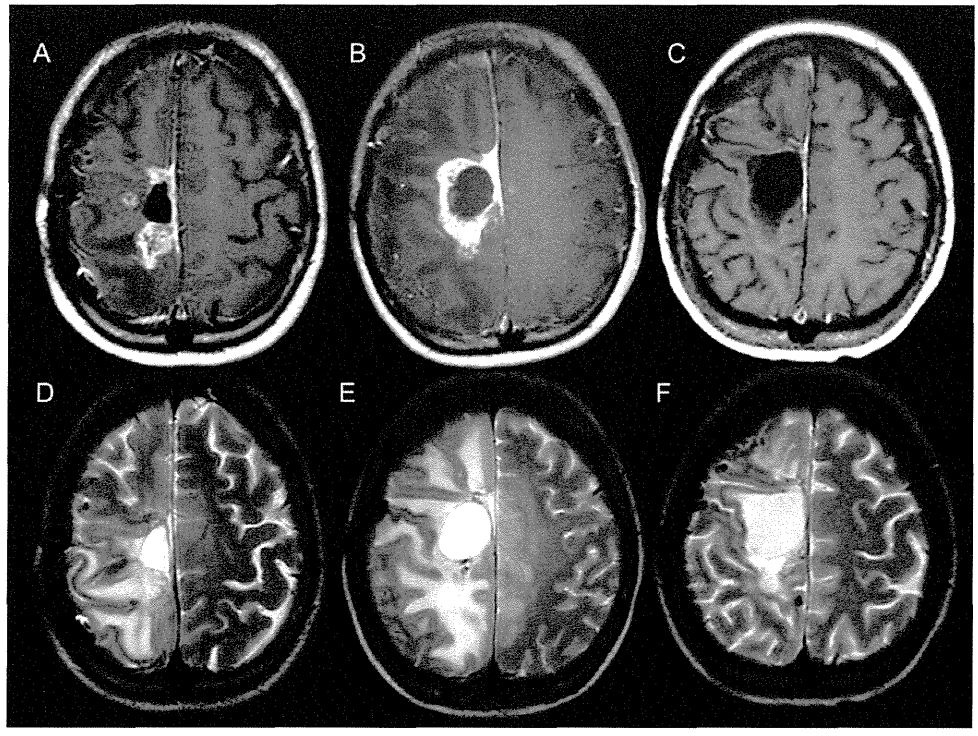

Fig. 3. Periodic MRI changes in case 2. (A–C) Gd-enhanced T1-weighted MRI. (D–F) T2-weighted MRI. (A and D) Just prior to BNCT; (B and E) 2 months after BNCT; (C and F) 6 months after BNCT (4 cycles after initial bevacizumab treatment).

BNCT. This patient and her physician in charge also accepted our proposal of bevacizumab treatment on the same schedule and dosage described in case 1. The patient was bed-ridden just prior to bevacizumab treatment, but her hemiparesis improved markedly and she could walk after 2 cycles of the treatment. MRI taken after 4 cycles, at 6 months after BNCT, showed marked improvement not only in Gd enhancement but also in the perilesional edema in FLAIR images, as shown in Fig. 3C and F. Her clinical condition has remained stable and good since the treatment ended.

Discussion

In our limited experience, there is no obvious histological difference between RN and psPD.[8,11] Necrosis is the central histopathological feature of each, and prominent angiogenesis is common at the boundary of central necrosis and normal brain tissue in each clinicopathological entity. Clinically, psPD usually occurs at a relatively early stage after some intensive treatments and is self-limiting. In most cases it improves over time without intensive treatments. On the other hand, RN often shows severe symptoms and occurs at least 6 months after radiotherapy. It is often long-lasting and improves only with intensive treatment, such as lesionectomy or bevacizumab administration. In human surgical specimens of RN, we previously demonstrated that overproduction of VEGF in reactive astrocytes in the perinecrotic area caused leaky angiogenesis, and this is the cause of perifocal edema in RN.[10] So we speculated that bevacizumab might neutralize this overproduced VEGF in the perinecrotic area and subsequently reduce the edema.[10] This is why we used bevacizumab for symptomatic psPD.

Originally, F-BPA-PET was developed for the simulation of absorbed dose in BNCT.[6,12,13] On the other hand, the background uptake of the tracer F-BPA is very low compared with that of fluorodeoxyglucose and even with that of methionine as a tracer. Thereafter, RN and psPD have been differentially diagnosed from tumor progression by F-BPA-PET.[8,14] On the basis of our experience, an L/N ratio of <2.0 in F-BPA-PET indicates a high possibility of RN and does not indicate tumor progression. We are now performing a nationwide multicenter clinical trial of bevacizumab treatment for symptomatic RN in the brain with diagnosis made by amino acid tracer PET. F-BPA-PET and C-Met-PET are equally useful for the differential diagnosis between RN and tumor progression. Both PETs show the same tendencies of tracer uptake and distribution, as Nariai et al reported.[15]

Both cases presented here were recurrent MGs and had received fractionated X-ray treatment previously. They showed aggravated clinical symptoms and MRI results a couple of months after BNCT. Therefore, we considered both cases to be symptomatic psPD. Especially in case 1, repetitive F-BPA-PETs were applied before BNCT and upon aggravation after BNCT, as well as in a stable state during follow-up. The second F-BPA-PET showed a lower L/N ratio than the first, but it was still higher than our criterion for RN at the aggravation. This may suggest that the

pathology of case 1 was psPD and not RN. Although the essential difference between them is still unclear, we speculated that they may have similar pathophysiology.

Usually we can treat asymptomatic psPD only with corticosteroids, or we can only observe the patient in asymptomatic psPD without treatments. Unfortunately, both cases presented here continued their clinical deterioration despite the escalating doses of corticosteroids. Fortunately, however, we used bevacizumab thereafter, to which both cases responded well. The physicians in charge decreased the corticosteroid dose for each patient after bevacizumab treatment.

To improve the effectiveness of radiotherapy, one study used bevacizumab with hypofractionated stereotactic irradiation for the treatment of recurrent MGs.[16] However, the literature contains no obvious reports about bevacizumab's effects on symptomatic psPD. We applied bevacizumab treatment to symptomatic RN in some cases, and all the patients responded well.[9] Based on these findings, as noted, we are performing a nationwide multicenter clinical trial of bevacizumab treatment for symptomatic RN in the brain. We therefore treated the present 2 cases with bevacizumab and confirmed marked effects. Some of the literature supports this concept.[17]

We applied BNCT, a tumor-selective particle radiation, aggressively even for recurrent MGs with satisfactory results, as reported elsewhere.[7] In that previous report, we used Carson et al[18] as our reference regarding BNCT's effectiveness for recurrent MGs; those authors advocated, and we adopted, recursive portioning analysis (RPA) classification for recurrent MGs. In our previous report,[7] we showed good effectiveness, especially in poor prognosis groups (RPA classes 3 and 7[18]) in BNCT in comparison with Carson's original data sets. Those authors reported that RPA classes 3 and 7 showed the poorest prognosis, with median survival times (MSTs) of 3.8 months and 4.9 months, respectively, after recurrence that followed some treatments. Both of the cases presented here should be considered RPA class 3 because they showed poor performance status at recurrence and because the initial histological diagnosis was not GBM. Carson's data sets revealed an MST of 3.8 months in RPA class 3 after recurrence. Both cases presented here survived more than 8 months after BNCT without tumor progression, continuing up to the writing of this manuscript. Although the 2 cases reported here are the only 2 that we have experienced with symptomatic psPD treated by bevacizumab after BNCT, BNCT plus bevacizumab at psPD improves a patient's condition and may prolong survival more effectively for recurrent MGs than we suggested in our previous report.

Bevacizumab treatment had no adverse effect in either of the present cases. As we described for each case, we routinely used anticoagulant after BNCT for recurrent MGs. This was to prevent anticipated RN. This anticoagulant administration probably decreases the possible adverse effects of thromboembolitic complications of bevacizumab, as we and Levin et al have reported.[9,10]

As noted at the beginning of this paper, it is widely accepted that MGMT promoter methylation status plays a significant role in the incidence of psPD in newly diagnosed GBM cases treated by concomitant chemo therapy and radiation.[2] So let us add finally some information regarding MGMT in both cases presented here. In case 1, MGMT protein expression was positive in immunohistochemistry, and in case 2, the MGMT promoter was methylated. These observations might suggest that MGMT status is not so important for the incidence of symptomatic psPD for recurrent MGs receiving BNCT.

Funding

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Conflict of interest statement. None declared.

References

1. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352:987–996.
2. Brandes AA, Franceschi E, Tosoni A, et al. MGMT promoter methylation status can predict the incidence and outcome of pseudoprogression after concomitant radiochemotherapy in newly diagnosed glioblastoma patients. *J Clin Oncol*. 2008;26:2192–2197.
3. Brandsma D, Stalpers L, Taal W, Sminia P, van den Bent MJ. Clinical features, mechanisms, and management of pseudoprogression in malignant gliomas. *Lancet Oncol*. 2008;9:453–461.
4. Barth RF, Vicente MG, Harling OK, et al. Current status of boron neutron capture therapy of high grade gliomas and recurrent head and neck cancer. *Radiat Oncol*. 2012;7:146.
5. Kawabata S, Miyatake S, Kuroiwa T, et al. Boron neutron capture therapy for newly diagnosed glioblastoma. *J Radiat Res (Tokyo)*. 2009;50:51–60.
6. Miyatake S, Kawabata S, Kajimoto Y, et al. Modified boron neutron capture therapy for malignant gliomas performed using epithermal neutron and two boron compounds with different accumulation mechanisms: an efficacy study based on findings on neuroimages. *J Neurosurg*. 2005;103:1000–1009.
7. Miyatake S, Kawabata S, Yokoyama K, et al. Survival benefit of boron neutron capture therapy for recurrent malignant gliomas. *J Neurooncol*. 2009;91:199–206.
8. Miyatake S, Kawabata S, Nonoguchi N, et al. Pseudoprogression in boron neutron capture therapy for malignant gliomas and meningiomas. *Neuro Oncol*. 2009;11:430–436.
9. Furuse M, Kawabata S, Kuroiwa T, Miyatake S. Repeated treatments with bevacizumab for recurrent radiation necrosis in patients with malignant brain tumors: a report of 2 cases. *J Neurooncol*. 2011;102:471–475.

10. Levin VA, Bidaut L, Hou P, et al. Randomized double-blind placebo-controlled trial of bevacizumab therapy for radiation necrosis of the central nervous system. *Int J Radiat Oncol Biol Phys*. 2011;79:1487–1495.
11. Nonoguchi N, Miyatake S, Fukumoto M, et al. The distribution of vascular endothelial growth factor–producing cells in clinical radiation necrosis of the brain: pathological consideration of their potential roles. *J Neurooncol*. 2011;105:423–431.
12. Imahori Y, Ueda S, Ohmori Y, et al. Positron emission tomography–based boron neutron capture therapy using boronophenylalanine for high-grade gliomas: part I. *Clin Cancer Res*. 1998;4:1825–1832.
13. Imahori Y, Ueda S, Ohmori Y, et al. Positron emission tomography–based boron neutron capture therapy using boronophenylalanine for high-grade gliomas: part II. *Clin Cancer Res*. 1998;4:1833–1841.
14. Miyashita M, Miyatake S, Imahori Y, et al. Evaluation of fluoride-labeled boronophenylalanine-PET imaging for the study of radiation effects in patients with glioblastomas. *J Neurooncol*. 2008;89:239–246.
15. Nariai T, Ishiwata K, Kimura Y, et al. PET pharmacokinetic analysis to estimate boron concentration in tumor and brain as a guide to plan BNCT for malignant cerebral glioma. *Appl Radiat Isot*. 2009;67:S348–S350.
16. Gutin PH, Iwamoto FM, Beal K, et al. Safety and efficacy of bevacizumab with hypofractionated stereotactic irradiation for recurrent malignant gliomas. *Int J Radiat Oncol Biol Phys*. 2009;75:156–163.
17. Khasraw M, Simeonovic M, Grommes C. Bevacizumab for the treatment of high-grade glioma. *Expert Opin Biol Ther*. 2012;12:1101–1111.
18. Carson KA, Grossman SA, Fisher JD, Shaw EG. Prognostic factors for survival in adult patients with recurrent glioma enrolled onto the new approaches to brain tumor therapy CNS consortium phase I and II clinical trials. *J Clin Oncol*. 2007;25:2601–2606.

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Short Communication

Bevacizumab Treatment for Symptomatic Radiation Necrosis Diagnosed by Amino Acid PET

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Bevacizumab is effective in treating radiation necrosis; however, radiation necrosis was not definitively diagnosed in most previous reports. Here we used amino acid positron emission tomography to diagnose radiation necrosis for the application of bevacizumab in treating progressive radiation necrosis. Lesion/normal tissue ratios of <2.5 on ^{18}fluoride-labeled boronophenylalanine-positron emission tomography were defined as an indication of effective bevacizumab treatment. Thirteen patients were treated with bevacizumab at a dose of 5 mg/kg every 2 weeks. Two patients were excluded because of adverse events. The median reduction rate in perilesional edema was 65.5%. Karnofsky performance status improved in six patients after bevacizumab treatment. Lesion/normal tissue ratios on ^{18}fluoride-labeled boronophenylalanine-positron emission tomography ($P = 0.0084$) and improvement in Karnofsky performance status after bevacizumab treatment ($P = 0.0228$) were significantly associated with reduced rates of perilesional edema. Thus, ^{18}fluoride-labeled boronophenylalanine-positron emission tomography could be useful for diagnosing radiation necrosis and predicting the efficacy of bevacizumab in progressive radiation necrosis.

Key words: bevacizumab brain edema Karnofsky performance status positron emission tomography radiation necrosis

INTRODUCTION

Radiation necrosis, a well-known late adverse effect of radiotherapy, is an intractable iatrogenic disease. Symptomatic radiation necrosis negatively affects the patient's quality of life and can cause harmful lifelong effects, despite the possible positive effects on life span that intensive radiotherapy can provide. Recently, bevacizumab has been shown to dramatically decrease focal edema around the necrotic core, and thus, be an effective treatment for symptomatic radiation necrosis (1 4). With this discovery, the outlook for radiation necrosis has become hopeful, but accurate diagnosis of radiation necrosis remains problematic. Radiation necrosis was not definitively diagnosed in most reports to date, and some patients were diagnosed by magnetic resonance (MR) images alone. Differentiating tumor recurrence or progression from radiation necrosis remains difficult when the enhanced lesion and/or perilesional edema are enlarged on follow-up MR images, even if the tissue is surgically resected for histopathological examination. Positron emission tomography (PET) using an amino acid tracer is among the most promising modalities for the non-invasive diagnosis of radiation necrosis that causes radiographical worsening on MR images. We previously reported that differentiation between tumor progression and radiation necrosis can be achieved with ^{18}fluoride-labeled boronophenylalanine-PET (F-BPA)-PET (5). In the present study, we report the use of bevacizumab to treat patients with progressive radiation necrosis at our institution. Instead of using surgical biopsy, we diagnosed radiation necrosis in these patients based on a

review of MR images and clinical courses and by reference to our cut-off index for ^{18}F-BPA-PET. Our final goal is to establish a non-invasive and effective method of managing radiation necrosis from diagnosis to therapy.

PATIENTS AND METHODS

Patients

The protocol of this study was approved by our institutional review board. Between January 2009 and October 2010, 13 patients with symptomatic radiation necrosis were treated with bevacizumab at our institute. Radiation necrosis was defined as an enhanced lesion that grew slowly, accompanied by the massive perilesional edema on follow-up MR images. All patients underwent ^{18}F-BPA-PET and various first-line medical treatments, including the treatment with corticosteroids, anticoagulants and vitamin E, but had been refractory to these medications. Other inclusion criteria were as follows: $\geq$3 months elapsed after the initial radiotherapy; unresectable lesions; no systemically active lesion and life expectancy $\geq$3 months.

^{18}F-BPA-PET imaging

All ^{18}F-BPA-PET scans were performed at the Nishijin Hospital, Kyoto, Japan. BPA was originally synthesized as described previously (6,7), and the protocol for the PET measurements using a HEADTOME III (Shimadzu Co., Kyoto, Japan) has also been described elsewhere (8,9). Semi-quantitative analysis was performed using the lesion/normal tissue (L/N) ratio. Using Amide software (SourceForge, Inc., Mountain View, CA), regions of interest of 1 cm diameter were placed on the lesion with the maximal uptake of ^{18}F-BPA on PET and on the contralateral brain area. L/N ratios were generated by dividing the mean standardized uptake value (SUV) of the lesion by the mean SUV of the contralateral normal brain. We previously reported that an L/N ratio measured by ^{18}F-BPA-PET of $<$2.0 is indicative of radiation necrosis in patients with glioblastoma treated with radiation therapy (5). An L/N ratio $>$2.5 is strongly suggestive of tumor progression. Therefore, with regard to ^{18}F-BPA-PET, the L/N ratios of equal to or $<$2.0 were an absolute indication for bevacizumab treatment in the present study. Patients with an L/N ratio between 2.0 and 2.5 were also included, provided they had undergone ^{18}F-BPA-PET before tumor treatment and their current L/N ratio was lower than the previous value.

Bevacizumab treatment

Patients were treated with bevacizumab at a dose of 5 mg/kg every 2 weeks. Neurological status and MR images were evaluated after three cycles of bevacizumab treatment. Patients underwent three more cycles of bevacizumab treatment when any clinical or radiological response was obtained after the initial three cycles.

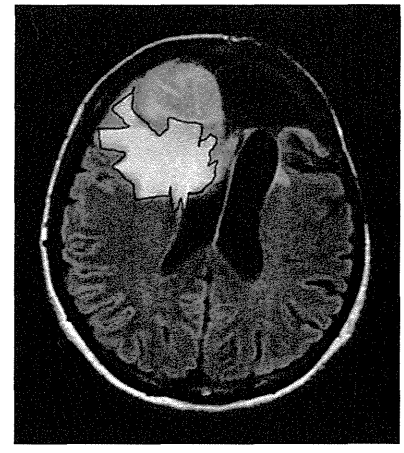

Figure 1. The area of hyperintensity was manually outlined on each FLAIR MR image (black line).

Data analysis

The volume of the hyperintense area on FLAIR MR images before and after bevacizumab treatment was measured in each case using ImageJ software (National Institutes of Health, Bethesda, MD, USA). On each axial MR slice, the area of hyperintensity was manually outlined (Fig. 1), measured and summed across slices. These sums were multiplied by the slice interval. The reduction rate of perilesional edema was calculated by dividing the post-treatment volume by the pretreatment volume. The outcomes were based on MR images, ^{18}F-BPA-PET and histopathological examination. Univariate analyses were conducted using analysis of variance.

RESULTS

Of the 13 patients, 2 were excluded from the analysis because of discontinuation of bevacizumab in response to adverse events. One patient exhibited an asymptomatic intracerebral hemorrhage after one dose of bevacizumab. Periodic MR images revealed this hemorrhage in an area of radiation necrosis without clinical aggravation. Another patient suffered a sudden cardiopulmonary arrest after marked clinical improvements had been observed following two doses of bevacizumab. This patient had a poor Karnofsky performance status (KPS) (KPS 20) and was bedridden prior to treatment. The cause of the cardiopulmonary arrest was not clear. Thus, a total of 11 patients were included in this analysis.

The demographics of the patients are listed in Table 1. The median duration between the final radiotherapy and the start of bevacizumab treatment was 11 months. The median L/N ratio on ^{18}F-BPA-PET was 1.8. The median volumes of perilesional edema before and after bevacizumab treatment were 65.0 and 23.6 cm^3, respectively. The median reduction ratio was 65.5%. KPS improved in six patients after bevacizumab treatment and did not change in five patients. Regarding original tumor pathology, the patients with metastatic brain tumors (Cases 2, 5 and 6) had a good treatment

Table 1. Patients' demographics

Case	Age	Gender	Primary tumors	Location	Size (cm)	Radiotherapies	Duration (months)	Cycles	L/N ratio	Perilesional edema		Reduction rate (%)	Pre-KPS	Post-KPS	T or N PFS (months)
										Pre-Tx (cm^3)	Post-Tx (cm^3)				
1	39	M	GBM	Parietal	6.1	BNCT, XRT	11	6	1.7	43.7	8.3	81.0	90	100	8.5
2	57	F	Met	Frontal	2.2	SRS x2	5	6	1.8	65.0	17.3	73.4	40	60	6.4
3	50	F	GBM	Parietal	6.0	Proton, XRT	37	5	1.6	151.0	77.9	48.4	60	70	15.6
4	55	F	AM	Parietal parasagittal	2.6	XRT, SRS, BNCT	6	6	2.2	31.8	25.7	19.4	60	60	13.8
5	74	F	Met	Frontal	2.3	SRS	47	6	1.5	12.9	3.3	74.4	60	60	11.5
6	55	M	Met	Frontal	1.5	SRS	49	6	2.0	101.0	22.8	77.5	80	90	10.3
7	38	M	GBMO	Frontal	3.2	XRT	6	4	1.8	133.0	37.4	71.9	60	70	12.7
8	27	F	AA	Frontal	4.6	BNCT, XRT	44	3	1.6	75.3	25.9	65.5	90	100	17.5
9	65	M	GBM	Frontal	6.0	XRT	11	3	2.2	95.8	93.9	2.0	40	40	1.3
10	76	M	AM	Frontal parasagittal	4.6	SRS x2, SRT x2	6	3	2.2	29.7	23.6	20.5	60	60	8.0
11	35	M	AM	Falco-tentorial	4.7	XRT, SRS	7	3	1.8	48.4	22.3	54.0	60	60	2.2

AA, anaplastic astrocytoma; AM, anaplastic meningioma; BNCT, boron neutron capture therapy; GBM, glioblastoma multiforme; GBMO, glioblastoma multiforme with oligodendroglial component; KPS, Karnofsky performance status; Met, metastatic brain tumor; SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy; T or N PFS, tumor or necrosis progression-free survival; Tx, treatment; XRT, X-ray radiotherapy.

response (>70% reduction, Fig. 2). The L/N ratio on ^{18}F-BPA-PET ($P = 0.0084$) and the improvement of KPS after bevacizumab treatment ($P = 0.0228$) were significantly associated with the response rate of then perilesional edema after bevacizumab treatment in univariate analysis (Table 2). A case is illustrated in Fig. 3.

During the median follow-up period of 14.4 months (range, 2.9 32.4), two patients were stable, radiation necrosis recurred in two patients and the tumor progressed or a new tumor lesion appeared in seven patients. The 6-month and 1-year tumor-progression-free survival rates from the PET study were 90.9 and 63.6%, respectively. The 6-month and 1-year tumor or necrosis progression-free survival rates after bevacizumab treatment were 81.8 and 36.4%, respectively.

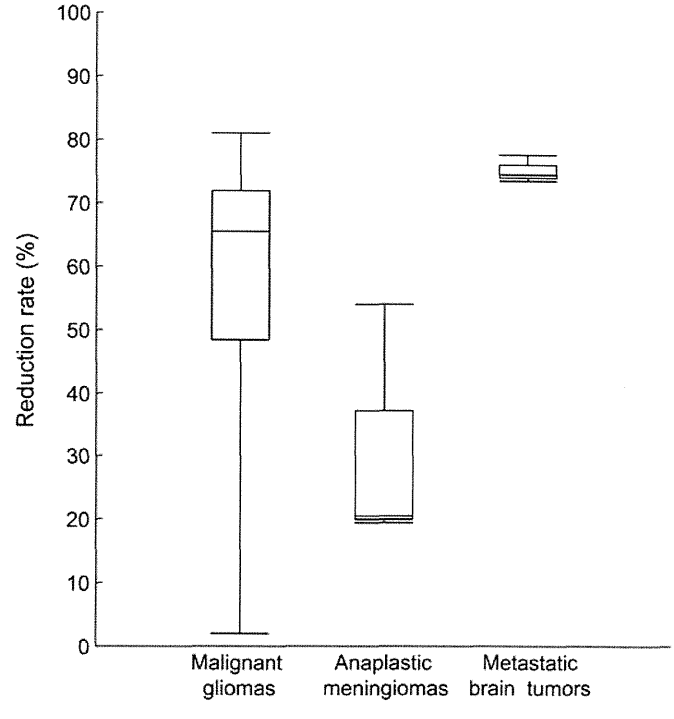

Figure 2. Box plots demonstrating reduction rates of perilesional edema in each tumor pathology.

DISCUSSION

Radiation necrosis has been treated with bevacizumab in an exploratory fashion and several papers have already reported its clinical effectiveness (1 4). In an animal model of radiation injury, hypoxia induces the vascular endothelial growth factor (VEGF) expression in reactive astrocytes (10). We also demonstrated that VEGF is involved in angiogenesis near the center of radiation necrosis in humans (11). In the present study, there were only two clinical factors, improvement of KPS and L/N ratios on ^{18}F-BPA-PET, which were significantly associated with the response rate of perilesional edema after bevacizumab treatment. Specifically, the reduction in perilesional edema contributed to the improvement in KPS after bevacizumab treatment. Although bevacizumab cannot induce functional recovery of necrotic tissue

Table 2. Regression analysis of clinical factors affecting the reduction rate of perilesional edema

	P value
Age	0.1990
Gender	0.7785
Primary tumor	
Malignant gliomas	0.9753
Metastatic brain tumors	0.1131
Malignant meningiomas	0.1053
Radiotherapy	
X-ray radiotherapy	0.4957
Stereotactic radiosurgery	0.9753
Times of radiation therapies	0.2460
Duration of bevacizumab	0.2293
Cycles of bevacizumab	0.1492
L/N ratio on ^{18}F-BPA-PET	0.0084*
Pretreatment of perilesional edema	0.8426
Pretreatment of KPS	0.1222
Improvement in KPS	0.0228*

*P values of < 0.05 were considered statistically significant.

per se, the improvement in perilesional edema around the necrotic core is clinically beneficial for patients with symptomatic radiation necrosis. High-dose radiation therapies and repeated radiotherapies prolong patient survival, but they inevitably increase the incidence of radiation necrosis. Therefore, bevacizumab is expected to produce further beneficial effects of high-dose radiation therapies or repeated radiotherapies in the treatment of central nervous system malignancies. However, it cannot be overlooked that 2 of the 13 patients in the present study experienced adverse events, although it is unknown whether these events were due to bevacizumab.

^{18}F-BPA is an amino acid tracer similar to ^{11}carbon (C)-labeled methionine. Initially, we used this type of PET to determine when BNCT was indicated for treatment of malignant gliomas (12). However, we recently used ^{18}F-BPA-PET to assist with the preliminary evaluation of biological tumor (lesion) activity, and we reported that there were significant differences between histologically proven tumor progression and radiation necrosis in L/N ratios observed on ^{18}F-BPA-PET imaging in patients with glioblastoma (5,13). ^{11}C-methionine PET has also been used to provide quantitative values to aid in the differentiation of tumor recurrence from radiation necrosis in patients with central nervous system malignancies (14). One pharmacokinetic analysis demonstrated that the estimated tumor/

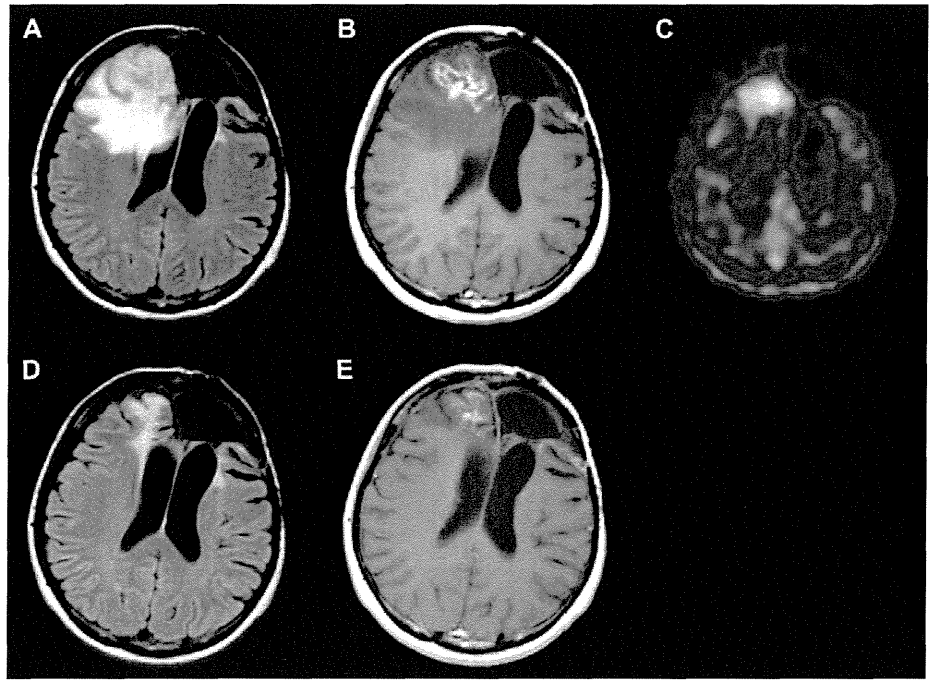

Figure 3. A 27-year-old woman (Case 8) with a left frontal anaplastic astrocytoma was treated with BNCT and X-ray radiotherapy after surgical resection. The patient had a convulsion due to enlarged perilesional edema 4 years later. MR images showed a heterogeneous enhancement with the massive perilesional edema in the right frontal lobe (A, B). The L/N ratio was 1.6 on F-BPA-PET (C). The patient was treated with bevacizumab. MR images after six cycles showed a remarkable reduction in perilesional edema and a weakening of the abnormal enhancement (D, E). The patient did not experience any further convulsions.

normal (T/N) ratio of tissue boron concentration, T/N ratio of ^{18}F-BPA and T/N ratio of ^{11}C-methionine showed significant linear correlations among each other in glioma patients (15). Pathological heterogeneity is the main reason for difficulty in distinguishing between tumor progression and radiation necrosis. Even if PET analysis suggests that a lesion is radiation necrosis, it does not exclude the possible existence of a few living tumor cells in or around the lesion. In other words, amino acid PET is useful for assessing whether the predominant cause of increasing radiographical enhancement and perilesional edema is tumor progression or radiation necrosis. The 6-month tumor-progression-free survival rates of 90.9% clearly show that ^{18}F-BPA-PET is a reliable tool that can be used to judge the predominant cause of the progressive perilesional edema in patients with brain tumors previously treated with radiotherapy.

In the present study, there was a statistically significant negative correlation between the L/N ratios on ^{18}F-BPA-PET and the reduction rates of perilesional edema. Although it is not easy to interpret the data, we hypothesize that an FLAIR-hyperintense area around a lesion with a high L/N ratio consists of not only vasogenic edema but also tumor invasion to some degree. This hypothesis is supported by the finding that perilesional edema in radiation necrosis with metastatic brain tumors responded much more strongly to bevacizumab treatment than perilesional edema in radiation necrosis with other tumors. Malignant gliomas and malignant meningiomas are presumably more infiltrative than metastatic brain tumors. Malignant gliomas showed varied responses to bevacizumab, and malignant meningiomas generally had low responses to bevacizumab. Cases with malignant meningiomas had long disease durations and underwent multiple radiotherapies before bevacizumab treatment. Therefore, FLAIR hyperintensity around the necrotic core may not indicate purely vasogenic edema in malignant meningiomas. Except for our previous case report (1), there have been no reports on the use of bevacizumab in the treatment of radiation necrosis occurring after radiotherapy for metastatic brain tumors. In the present study, radiation necrosis with metastatic brain tumors homogenously responded to bevacizumab very well, although the study only included three such cases. Bevacizumab treatment in patients with metastatic brain tumors is controversial because the risk of hemorrhagic complication is always a concern. However, Besse et al. recently reported that patients with central nervous system metastasis have a similar risk of developing cerebral hemorrhage independent of bevacizumab therapy (16). Thus, we believe patients with symptomatic radiation necrosis treated for metastatic brain tumors are good candidates for bevacizumab treatment. At present, our larger clinical trial of bevacizumab treatment of symptomatic radiation necrosis including patients with metastatic brain tumors treated with radiotherapy is ongoing under the system of investigational medical care approved by the Ministry of Health, Labour and Welfare.

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Conflict of interest statement

None declared

References

1. Furuse M, Kawabata S, Kuroiwa T, Miyatake SI. Repeated treatments with bevacizumab for recurrent radiation necrosis in patients with malignant brain tumors: a report of 2 cases. *J Neurooncol* 2011;102:471–5.
2. Gonzalez J, Kumar AJ, Conrad CA, Levin VA. Effect of bevacizumab on radiation necrosis of the brain. *Int J Radiat Oncol Biol Phys* 2007;67:323–6.
3. Levin VA, Bidaut L, Hou P, et al. Randomized double-blind placebo-controlled trial of bevacizumab therapy for radiation necrosis of the central nervous system. *Int J Radiat Oncol Biol Phys* 2011;79:1487–95.
4. Torcuator R, Zuniga R, Mohan YS, et al. Initial experience with bevacizumab treatment for biopsy confirmed cerebral radiation necrosis. *J Neurooncol* 2009;94:423–31.
5. Miyashita M, Miyatake S, Imahori Y, et al. Evaluation of fluoride-labeled boronophenylalanine-PET imaging for the study of radiation effects in patients with glioblastomas. *J Neurooncol* 2008;89:239–46.
6. Ishiwata K, Ido T, Mejia AA, Ichihashi M, Mishima Y. Synthesis and radiation dosimetry of 4-borono-2-[18F]fluoro-D,L-phenylalanine: a target compound for PET and boron neutron capture therapy. *Int J Rad Appl Instrum* 1991;42:325–8.
7. Mishima Y, Imahori Y, Honda C, et al. In vivo diagnosis of human malignant melanoma with positron emission tomography using specific melanoma-seeking 18F-DOPA analogue. *J Neurooncol* 1997;33:163–9.
8. Imahori Y, Ueda S, Ohmori Y, et al. Fluorine-18-labeled fluoroboronophenylalanine PET in patients with glioma. *J Nucl Med* 1998;39:325–33.
9. Takahashi Y, Imahori Y, Mineura K. Prognostic and therapeutic indicator of fluoroboronophenylalanine positron emission tomography in patients with gliomas. *Clin Cancer Res* 2003;9:5888–95.
10. Li YQ, Ballinger JR, Nordal RA, Su ZF, Wong CS. Hypoxia in radiation-induced blood-spinal cord barrier breakdown. *Cancer Res* 2001;61:3348–54.
11. Nonoguchi N, Miyatake SI, Fukumoto M, et al. The distribution of vascular endothelial growth factor-producing cells in clinical radiation necrosis of the brain: Pathological consideration of their potential roles. *J Neurooncol* 2011;105:423–31.
12. Miyatake S, Kawabata S, Kajimoto Y, et al. Modified boron neutron capture therapy for malignant gliomas performed using epithermal neutron and two boron compounds with different accumulation mechanisms: an efficacy study based on findings on neuroimages. *J Neurosurg* 2005;103:1000–9.
13. Miyatake SI, Kawabata S, Nonoguchi N, et al. Pseudoprogression in boron neutron capture therapy for malignant gliomas and meningiomas. *Neuro Oncol* 2009;11:430–6.
14. Terakawa Y, Tsuyuguchi N, Iwai Y, et al. Diagnostic accuracy of 11C-methionine PET for differentiation of recurrent brain tumors from radiation necrosis after radiotherapy. *J Nucl Med* 2008;49:694–9.
15. Nariai T, Ishiwata K, Kimura Y, et al. PET pharmacokinetic analysis to estimate boron concentration in tumor and brain as a guide to plan BNCT for malignant cerebral glioma. *Appl Radiat Isot* 2009;67:S348–50.
16. Besse B, Lasserre SF, Compton P, et al. Bevacizumab safety in patients with central nervous system metastases. *Clin Cancer Res* 2010;16:269–78.

1）脳放射線壊死に対するベバシズマブ(アバスチン)療法

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key words　angiogenesis, bevacizumab, positron emission tomography, radiation necrosis, vascular endothelial growth factor

要　旨

脳腫瘍もしくは頭頸部がんを治療するほとんどの医師が，脳放射線壊死に遭遇していると思われる．脳放射線壊死はよく知られている疾患であるが，実際の診断や治療には難渋することが多い．治療には副腎皮質ステロイドが多く使用されるが，その効果は限定的である．近年では，血管新生阻害薬であるベバシズマブの脳放射線壊死に対する治療効果が報告され，新規治療として期待されている．症例報告においては，ベバシズマブの投与にてMRIでの浮腫や造影域が著明に縮小し，多くの症例で臨床症状が改善した．ステロイド投与例では治療後にステロイドの減量も報告されている．2011年に報告された無作為二重盲検プラセボ対照試験にてもベバシズマブ治療群にて同様の結果が得られた．われわれは現在，高度医療評価制度の下，多施設共同試験を行っており，公知申請にて薬事承認を目指している．

動　向

全身の腫瘍性疾患と同じく，脳腫瘍の治療は各方面とも著しい進歩がみられている．放射線治療では，定位放射線をはじめとして，強度変調放射線治療，陽子線や硼素中性子捕捉療法などの粒子線治療により腫瘍に対して高線量を照射することが可能となってきた．いずれの治療も理論上は正常脳には低線量の照射に抑えることができるはずであるが，一定頻度で放射線壊死に遭遇していることも事実である．この遅発性放射線障害である放射線壊死は，難治性で，かつ医原性であるため，治療を施した医師としては何としても克服したい疾患であることはいうまでもない．従来，教科書的には副腎皮質ステロイドの投与が記載されているが，その効果についてのまとまった報告はなく，遅発性放射線壊死に対してはその効果も限定的である．

近年，血管新生阻害薬であるベバシズマブ（アバスチン）が脳放射線壊死の治療に有効であることが期待されている．実際に臨床で使用し，有効であったいくつかの症例報告を経て，米国にて二重盲試験による有効性も証明された．しかし，データとしては未だ不十分であり，全世界にてベバシズマブが脳放射線壊死の治療薬として承認される動向は確認できていない．われわれは，平成23年4月1日より高度医療評価制度を利用し，多施設共同での臨床試験を開始した．本試験で良好な結果を得ることができれば，公知申請にて医薬品医療機器総合機構への申請を行い，薬事の承認を

得るよう進めていく予定である．

A. 脳放射線壊死に対する従来の治療方法

脳放射線壊死は約80年前から報告されている，古くから知られる疾患であるが，脳放射線壊死に対する治療法は未だに確立されていない．教科書的には副腎皮質ステロイドが脳放射線壊死の初期治療としてあげられ，臨床の場では多用されているが，実際にはまとまった報告はない．軽症例や早期例では一定の効果を経験的に認めるが，進行性の症候性脳放射線壊死に対しては効果を示さない．文献を渉猟すると，39例の脳放射線壊死症例のレビューでは，ステロイドが使用されたのはわずか5例であり，その内4例は壊死巣除去術との併用であった[1]．その他の内科的治療としては，抗凝固薬の使用がある．抗凝固薬に関しては，8例の脳放射線壊死例に使用したところ5例で改善を認め（1例で著明な改善，4例は軽度から中等度），1例で不変，2例で悪化した．効果を示した例では3～6カ月抗凝固剤を投与したが，1例で抗凝固薬を中止した後に症状の再燃を認めている[2]．その他の治療法としては，高圧酸素療法も試みられている．脳放射線壊死に対する高圧酸素療法の報告は症例報告のみである．遅発性放射線障害に対する使用では，神経症状を呈する遅発性放射線障害6例のうち，治療後症状が改善したのは1例のみ（軽度改善）であった[3]．

われわれは内科的治療に不応性の放射線壊死に対しては，積極的に外科治療を行ってきた．脳放射線壊死に対する手術の治療効果については，ガンマナイフ照射後の転移性脳腫瘍32例38病変に対し，42回の切除術を行った報告があり，34例で術後画像上もしくは臨床上の改善がみられたが，7例にて術後合併症を認め，1例は死亡している[4]．術中MRIを用いた11例の悪性脳腫瘍の治療後脳放射線壊死のシリーズの報告では，術後Karnofsky Performance Statusは4例（36%）で改善，4例で不変，3例で悪化している[5]．3例で手術合併症を認めている．壊死巣除去術は，治療による改善効果は充分見込める手段ではあるが，脳放射線壊死の症例はperformance statusが低下している，もしくは全身状態が良好ではない例が多く含まれ，治療に伴う合併症率は決して低いものではない．

B. 放射線壊死に対するベバシズマブの作用

ベバシズマブは血管内皮増殖因子（vasuclar endothelial growth factor: VEGF）のモノクローナル抗体であり，現在ではいくつかの固形癌に抗癌剤とともに使用されている．腫瘍では血管新生が亢進しており，VEGFが腫瘍細胞に高発現している．抗癌剤と併用することにより，腫瘍の血管新生を抑制することで腫瘍の進展を抑え，正常血管を安定させることで，薬剤を腫瘍へ安定して届けることもできると考えられている．一方，放射線壊死の病理学的所見は，中心部に凝固壊死があり，その周囲に広範な浮腫を認める．脊髄の放射線障害の動物実験では，一見正常に見える照射範囲にまずhypoxia inducible factor 1α (HIF-1α)が発現し，脱髄や壊死とともにその周囲にVEGFが発現することが報告されている[6]．われわれも放射線壊死の臨床病理検体で検討している．壊死巣周囲に拡張した新生血管を認め，周囲に微小出血や細胞間隙に浮腫を認めた[7]．免疫染色を施行すると，同部位にHIF-1αおよびVEGFが発現し，これらの因子が血管新生に大きく寄与していることが示唆された．よってベバシズマブによりVEGFの働きを抑制することで放射線壊死の壊死巣周囲に発生する浮腫を抑え，放射線壊死の増悪を防ぎ，浮腫改善により臨床症状が改善できることが期待される．

C. 脳放射線壊死に対するベバシズマブの治療効果

脳放射線壊死に対するベバシズマブの有効性を初めて報告したのは2007年のGonzalezらによるもので，彼らはベバシズマブにより治療した15例の再発原発性悪性脳腫瘍症例を後ろ向きに検討している[8]．各症例のMRIを神経放射線科医が経時的に見返してみると，脳放射線壊死症と診断されるものが8例含まれていた．その8例のうち1例を除いて，何らかの抗癌剤とともにベバシズマブが投与されている．ベバシズマブの投与により全例画像上造影域ならびに周囲浮腫の縮小を認め，ステロイドの内服を減量することができたと報告しているが，症状の変化については記載がなかった．2008年には米国臨床腫瘍学会において症例報告がなされている[9]．鼻咽頭癌に対する放射線治療にて側頭葉に放射線壊死をきたした症例にベバシズマブを投与している．放射線治療2年後に脳放射線壊死をきたし，5mg/kgのベバシズマブの投与を4回行ったところ，浮腫はほぼ消失し症状も回復した．もう1つの症例対象研究では，生検にて診断された脳放射線壊死6例に対して同様にベバシズマブを投与したところ，著明な画像所見の改善を認めたと報告している[10]．3例は臨床症状の改善を認め生存しているが，残り3例は死亡し，2例が腫瘍伸展，1例が肺炎によるものであった．2010年になり初めて，脳放射線壊死に対するベバシズマブの無作為二重盲検プラセボ対照試験が報告された[11]．全14例の脳放射線壊死に対して生理食塩水を投与するプラセボ群とベバシズマブ治療群を比較している．ベバシズマブ群では，7.5mg/kgを3週ごとに計4回投与を計画し，2回投与後に改善を認めない場合は，

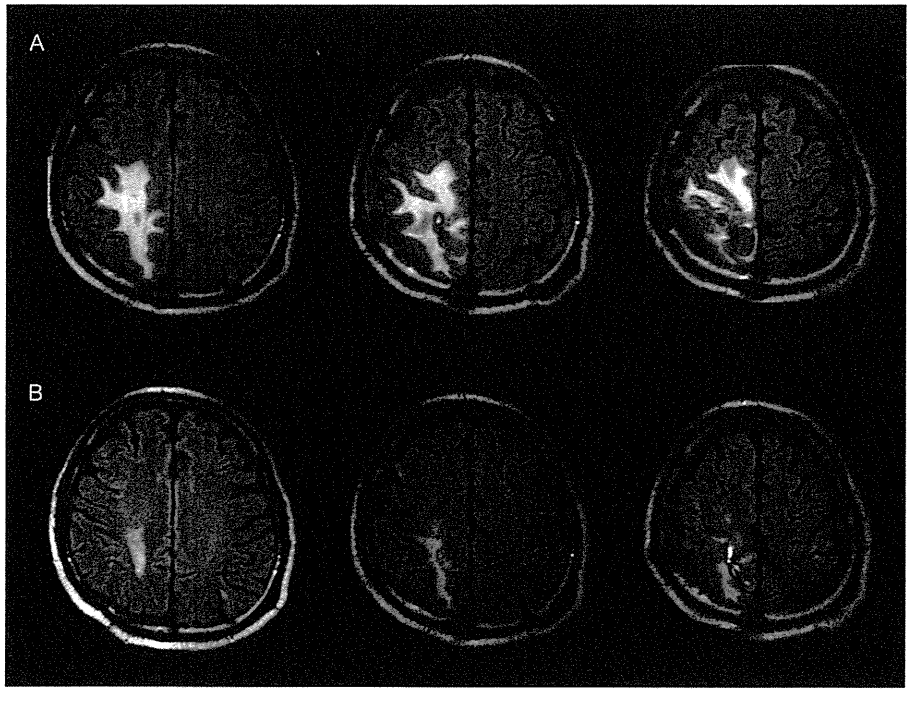

図1　症例1（文献12より改変）
ベバシズマブ投与前に著明な浮腫を認めていたが(A)，
ベバシズマブの投与にて浮腫はかなり改善を認めた(B)．

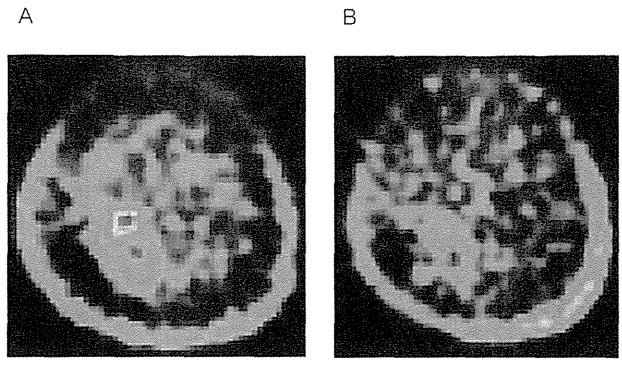

図2　症例1（文献12より改変）
腫瘍再発時はF-BPA-PETでは病変部の取り込みが高かったが(A)，放射線壊死の場合には病変部へのtracerの取り込みは高くない(B)．

crossoverを行うこととなっている．ベバシズマブ群では全例で画像上，臨床上の効果を認めた．一方，プラセボ群では全く効果を認めなかったため，全例crossoverにてベバシズマブ治療を行ったところ，反応を認めている．6例で有害事象を認め，そのうち嚥下性肺炎，肺塞栓，静脈洞血栓症は重症であった．残りの3例は小動脈の虚血性変化であり，重篤ではなかった．有害事象の発現を認めるも，脳放射線壊死に対するベバシズマブの治療効果はかなり高率と思われた．われわれも2例の自験例を報告している[12]．1例目は再発の神経膠芽腫に硼素中性子捕捉療法とX線照射を行ったところ，11カ月後に麻痺が生じ，痙攣を頻発するようになった（図1A）．MRIおよびF-BPA-PETにて放射線壊死と診断し（図2），ベバシズマブを5mg/kgを2週間ごとに計6回投与した．投与後，麻痺が改善し，痙攣もコントロール可能となり，ステロイドが不要となった．画像上も浮腫の著明な改善を認めた（図1B）．6カ月後に浮腫が再増悪したが，ベバシズマブの再投与で改善を認めている．2例目は転移性脳腫瘍に2度定位放射線が照射され，脳放射線壊死を生じた．麻痺および痙攣にて臥床状態であったが，ベバシズマブの投与にて麻痺が改善し，短い距離であれば独歩が可能となった．ともに有害事象を認めず，本治療の有効性が示唆された．

今までの脳放射線壊死に対するベバシズマブ治療例の文献のサマリーを表1に示す[8-16]．

D. 脳放射線壊死の臨床上の問題点

脳放射線壊死は前述したように古くから知られる疾患であるが，診断には苦慮することが多い．組織診断がgold standardであることはいうまでもないが，放射線治療が複数回施行される病変は多くが機能野もしくは機能野近傍に存在し，手術による脳機能の悪化が懸念されるものが多い．一方，定位的生検術で組織診断を行うこともあるが，われわれは定位的生検術による放射線壊死の組織診断には懐疑的である．放射線壊死は不均一な病変であり，一部には腫瘍細胞が残存していることもある．組織診断の重要性は，脳に広範な浮腫を起こし，患者の臨床症状を悪化させている根源をつきとめることであり，腫瘍細胞の存在有無ではない．画像診断より生検部位を定めて行わないと，より診断に迷うことが生じうる．よって，われわれは病変の全体像を把握して診断するにはPET検査が望ましいと考えている．われわれは，アミ

表1　脳放射線壊死に対するベバシズマブ治療報告の一覧

著者/出版年	数	原疾患	診断方法	治療方法	結果	有害事象
Gonzalez Jら, 2007[8]	8	Malignant gliomas, hemangiopericytoma	Biopsy: 2例 MRI: 6例	5mg/kg/2-week 7.5mg/kg/3-week	FLAIR: 60%減少 Gd-T1: 48%減少 Steroid: 8.6mg減量	記載なし
Wong ETら, 2008[9]	1	Head and neck cancer	MRI	5mg/kg/2-week 4回投与	MMSEが改善	なし
Torcuator Rら, 2009[10]	6	Gliomas	Biopsy	10mg/kg/2-week 6.8回投与	FLAIR: 49%減少 Gd-T1: 79%減少 臨床症状改善: 50% Steroid: 全例中止	創部感染 重篤な倦怠感
Liu AKら, 2009[13]	4	Pediatric pontine gliomas	MRI	10mg/kg/2-week	3人で臨床上, 画像上の改善あり	なし
Levin VAら, 2011[11]	14	Gliomas, head and neck cancers, malignant schwannoma, hemangiopericytoma, pituitary adenoma	MRI または biopsy	7.5mg/kg/3-week 2回投与後crossoverあり 全4回投与	bevacizmab群にて臨床上, 画像上改善あり placebo群は全例悪化し, crossed overした	重大な有害事象; 嚥下性肺炎, 肺梗塞, 静脈洞血栓症 虚血変化3例
Furuse Mら, 2011[12]	2	Glioblastoma, metastatic brain tumor	MRI PET	5mg/kg/2-week 6回投与	いったん改善するも, 壊死の再発あり 再発壊死にも効果あり	なし
Jeyaretna DSら, 2011[14]	1	Oligoastrocytoma	MRI (bevacizumab投与後にbiopsy)	5mg/kg/2-week 4回投与	いったん改善するも, 運動機能が徐々に悪化 DWIにて新規病変あり	なし
Matuschek Cら, 2011[15]	1	Astrocytoma grade III	MRI PET	10mg/kg/2-week 3カ月間投与	一部, 神経認知機能改善 Gd-T1にて著明な改善 Steroidは減量, 中止した	重篤な肺炎
Benoit Aら, 2011[16]	1	Head and neck cancer	Perfusion MRI MR spectroscopy	5mg/kg/2-week 4回投与	造影と浮腫はほぼ消失 神経所見は改善せず	なし

DWI = diffusion weighted image, FLAIR = fluid attenuation image of recovery, Gd-T1 = gadolinium-enhanced T1 weighted image, MMSE = Mini-mental state examination, MRI = magnetic resonance image, PET = positron emission tomography

ノ酸PETであるF-BPA-PETを術前に撮影し，摘出組織の病理診断と比較検討を行った[17]．病理学的所見は再発神経膠芽腫と治療後放射線壊死および壊死と腫瘍の混在した病変であったが，放射線壊死と再発腫瘍はPETのmean standard uptake valueを用いたLesion/normal tissue ratioにて鑑別が可能と思われた．アミノ酸PETにて診断ができれば低侵襲であり，術後管理もないためすぐに治療へと移行できると考えている．現在の大きな問題点は，アミノ酸PETは薬事未承認であるため，一般臨床で使用するためには今後保険収載へ向けたアミノ酸PETの大規模臨床試験が必要であり，現在日本核医学会と歩調をそろえた戦略の構築中である．

E. ベバシズマブ(アバスチン)治療の今後

現時点で欧米をはじめとする全世界において脳放射線壊死をベバシズマブの適応疾患として薬事承認を得ようとする動きはない．そこでわれわれは，高度医療評価制度の下，平成23年4月より多施設共同臨床試験を開始した（試験名：症候性脳放射線壊死に対する核医学的診断とベバシズマブの静脈内投与による治療）．本試験は2年間で約40症例登録する予定である．適応は外科的治療が困難であり，かつ内科的治療不応性の症候を

呈した脳放射線壊死であり，転移性脳腫瘍加療後の脳放射線壊死も適応に含めていることは，本試験の最大の特長の一つである．また前述の如くアミノ酸PETの診断能力の信頼性より，PETを用いた核医学診断を基に脳放射線壊死を診断し，適応を判断している．診断および治療において外科手技を要せず，低侵襲であることも本試験の特長の一つである．高度医療評価制度を利用しているため，良好な結果を得ることができれば，公知申請による薬事承認も可能であり，一日でも早く多くの患者に使用できるようにしていくことを目的としている．

文献

1) Shaw PJ, Bates D. Conservative treatment of delayed cerebral radiation necrosis. J Neurol Neurosurg Psychiatry. 1984; 47: 1338-41.
2) Glantz MJ, Burger PC, Friedman AH, et al. Treatment of radiation-induced nervous system injury with heparin and warfarin. Neurology. 1994; 44: 2020-7.
3) Bui QC, Lieber M, Withers HR, et al. The efficacy of hyperbaric oxygen therapy in the treatment of radiation-induced late side effect. Int J Rad Oncol Biol Phys. 2004; 60: 871-8.
4) Truong MT, St Clair EG, Donahue BR, et al. Results of surgical resection for progression of brain metastases previously treated by gamma knife radiosurgery. Neurosurygery. 2006; 59: 86-97.
5) McPherson CM, Warnick RE. Results of contemporary surgical management of radiation necrosis using frameless stereotaxis and intraoperative magnetic resonance imaging. J Neurooncol. 2004; 68: 41-7.
6) Nordal RA, Nagy A, Pintilie M, et al. Hypoxia and hypoxia-inducible factor-1 target genes in central nervous system radiation injury: A role for vascular endothelial growth factor. Clin Cancer Res. 2004; 10: 3342-53.
7) Nonoguchi N, Miyatake S, Fukumoto M, et al. The distribution of vascular endothelial growth factor-producing cells in clinical radiation necrosis of the brain: pathological consideration of their potential roles. J Neurooncol. 2011; 105: 423-31.
8) Gonzalez J, Kumar AJ, Conrad CA, et al. Effect of bevacizumab on radiation necrosis of the brain. Int J Radiat Oncol Biol Phys. 2007; 67: 323-6.
9) Wong ET, Huberman M, Lu XQ, et al. Bevacizumab reverses cerebral radiation necrosis. J Clin Oncol. 2008; 26: 5649-50.
10) Torcuator R, Zuniga R, Mohan YS, et al. Initial experience with bevacizumab treatment for biopsy confirmed cerebral radiation necrosis. J Neurooncol. 2009; 94: 63-8.
11) Levin VA, Bidaut L, Hou P, et al. Randomized double-blind placebo-controlled trial of bevacizumab therapy for radiation necrosis of the central nervous system. Int J Radiat Oncol Biol Phys. 2011; 79: 1487-95.
12) Furuse M, Kawabata S, Kuroiwa T, et al. Repeated treatments with bevacizumab for recurrent radiation necrosis in patients with malignant brain tumors: A report of 2 cases. J Neurooncol. 2011; 102: 471-5.
13) Liu AK, Macy ME, Foreman NK. Bevacizumab as therapy for radiation necrosis in four children with pontine gliomas. Int J Radiat Oncol Biol Phys. 2009; 75: 1148-54.
14) Jeyaretna DS, Curry Jr WT, Batchelor TT, et al. Exacerbation of cerebral radiation necrosis by bevacizumab. J Clin Oncol. 2011; 29: e159-62.
15) Matuschek C, Bölke E, Nawatny J, et al. Bevacizumab as a treatment option for radiation-induced cerebral necrosis. Strahlenther und Onkol. 2011; 87: 135-9.
16) Benoit A, Ducray F, Cartalat-Carel S, et al. Favorable outcome with bevacizumab after poor outcome with steroids in a patient with temporal lobe and brainstem radiation necrosis. J Neurol. 2011; 258: 328-9.
17) Miyashita M, Miyatake SI, Imahori Y, et al. Evaluation of fluoride-labeled boronophenyl-alanine-PET imaging for the study of radiation effects in patients with glioblastomas. J Neurooncol. 2008; 89: 239-46.

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総説
Review

症候性脳放射線壊死の診断と治療*

宮武　伸一**

Key words bevacizumab, positron emission tomography, radiation necrosis, vascular endothelial growth factor
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Ⅰ．はじめに

高線量放射線治療は膠芽腫を中心とする悪性脳腫瘍の生命予後を確実に延長している[3,6,9,24]．また転移性脳腫瘍に対しては定位放射線治療が積極的に適応され，これも生命予後の改善につながっている[21]．一方でこれら高線量，高精度放射線治療の適応により，症候性脳放射線壊死が問題となっている．

この症候性脳放射線壊死に対してはステロイドホルモンなどが経験的に投与されてはいるが，有効な治療法は確立されていない．またその診断も通常のMRIでは難しい．右後頭葉と左頭頂葉の多発性の転移性脳腫瘍（原発巣は乳癌）に定位放射線治療を行った後で生じた脳放射線壊死に対して，壊死巣除去術を行った症例の術前後のMRIを**Fig. 1**に示す．術前の画像では，gadolinium (Gd) で造影増強され，その病変を中心とした広範な脳浮腫を認めている．このMRIの所見からは腫瘍の再発との鑑別が不可能であるが，後に述べるアミノ酸トレーサを用いたpositron emission tomography (PET) により，脳放射線壊死と診断した．この浮腫により右片麻痺を生じていたが，ステロイドホルモンの投与によっても症状は改善しなかったので，壊死巣除去術を行った．この症例はわれわれに多くのことを教えてくれた．手術操作は2個の造影病変のみを摘出したが，この手術操作により，術後早期から浮腫の劇的な軽快を認めた．われわれ脳神経外科医は，造影される壊死巣本体を摘出すれば，このような浮腫の軽減につながることを経験的に認識していたが，なぜ造影病変のみを摘出すれば，浮腫の軽減につながるかは不明であった．この手術により，患者は歩行可能となったが，一方で視野狭窄は悪化した．当時はステロイドホルモン以外には手術しか浮腫の軽快は望めなかったので手術を選択したが，時には術前より症状を増悪させることもあり得る．

以下に，われわれが壊死巣除去術を行った病理組織標本での組織学的，免疫組織学的な解析から，脳放射線壊死の病態を解説する．

*Diagnosis and Treatment of Symptomatic Radiation Necrosis in the Brain

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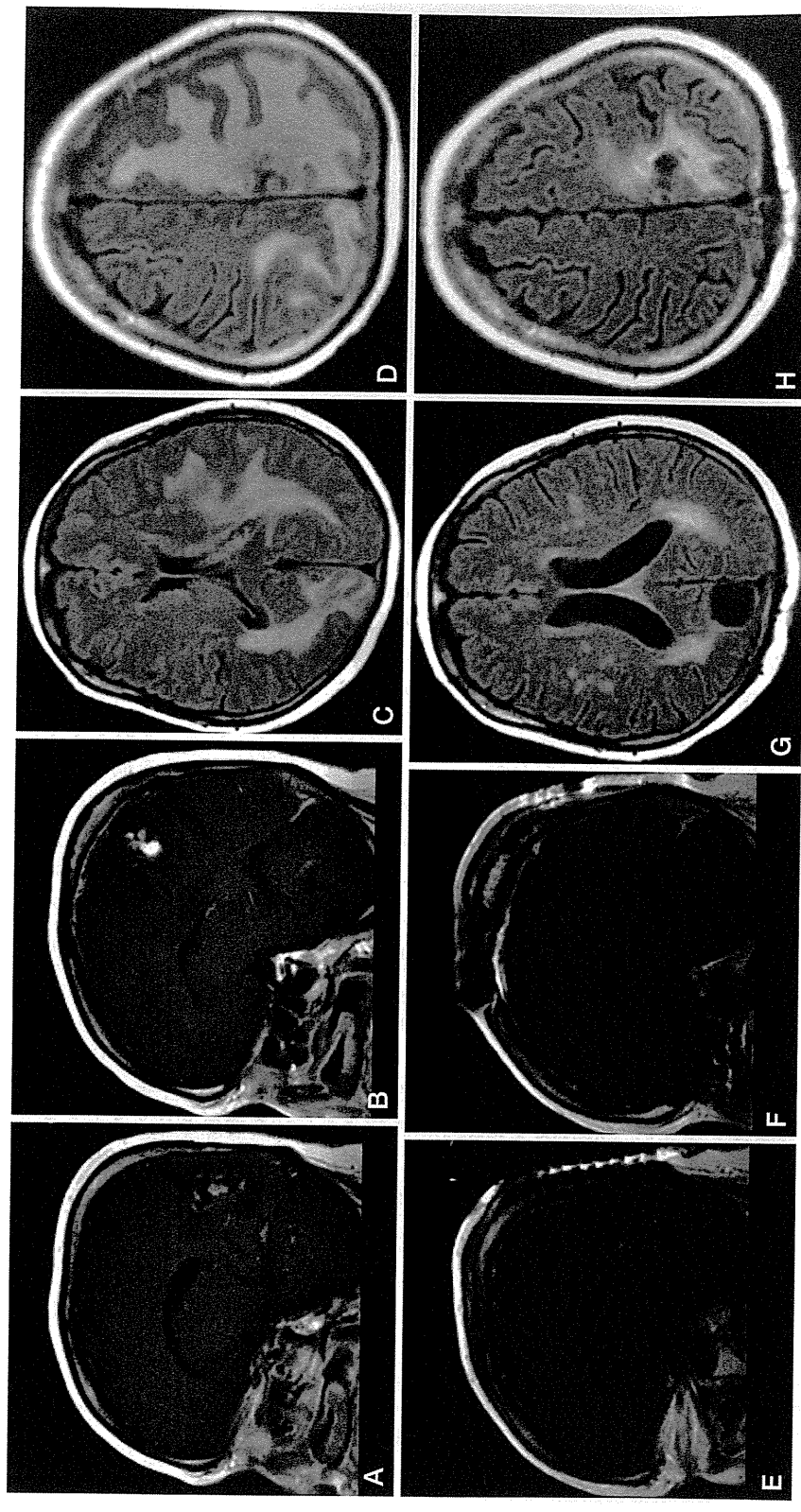

Fig. 1 Typical MRI findings of radiation necrosis. This radiation necrosis was derived from metastatic brain tumors treated by stereotactic radiosurgery (SRS). **A**, **B**: Preoperative Gd-T1 MRI, **C**, **D**: Preoperative FLAIR MRI, **E**, **F**: Postoperative Gd-T1 MRI, **G**, **H**: Postoperative FLAIR MRI.

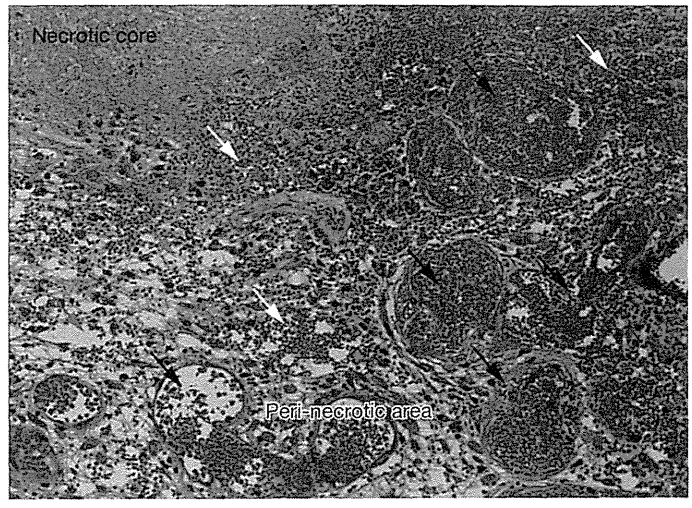

Fig. 2 Typical H & E staining of the radiation necrosis in the brain. This radiation necrosis was derived from recurrent glioblastoma multiforme treated by BNCT. **Black arrows** show the leaky angiogenesis and **white arrows** show the bleeding in the interstitial space. **Blue arrows** show the cerebral edema caused by extravasations of the plasma from leaky vessels.

II．脳放射線壊死の病態（血管新生を中心として）

この章では，脳放射線壊死において，症状の発現に最も大きく関与すると思われる浮腫の発現病態を自験例をもとに考察する．われわれは過去6年間に30例あまりの脳放射線壊死に対して積極的に壊死巣除去術を適応してきた．その中から，最も放射線壊死の病態を反映していると思われる組織像を提示する．この症例は標準治療である60GyのX線分割照射とtemozolomide（TMZ）による化学療法後に再発した膠芽腫に対してホウ素中性子捕捉療法（boron neutron capture therapy：BNCT）を行い，その半年後に放射線壊死を来した症例であり，そのHE染色像を**Fig. 2**として示す．図左上方に壊死巣本体を認め，ここには細胞構築を認めない．図右下より正常脳組織に移行するが，この両者の移行部分（以下，peri-necrotic area）に広範な血管新生を認める．一部の血管は一層の血管内皮のみで外壁が形成され，いわゆるcapillary telangiectasiaを認め，この脆弱な血管から血漿成分が漏出して，浮腫の原因になっていることが容易に想像できる．また，この脆弱な血管の破綻によると思われる微小出血も広範に認める．このような組織像は，もともとの腫瘍型や用いた放射線の種類を問わず，どの壊死組織でも普遍的に認めるものである[20]．

この脆弱な血管新生が脳浮腫につながるとすれば，血管新生への寄与には，血管内皮増殖因子（vascular endothelial growth factor：VEGF）の関与が最も考えやすい．よって，抗VEGF抗体による免疫組織染色を行ったところ，これも共通の所見を認めた．そのうちの代表的な免疫組織染色像をHE染色像とともに，**Fig. 3**に示す．なお，この症例は**Fig. 1**として紹介した症例よりの標本である．HE染色（**Fig. 3A**）では**Fig. 2**と同様に血管新生とその周囲に浮腫を認めている．抗VEGF抗体による免疫組織染色を行うとperi-necrotic areaにおいて一見して反応性アストロサイトと思われる細胞がVEGFを産生していることがわかった．よって後に述べる抗VEGF抗体製剤であるベバシズマブを用いた症候性脳放射線壊死の治療は，極めて理にかなったものと思われる．

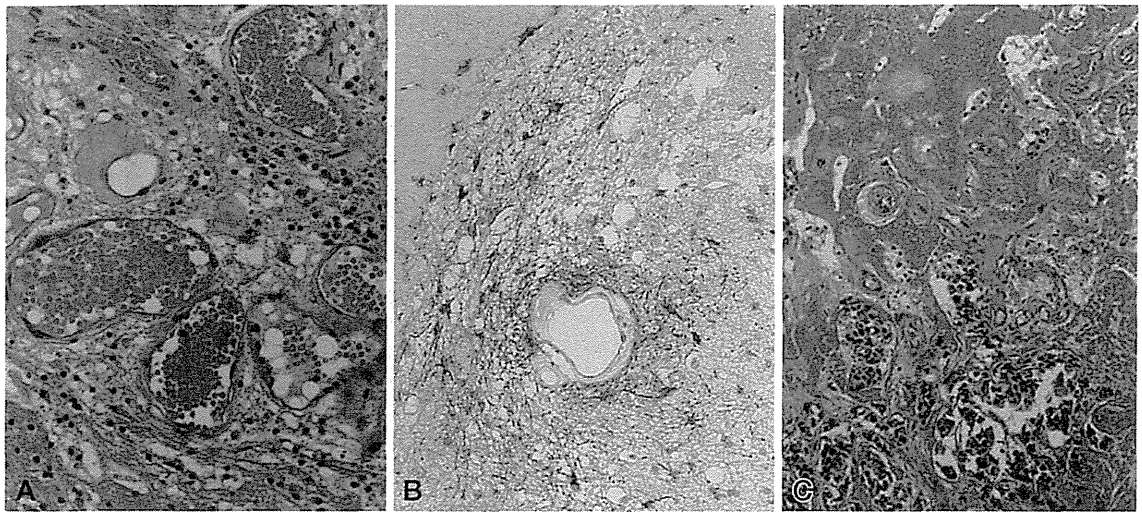

Fig. 3 Histological and immunohistological analysis of radiation necrosis in the brain. The specimen was obtained from the patient, depicted in **Fig. 1**. **A**: Typical H & E staining of the specimen. Marked angiogenesis and interstitial edema was recognized. **B**: Immunohistochemical staining of the specimen with anti-VEGF antibody. Abundant expression of VEGF was recognized in reactive astrocytes. **C**: Some of the H & E staining show the mixture of viable tumor cells in necrotic tissue.

Ⅲ. 脳放射線壊死の診断として生検術は妥当か？

まず，最初に断っておく必要があるのは，ここでいう「診断」の意味である．脳腫瘍に放射線治療を行った際に，一定の治療効果を確認した後，造影病変の拡大とそれに伴う脳浮腫の悪化を経験する．多くの臨床医にとって，このタイミングで腫瘍再発と放射線壊死との鑑別「診断」が必要になる．手術可能なら両者とも手術による摘出の対象になるが，多くの場合手術の対象になりにくい病変に放射線治療を選択することが多い．よって，この浮腫の原因が腫瘍再発と診断されれば再照射も選択肢に入り，壊死が浮腫の原因と診断されれば，壊死に対する治療が選択されるべきである．間違ってもこのような症例に再照射を選択してはならない．はたしてその診断に生検術は有効であろうか？　ここで再度，**Fig. 3** を振り返ってみる．この症例の組織の多くは **Fig. 3C** の左上半分に認めるような細胞構築のない壊死巣であるが，その周囲に **Fig. 3C** 右下半分に認めるようなviable な腫瘍細胞の集簇を散見する．もし針生検術で，このような組織が主として得られた場合，臨床医は次の一手の選択を大いに迷ってしまうことになる．

この症例ではこの viable な腫瘍は VEGF を産生しておらず，浮腫の原因は peri-necrotic area で産生される VEGF による血管新生であったわけである．「木をみて，森をみず」になってはいけない．

Ⅳ. アミノ酸トレーサによる PET での診断

「木をみて，森をみず」を避け，脳浮腫発生時に客観的に次の一手を打つために，どのような診断法を用いるべきか？　文献上は，Tl-SPECT，proton-MRS，FDG-PET などが非侵襲的検査として有用であるとの報告があるが[8,23]，現時点でわれわれが最も信頼している検査がアミノ酸トレーサによる PET である．アミノ酸トレーサとして最も広く活用されているものは C-11 標識の methionine であるが，われわれは脳内でのバックグラウンドがより低く，S/N 比の高いトレーサとして，F-18 標識の boronophenylalanine（^{18}F-BPA）を用いた BPA-PET を使用している．当初本 PET は，BNCT の適応決定や線量シミュレーションに用いていた[15]．本 PET は ^{11}C-MET-PET と同等も

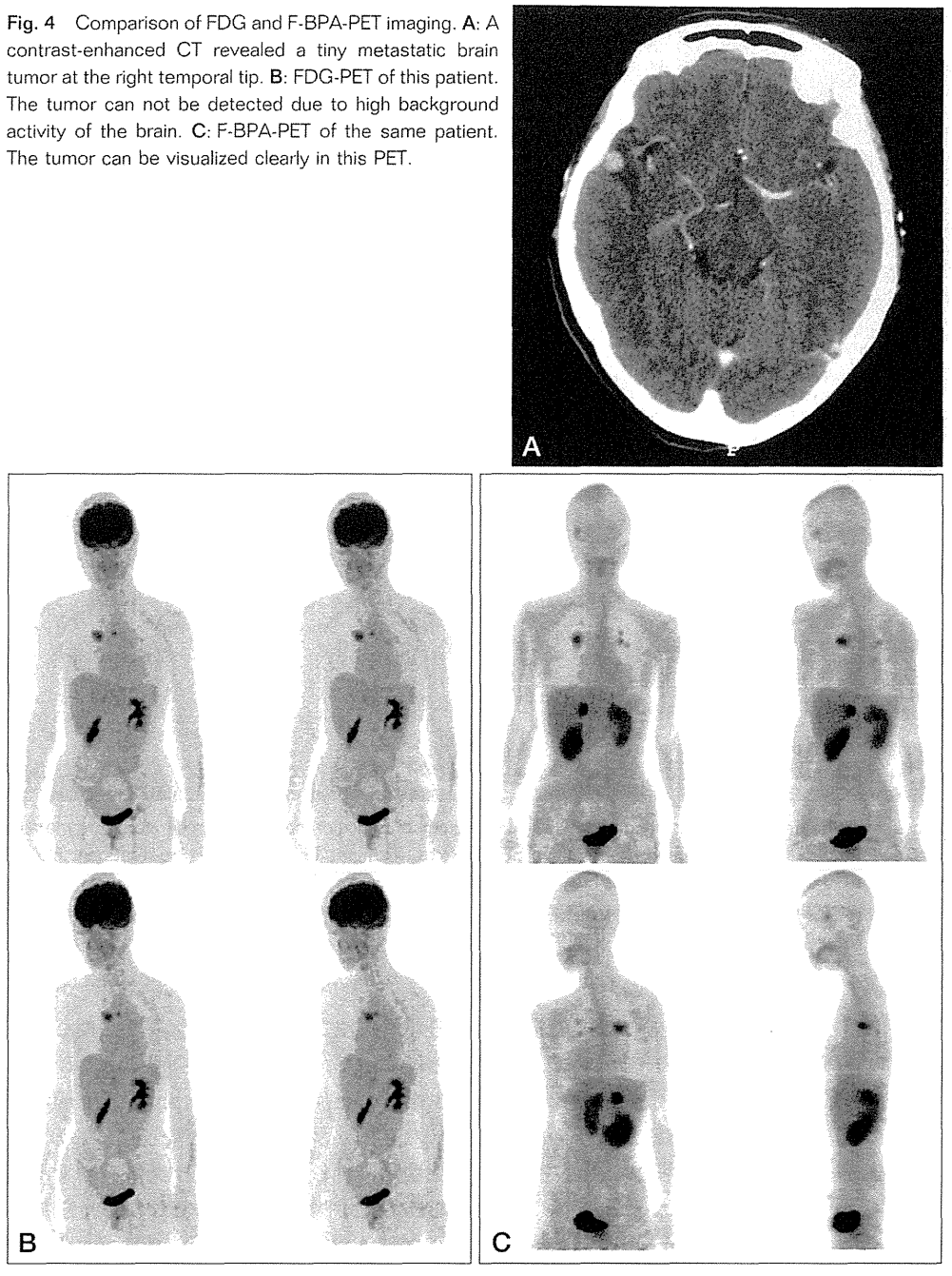

Fig. 4 Comparison of FDG and F-BPA-PET imaging. **A**: A contrast-enhanced CT revealed a tiny metastatic brain tumor at the right temporal tip. **B**: FDG-PET of this patient. The tumor can not be detected due to high background activity of the brain. **C**: F-BPA-PET of the same patient. The tumor can be visualized clearly in this PET.

しくはそれ以上のコントラストで腫瘍の描出が可能であり，腫瘍の検出や，治療後効果判定，壊死と再発の鑑別などに用いるようになった．**Fig. 4** に右側頭葉先端の微小転移性脳腫瘍（悪性黒色腫）に対する，FDG-PET と F-BPA-PET を提示する．FDG-PET では正常脳のバックグラウンドが高く，腫瘍の描出が不能であるが，F-BPA-PET では正常脳のバックグラウンドが低く，このような微小な病変も容易に検出可能である．また，肺，肝臓などの全身への転移巣に対しても F-BPA-