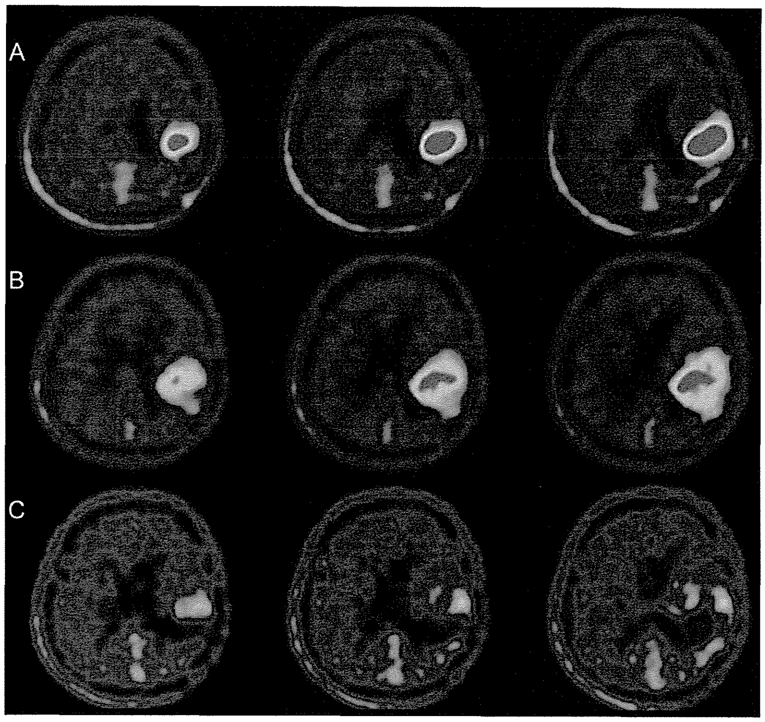

Fig. 2. F-BPA-PET in case 1, prior to BNCT and at aggravation as well as in follow-up with the patient in good condition. (A) Prior to BNCT; (B) 4 months after BNCT (at aggravation); (C) 8 months after BNCT.

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

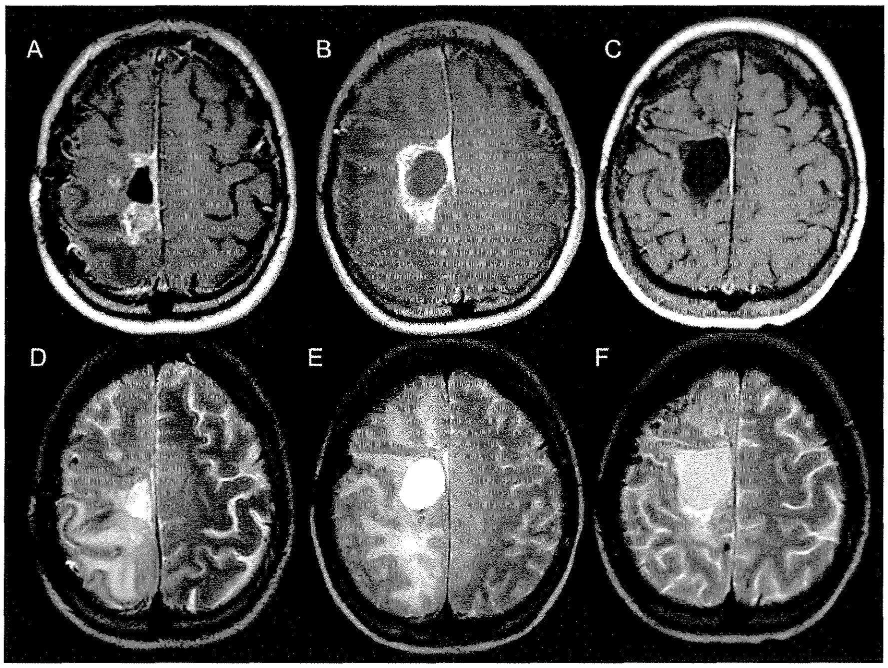

Fig. 3. Periodic MRI changes in case 2. (A–C) Gd-enhanced T1-weighted MRI. (D–F) T2-weighted MRI. (A and D) Just prior to BNCT; (B and E) 2 months after BNCT; (C and F) 6 months after BNCT (4 cycles after initial bevacizumab treatment).

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.

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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

Motomasa Furuse[1,*], Naosuke Nonoguchi[1], Shinji Kawabata[1], Erina Yoritsune[1], Masatsugu Takahashi[2], Taisuke Inomata[2], Toshihiko Kuroiwa[1] and Shin-Ichi Miyatake[1]

[1]Department of Neurosurgery, Osaka Medical College and [2]Department of Radiology, Osaka Medical College, Takatsuki, Osaka, Japan

*For reprints and all correspondence: Motomasa Furuse, Department of Neurosurgery, Osaka Medical College, 2-7, Daigakumachi, Takatsuki, Osaka 569-8686, Japan. E-mail: neu054@poh.osaka-med.ac.jp

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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: ≥3 months elapsed after the initial radiotherapy; unresectable lesions; no systemically active lesion and life expectancy ≥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.

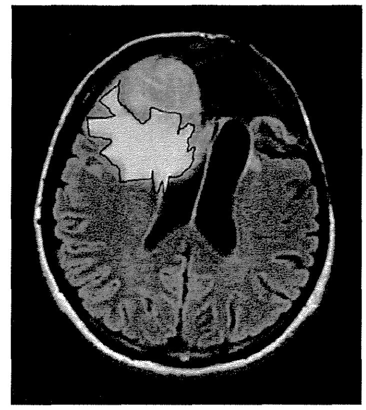

Figure 1. The area of hyperintensity was manually outlined on each FLAIR MR image (black line).

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 Pre-Tx (cm^3)	Perilesional edema Post-Tx (cm^3)	Reduction rate (%)	Pre-KPS	Post-KPS	T or N PFS (months)
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.

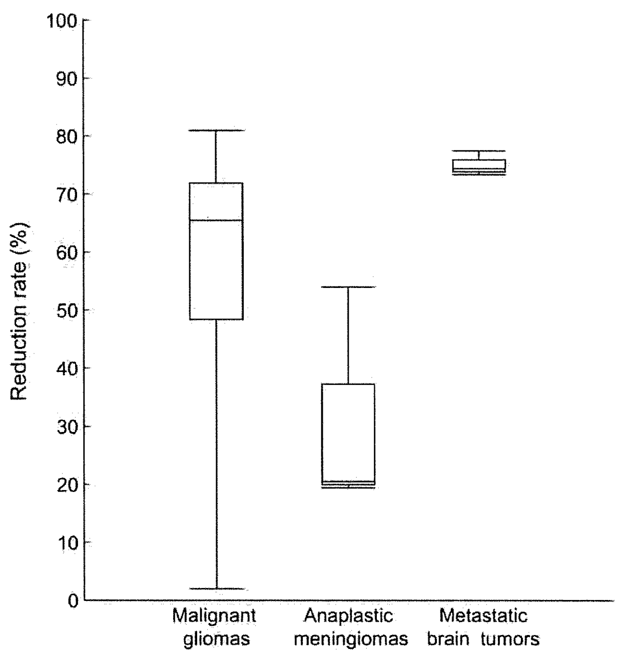

Figure 2. Box plots demonstrating reduction rates of perilesional edema in each tumor pathology.

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/

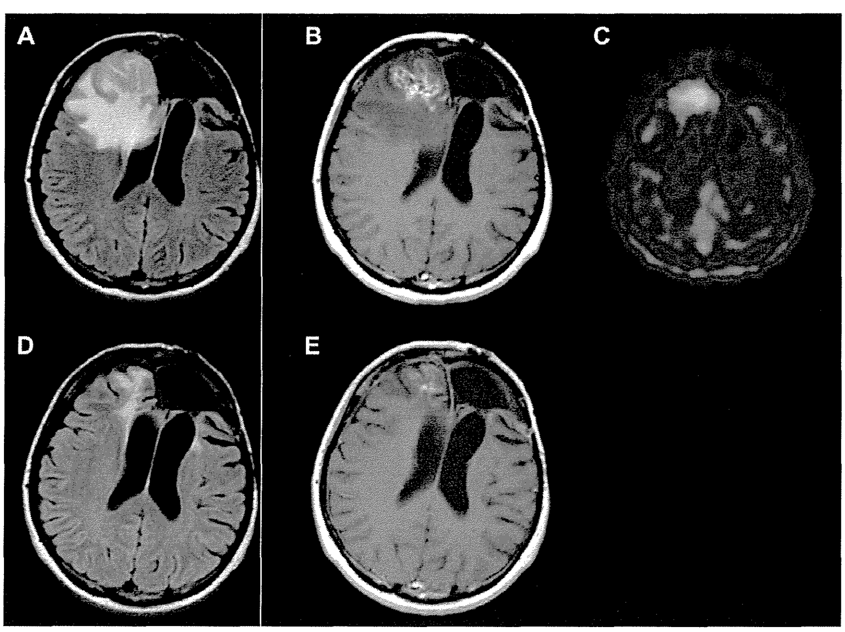

Figure 3. A 27-year-old woman (Case 8) with a left frontal anaplastic astrocytoma was treated with BNCT and X-ray radiotherapy after surgical resection. The patient had a convulsion due to enlarged perilesional edema 4 years later. MR images showed a heterogeneous enhancement with the massive perilesional 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.

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Boron neutron capture therapy for recurrent high-grade meningiomas

Clinical article

*Shinji Kawabata, M.D., Ph.D.,[1] Ryo Hiramatsu, M.D., Ph.D.,[1] Toshihiko Kuroiwa, M.D., Ph.D.,[1] Koji Ono, M.D., Ph.D.,[2] and Shin-Ichi Miyatake, M.D., Ph.D.[1]

[1]*Department of Neurosurgery, Osaka Medical College, Takatsuki;* [2]*Radiation Oncology Research Laboratory, Research Reactor Institute, Kyoto University, Kumatori, Osaka, Japan*

Object. Similar to glioblastomas, high-grade meningiomas are difficult pathologies to control. In this study, the authors used boron neutron capture therapy (BNCT), a tumor-selective intensive particle radiation modality, to treat high-grade meningioma.

Methods. From June 2005 to September 2011, BNCT was applied 28 times in 20 cases of recurrent high-grade meningioma. All patients had previously undergone intensive treatments such as repetitive surgeries and multiple sessions of radiation therapy. Fluorine-18–labeled boronophenylalanine (^{18}F-BPA) PET was performed before BNCT in 19 of the 20 cases; BPA is itself a therapeutic compound. Compound uptake, tumor shrinkage, long-term control rate including survival time, and failure pattern of the treated patients were all evaluated.

Results. Eighteen of 19 cases studied using ^{18}F-BPA PET showed good BPA uptake, with ratios of tumor to normal brain greater than 2.7. These ratios indicated the likely effects of BNCT prior to neutron irradiation. The original tumor sizes were between 4.3 cm^3 and 109 cm^3. A mean tumor volume reduction of 64.5% was obtained after BNCT within just 2 months. The median follow-up duration was 13 months. Six patients are still alive; at present, the median survival times after BNCT and diagnosis are 14.1 months (95% CI 8.6–40.4 months) and 45.7 months (95% CI 32.4–70.7 months), respectively. Clinical symptoms before BNCT, such as hemiparesis and facial pain, were improved after BNCT in symptomatic cases. Systemic metastasis, intracranial distant recurrence outside the radiation field, CSF dissemination, and local tumor progression were observed in 6, 7, 3, and 3 cases, respectively, during the clinical course. Apparent pseudoprogression was observed in at least 3 cases. Symptomatic radiation injuries occurred in 6 cases, and were controllable in all but 1 case.

Conclusions. Boron neutron capture therapy may be especially effective in cases of high-grade meningioma. *(http://thejns.org/doi/abs/10.3171/2013.5.JNS122204)*

Key Words • **boron neutron capture therapy** • **boronophenylalanine** • **epithermal neutron** • **high-grade meningioma** • **oncology**

The management of high-grade meningiomas, especially malignant meningiomas, is very difficult. In a large series of patients with this disease, the 5-year recurrence rate of high-grade meningiomas was reported to be 78%–84% and the median survival time was reported to be 6.89 years;[17] in another series, the rate of late mortality due to recurrence after the initial surgery was reported to be 69%.[28] Although some treatments for recurrent high-grade meningioma have been reported, including chemotherapeutic regimens,[4] no standard treatment has yet been established.

For several years now, we have been applying BNCT for recurrent and refractory high-grade meningioma cases shown to be refractory to any intensive treatments currently available.[23,32] Boron neutron capture therapy is a targeted radiation approach that significantly increases the therapeutic ratio compared with that of conventional radiotherapeutic modalities. Boron neutron capture therapy is a binary approach: a boron-10–labeled compound delivers high concentrations of boron-10 to the target tumor, relative to the surrounding normal tissues. This is followed by irradiation with thermal or epithermal neutrons that become thermalized at a certain depth within

Abbreviations used in this paper: ^{18}F-BPA = fluorine-18–labeled BPA; BNCT = boron neutron capture therapy; BPA = boronophenylalanine; BSH = sodium borocaptate; EBRT = external bean radiation therapy; SRS = stereotactic radiosurgery; SRT = stereotactic radiation therapy.

* Drs. Kawabata and Miyatake contributed equally to this work.

the tissues. The short range (5–9 μm) of the α and lithium-7 particles released from the boron-10 (neutron, α) lithium-7 neutron capture reaction makes the microdistribution of boron-10 critically important in therapy.[7] The release of these particles constitutes high linear energy transfer radiation. These characteristics contribute to tumor-selective and strong tumoricidal activity with minimal damage to normal tissue. If sufficient quantities of boron compounds can be made to accumulate selectively in the tumor tissues, BNCT becomes an ideal intensive particle radiotherapy.

The concept of this unique particle radiation therapy with selective uptake of a suitable isotope was first introduced by Locher in 1936.[19] The first clinical trial of BNCT for patients with glioblastoma was reported by Farr et al. in the 1950s.[10] However, the previously used version of BNCT suffered from numerous problems: a lack of neutron penetration, especially for deep-seated tumors; insufficient contrast in boron concentration between tumor and normal tissues; an absolute lack of boron in tumor tissues; and uncertain estimation of the neutron flux captured by the boron-10 atoms in tumor cells. We modified several parts of the procedure to resolve these problems and applied the modified BNCT to the treatment of malignant gliomas.[21] In addition, we reported the effectiveness of BNCT for high-grade meningiomas, with special reference to tumor shrinkage, as a case report and an early case series.[23,32] Now that we have treated 20 patients with high-grade meningioma by BNCT, and observed these patient for more than 1 year, we share further details in this paper, not only about the tumor volume reduction, but also about long-term control rate, including cumulative survival data and treatment failure patterns.

Methods

Patient Population

Twenty patients with recurrent high-grade meningioma were treated with BNCT in the Department of Neurosurgery at Osaka Medical College between June 2005 and September 2011. We report the results from these 20 patients, all of whom were followed up for more than 1 year. The cases consisted of 12 anaplastic, 4 atypical, 2 papillary, and 1 rhabdoid meningioma, and 1 sarcoma that began as an anaplastic meningioma. Patient profiles are detailed in Table 1. All cases were referred to our institute for BNCT due to uncontrolled tumor growth after repetitive surgeries and EBRT or SRS. These patients had already undergone treatment by EBRT alone in 4 cases, by SRS or SRT alone in 13 cases, and by a combination of both in 3 cases.

Fluorine-18–Labeled BPA PET Analysis

The patients underwent ^{18}F-BPA PET to assess the distribution of BPA and to estimate the boron concentration in tumors before neutron irradiation.[15,16,21,23,32] Notably, BPA is itself a therapeutic boron compound. The tumor-to-normal-brain ratio of BPA uptake can be estimated from ^{18}F-BPA PET, and subsequent dose planning is based on this ratio; each ratio of the patients is included in Table 1. The PET study had to be omitted in 1 case of anaplastic meningioma (Case 3) because of machine malfunction.

Clinical Regimen of BNCT for Malignant Meningiomas

This project was approved by the Ethical Committee of Osaka Medical College, and each candidate was also discussed and approved by the board of reviewers at Osaka Medical College and Kyoto University Research Reactor Institute. The clinical regimen of BNCT for malignant meningiomas was modified slightly from that for malignant gliomas.[21] Patients were typically administered 500 mg/kg of BPA with or without 5 or 2.5 g of BSH (Katchem Ltd) per person. Boronophenylalanine was kindly supplied by the Stella Pharma Corporation in the initial cases and afterward was purchased mainly from Interpharma Praha, a.s. As the study period progressed, BSH became difficult to obtain due to its exorbitant cost. Thus, BSH administration was omitted from Cases 7 through 20.

Boronophenylalanine was administered in the 2 hours just prior to neutron irradiation (200 mg/kg/hr) and then during neutron irradiation (100 mg/kg/hr). This administration method was adopted to maintain a steady blood BPA concentration throughout the entire neutron irradiation. When BSH was available, the compound solution was administered for 1 hour, starting at 12 hours prior to neutron irradiation. The boron concentration in the blood was monitored by sampling every 1 to 2 hours after boron compound administration until neutron irradiation was completed. The boron concentrations from BSH in the tumor and brain tissue were assumed to be the same as the blood concentration. The boron concentrations from BPA in the tumor and normal brain were estimated from the tumor-to-normal-brain ratio of ^{18}F-BPA on PET. Judging from the contribution of each boron compound and the relative biological effectiveness of neutron beams and compounds described previously,[24,25] the neutron fluence rate was simulated by the dose-planning system SERA (Simulation Environments for Radiotherapy Applications; Idaho National Engineering and Environmental Laboratory), and the total doses to the tumor and normal brain were estimated. The duration of neutron irradiation was determined not to exceed 15 Gy-Eq to the normal brain. In this instance, Gy-Eq (Gray Equivalent) means an x-ray dose that can provide biologically equivalent effects to total BNCT radiation. After the treatment, the doses given were precisely reestimated.

Assessment of Effectiveness

The effectiveness of this treatment was volumetrically assessed in serial radiographic analysis. The Gd-contrasted lesion on MRI was semiautomatically selected, and the area was measured on each slice based on the contrast cutoff value (increased intensity on MRI by Gd) from the background. The value of the area was calculated as tumor volume by adding the areas of all slices using I-Response software (Cedara Corp.). Based on the diagnostic images before BNCT, the relative values of the tumor volume (percentage of control) were calculated from

TABLE 1: Patient profile and parameters of BNCT in 20 patients with malignant meningiomas*

Case No.	Histology	Age (yrs), Sex	Treatment Prior to BNCT (no. of times)	Tumor Size (mm)	Tumor Depth (mm)	BPA PET (T/N)	First BNCT Dose (Gy-Eq)		No. of BNCTs
							Max	Min	
1	papillary	29, F	SRS (3), resection (2)	52	39	5.0	93.9	39.7	3
2	anaplastic	48, F	EBRT, SRS, resection (5)	31	59	2.8	73.2	44.2	3
3	anaplastic	60, F	SRS, resection (5)	50	49	none	49.0	32.0	1
4	papillary	67, M	EBRT, resection (2)	42	70	5.0	71.8	22.1	2
5	anaplastic	77, F	SRS (3), resection (4)	24	70	4.5	86	37.2	1
6	atypical	72, F	SRS, resection (2)	66	69	2.0	65.6	19.0	2
7	sarcoma	57, F	SRS (2), resection (4)	47	92	2.7	48.3	14.3	2
8	rhabdoid	26, F	EBRT, resection (3)	24	66	3.1	75.8	18.8	1
9	anaplastic	62, M	EBRT, resection (3)	70	66	4.4	111.5	50.7	1
10	anaplastic	56, F	SRS, resection (2)	25	74	3.9	77.3	26.0	1
11	anaplastic	38, M	EBRT, resection (3)	27	68	3.9	88.9	28.8	1
12	anaplastic	67, F	SRS, resection (4)	24	54	3.5	58.0	22.1	1
13	anaplastic	65, F	EBRT, SRS (2), resection (4)	34	64	3.6	50.2	24.2	1
14	atypical	75, F	SRS (3), resection (3)	80 + 40	29	4.0	72.9	42.3	1
15	anaplastic	79, M	SRT, resection (5)	88	26	3.7	61.0	57.2	1
16	atypical	68, M	SRS (2), resection (2)	52	45	2.7	67.0	52.0	1
17	anaplastic	49, F	SRS, resection (6)	61	74	4.0	68.5	15.0	1
18	anaplastic	50, M	SRS (4), resection (3)	43	52	4.4	100.0	59.0	1
19	anaplastic	63, F	SRS (2), SRT, resection (4)	94	76	4.0	69.5	31.0	2
20	atypical	41, M	SRS (4), resection (5)	48	60	3.0	80.2	32.0	1

* T/N = tumor-to-normal-brain ratio.

consecutive images obtained in each patient's follow-up evaluation. Then, changes in these values over time were graphed and investigated for trends among our 20 patients with high-grade meningiomas undergoing BNCT.

Survival Analysis

Patient survival was defined in 2 ways: the number of months survived after diagnosis of high-grade meningioma and the number after the application of BNCT.

Results

Absorbed Dose in Tumor Tissue

The duration of irradiation was planned to not exceed 15 Gy-Eq in normal brain tissue. The absorbed dose to the tumor tissue was dependent on both the boron concentration in the tumor tissue and the neutron irradiation time, which varied in each case. Therefore, the absorbed dose to the tumor tissue in our protocol was not uniform from case to case. The mean maximum and minimum absorbed doses in our series were 73.4 Gy-Eq (95% CI 65.6–81.3 Gy-Eq) and 33.3 Gy-Eq (95% CI 26.9–39.9 Gy-Eq), respectively (Table 1). These absorbed doses were administered not in fractionation but in 1-time irradiation in BNCT.

Volume Reduction of the Treated Mass During Follow-Up

As we reported previously, all of the initial case series (Cases 1–7) showed volume reduction of the mass during the observation.[23,32] In Fig. 1 we show representative volume reductions of the treated masses from more recent cases (Cases 14, 17, 18, and 20). All other treated tumors also showed definitive shrinkage during follow-up; this tendency toward volume reduction is illustrated in Fig. 2. Although all tumors showed a trend of gradual reduction in volume, a transient increase after BNCT was observed in some cases, usually within a month of treatment, before decreasing; this pattern was called pseudoprogression. The mean tumor size prior to BNCT was 52.2 cm^3, ranging from 4.3 cm^3 to 109 cm^3. A mean volume reduction of 64.5% was achieved within only 2 months of BNCT (Fig. 2).

Treatment Failure

Among the 20 cases of high-grade meningioma treated by BNCT, 6 cases demonstrated systemic metastasis, including lung, vertebral bone, clavicle, liver, and lymph node metastasis (Table 2). Four of these 6 patients died from these metastatic lesions and not the original intracranial lesions. A typical systemic metastasis is depicted in Fig. 3 (Case 13, A–D; Case 7, E–H). Figures 3A and B show good local control of the anaplastic meningioma over the first 3 years, compared with the patient's repeated local tumor recurrence every few months prior to BNCT, even with repetitive SRS treatment. This patient died due to lung metastasis (Fig. 3D). Prior to BNCT, the patient had had a metastatic lesion in the left clavicle, which was controlled by EBRT for 3 years during the observation

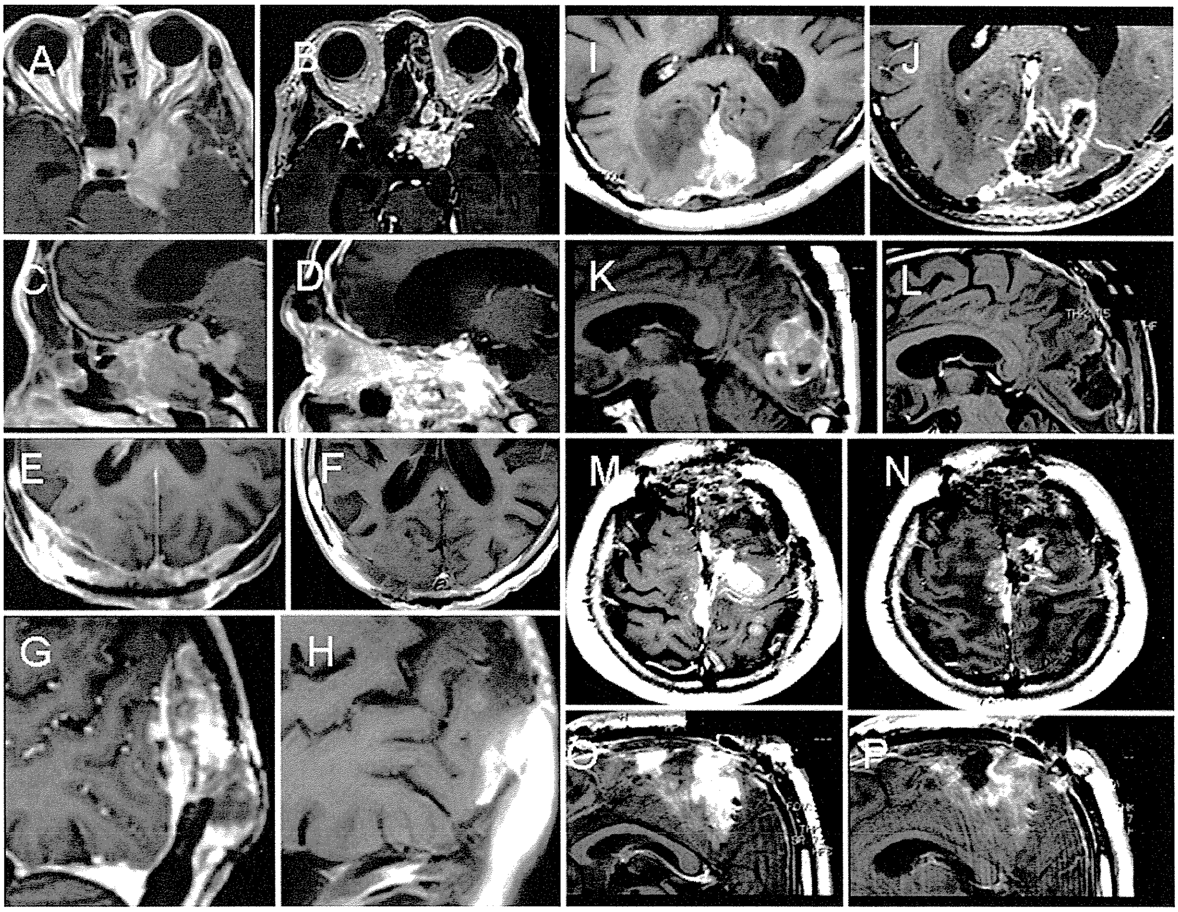

Fig. 1. Representative tumor shrinkage after BNCT demonstrated on axial (A, B, E, F, I, J, M and N) and sagittal (C, D, G, H, K, L, O, and P) Gd-enhanced MR images. Each case shows marked tumor volume reduction after BNCT. **A–D:** Case 17. Images of an anaplastic meningioma before (A and C) and 10 months after BNCT (B and D). **E–H:** Case 14. Images of an atypical meningioma before (E and G) and 6 months after BNCT (F and H). **I–L:** Case 18. Images of an anaplastic meningioma before (I and K) and 10 months after BNCT (J and L). **M–P:** Case 20. Images of an atypical meningioma before (M and O) and 4 months after BNCT (N and P).

period. Also in this case, we experienced tumor recurrence out of the field of neutron irradiation (Fig. 3C).

In Case 7, in which anaplastic meningioma developed into sarcoma, there was continuous tumor shrinkage during the 7 months of follow-up (Fig. 3E and F). This patient developed liver metastasis (Fig. 3G), and died due to dyspnea from the lung metastasis (Fig. 3H). Unfortunately we had no chance to verify that the histological diagnosis of the metastatic lesions was the same as that of the original high-grade meningioma.

Seven of the 20 BNCT-treated high-grade meningioma cases showed recurrence outside the field of neutron irradiation (Table 2). A representative recurrence outside the field of neutron irradiation is depicted in Fig. 3C; this lesion was discovered incidentally 33 months after BNCT. We did not apply a second BNCT for this recurrent lesion because multiple metastases had already been identified in the lung. One patient (Case 14, atypical meningioma) chose to abandon further treatment because of financial difficulties and died due to the metastatic lesion.

Three of the 20 cases experienced increased intracranial pressure by intractable hydrocephalus due to CSF dissemination (Table 2). This type of hydrocephalus could not be controlled by a shunting operation due to the viscosity of the CSF. Typical images are depicted in Fig. 3I–K (Case 11, anaplastic meningioma).

Only 3 of 20 patients died due to local tumor progression (Table 2). Two of these 3 local tumor progression cases were complicated with symptomatic radiation necrosis.

Survival Analysis After Diagnosis and BNCT

The median follow-up duration was 13 months. Six patients are still alive; at present, the median survival times after BNCT and diagnosis are 14.1 months (95% CI 8.6–40.4 months) and 45.7 months (95% CI 32.4–70.7 months), respectively (Fig. 4). It is rather difficult to compare our results to other reports[28] because our patients were refractory to any existent treatments; therefore our study sample was biased due to multiple treatments with repetitive surgeries and radiotherapies (Table 1). Also, many patients in our study died due to systemic metastasis and recurrence outside of the radiation field, as noted above (Table 2).

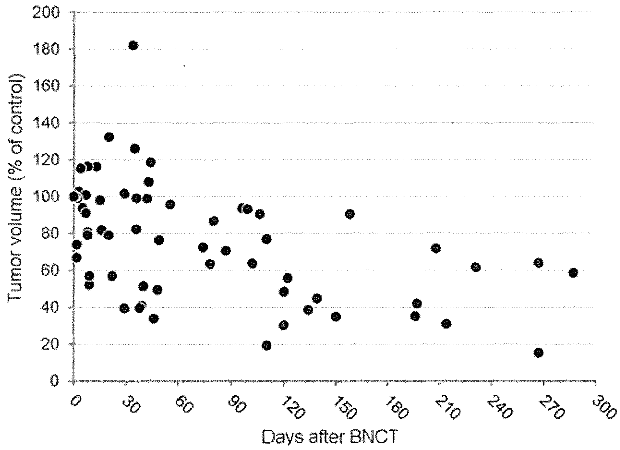

Fig. 2. Scatterplot of the relationship of tumor volume relative to the elapsed time (days) after BNCT. Day 0 means the date of the treatment, and the value (100%) plotted on Day 0 was actually acquired 1–3 weeks before treatment. All the values obtained from each patient from BNCT to relapse were plotted on the same graph.

Discussion

In this report, we present evidence of favorable local control of high-grade meningiomas using BNCT. Only 3 patients died due to local treatment failure, although the follow-up observation periods were rather brief in several recent cases. However, irrespective of good local control of high-grade meningiomas by BNCT, many patients died and the median patient survival time in high-grade meningiomas after BNCT was 14.1 months (Fig. 4). The most prominent pattern of treatment failure in our series was intracranial distant recurrence outside the radiation field, experienced in 7 of 20 cases. The other patterns of treatment failure were systemic metastasis in 6 cases and CSF dissemination in 3 cases. Given that the reported incidence of CSF dissemination in meningioma is only 2%,[5] our series shows a rather high incidence rate. With regard to systemic metastasis in high-grade meningioma, such high incidences have been previously reported in the literature.[5,9] We are not entirely sure of the reason for this high incidence of systemic metastasis. It may be possible that the treatment-refractory nature of our cases resulted in a selection bias for aggressive care and longer survival. Overall, the high incidences of out-of-field recurrence, CSF dissemination, and systemic metastasis might be ascribed to the advanced stage of the patients in our series, as all cases were referred to us after the failure of local tumor control, even using repetitive surgeries and radiotherapies. This selection bias for refractory cases makes it difficult to compare our treatment failure results with the incidence rates reported in the literature. Our patients' advanced tumor stage also makes it difficult to compare the survival data with that of other treatments. All high-grade meningioma cases in this series were recurrent, complicated cases.

TABLE 2: Clinical results and treatment failure patterns after BNCT in 20 patients with malignant high-grade meningiomas*

	Longevity (mos)					Local Recurrence		
Case No.	From Diagnosis	From BNCT	Systemic Metastasis	Dissemination	Symptomatic Radiation Necrosis	Out of Field	In Field	Cause of Death
1	44.2	22.4	yes	no	yes	yes	yes	local progression, radiation necrosis
2	43.2	14.1	yes	no	no	no	no	metastasis
3	32.4	12.9	no	no	yes	yes	no	gastric cancer metastasis
4	70.7	13.1	no	no	no	no	yes	local progression
5	45.7	24.6	no	no	no	no	no	senility
6	64.3	6.4	no	no	yes	no	no	radiation necrosis (DIC)
7	113.4	8.6	yes	no	no	no	no	metastasis
8	30.4	7.3	no	yes	no	no	no	dissemination
9	36.8	9.4	no	yes	yes	no	no	dissemination
10	47.5	44.0	no	no	yes	yes	yes	local progression, radiation necrosis
11	28.3	12.4	no	yes	no	no	no	dissemination
12	56.8	55.6	no	no	no	no	yes	alive
13	59.6	40.4	yes	no	no	yes	no	metastasis (lung, and others)
14	12.3	7.7	no	no	no	yes	no	remote recurrence
15	12.8	8.3	yes	no	no	no	no	metastasis (lung, liver)
16	69.1	15.0	yes	no	no	no	no	alive w/ metastasis (lung)
17	22.1	15.6	no	no	no	no	no	alive
18	68.6	10.7	no	no	no	yes	no	alive
19	32.4	10.4	no	no	no	no	no	alive
20	30.1	8.6	no	no	no	yes	no	alive

* DIC = disseminated intravascular coagulation.

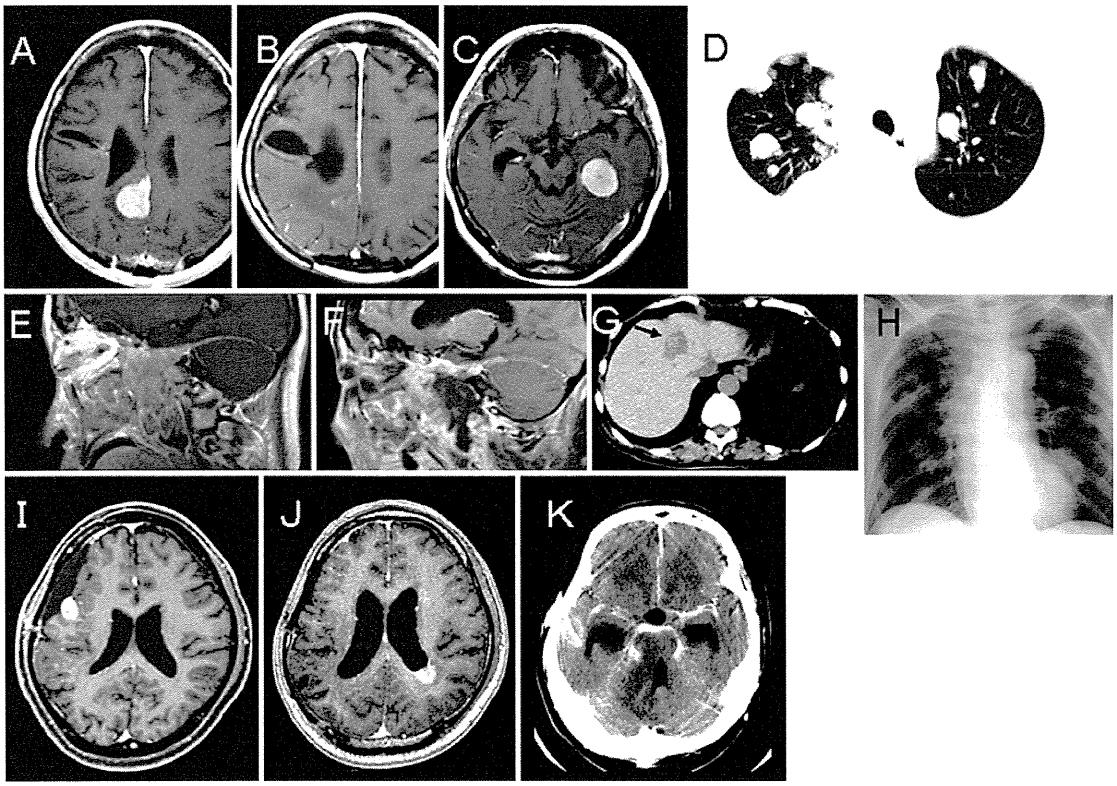

Fig. 3. Typical images of systemic metastasis, intracranial recurrence outside the field of neutron irradiation, and CSF dissemination. **A–D:** Case 13 (anaplastic meningioma). Axial contrast-enhanced MR images obtained prior to BNCT (A) and 33 months after BNCT (B and C), and plain chest CT scan obtained 39 months after BNCT (D). The MRI (C) shows intracranial recurrence out of the field of neutron irradiation. The chest CT scan (D) shows lung metastasis of the meningioma. This patient died due to dyspnea. The patient had already suffered from metastasis of the meningioma at the left clavicle prior to BNCT. **E–H:** Case 7 (sarcoma transformed from anaplastic meningioma). Sagittal contrast-enhanced MR image obtained prior to BNCT (E); sagittal contrast-enhanced MR image (F), plain abdominal axial CT scan (G), and chest radiograph (H) obtained 7 months after BNCT. The original, very large tumor was well controlled by BNCT, but lung and liver metastasis occurred. This patient died due to dyspnea. The *black arrow* (G) shows liver metastasis. **I–K:** Case 11 (anaplastic meningioma). Axial contrast-enhanced MR images obtained prior to BNCT (I) and 7 months after BNCT (J); axial contrast-enhanced CT scan (K) obtained 10 months after BNCT. The original tumor was controlled well, but CSF dissemination with untreatable hydrocephalus occurred.

Historically, conventional EBRT was first used to treat high-grade meningiomas, but with unsatisfactory results.[20] In our series, the original high-grade meningiomas were not controlled locally by EBRT alone. Thereafter, SRS was used for the treatment of high-grade meningiomas, as reported in the literature.[13,27,29,31] The gross tumor volume treated by SRS in these studies was relatively small in comparison with that in our series. Additionally, in our series, 9 patients had already received repetitive SRS but experienced recurrence nonetheless. The typical treatment failure pattern of high-grade meningiomas by SRS in our series was marginal recurrence at the SRS fields. Even for these SRS-refractory cases, BNCT was able to provide good local tumor control.

Particle radiotherapies using proton beams[2,6,14,26,30,33] and carbon ion beams[8,30] have been more recently applied

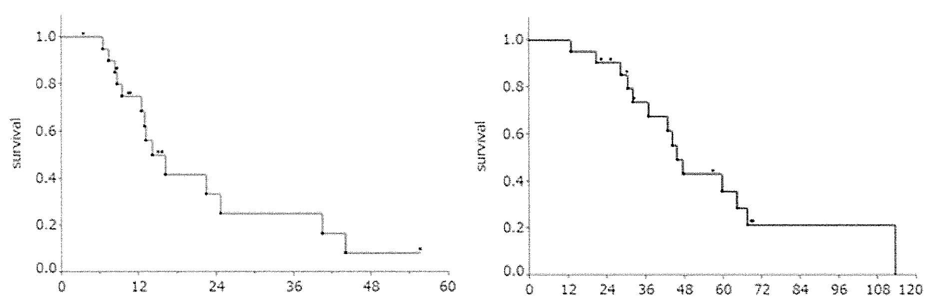

Fig. 4. Graphs of Kaplan-Meyer survival curves after BNCT **(left)** and diagnosis **(right)**. The median survival times after BNCT and diagnosis were 14.1 months (95% CI 8.6–40.4 months) and 45.7 months (95% CI 32.4–70.7 months), respectively.

to cases of high-grade meningioma. Again, it is very difficult to compare our data to the data from particle radiotherapies. First, almost all reported series, including our own, have comprised a limited number of cases. The protocols have varied as well: in some studies, particle therapy was applied just after surgery as the initial radiotherapy, and in others it was applied at recurrence. The applied doses varied and in some trials, particle radiation was followed by fractionated EBRT. In addition, the data on tumor shrinkage after particle irradiation have been scarce. There has been only 1 preliminary report addressing this subject, and the results indicated no prominent early tumor shrinkage using proton and carbon ion beams for the treatment of high-grade meningiomas.[30]

One of the advantages of BNCT is that the radiation field may be planned rather more ambiguously than in SRS and other particle radiotherapies. This merit of BNCT might decrease recurrence in the peri-irradiated field in comparison with other radiation techniques, even with the same absorbed dose as described as "Gy-Eq." Encouragingly, almost all masses in our series responded well, with rapid shrinkage after BNCT (Figs. 2 and 3), as also reported elsewhere.[23] This rapid shrinkage might contribute to the prompt recovery of symptoms in some cases. Our patient in Case 1 became ambulatory 1 week after BNCT, and our patient in Case 7 experienced relief from facial pain within 2 weeks of BNCT, as reported previously.[23,32]

In BNCT, most potent antitumor effects are caused by particles, and we applied 33.3 Gy-Eq and 73.4 Gy-Eq for tumor tissue as minimum and maximum 1-time tumor doses, respectively (Table 1). In the literature on particle radiation, some clinical trials have used proton or carbon particle doses between 18 Gy-Eq and 56 Gy-Eq with fractionation.[8,33] The difference in tumor shrinkage between α and lithium particles and other particles such as carbon and protons may be ascribed to the difference of linear energy transfer. The linear energy transfer of α and lithium particles is higher than that of both protons and carbon particles. It is widely accepted that high linear energy transfer particles have greater biological effects than low linear energy transfer particles;[1,3] of course, there might be other causes. For example, in BNCT a large dose can be delivered at a single time, while other particles are usually applied with fractionation and additional low linear energy transfer EBRT. Because of this difference in protocol, other particles might have less impact on tumor shrinkage.

With respect to adverse effects of BNCT, we experienced 6 cases of symptomatic radiation injury among our 20 cases. One instance was the occurrence of subacute brain swelling after BNCT, as reported previously,[23] while the other 5 cases appeared to show radiation necrosis. Because all cases were introduced to our institute after intensive radiotherapies prior to BNCT, radiation necrosis may have been inevitable, despite the tumor-selective nature of BNCT. Recently, we applied BNCT to a patient with a high-grade meningioma who had never been treated with any radiotherapy, and are now observing this case carefully. Bevacizumab has shown potent effects treating symptomatic radiation necrosis in the brain,[12,18] and we have applied this drug for symptomatic radiation necrosis after BNCT for malignant gliomas.[11] This strategy should be applicable and effective for the treatment of radiation necrosis after BNCT for high-grade meningiomas.

We should emphasize that we found pseudoprogression after BNCT in at least 3 of our 20 high-grade meningioma cases. As we described previously,[22] this phenomenon could itself be an indicator of how promising and intensive the effects of this treatment are.

Conclusions

Boron neutron capture therapy is a new treatment concept and method that has already been used on malignant gliomas, including glioblastomas. Our study suggests that high-grade meningiomas may be an even better candidate for BNCT than those lesions. The meningiomas in our series were somewhat superficial (located on the surface of the brain), except for some specific situations at the skull base, which is advantageous to neutron penetration.

With regard to BPA accumulation, high-grade meningiomas showed a good ratio of tumor to normal brain, even compared with malignant gliomas (Table 1). In addition, judging from the rapid shrinkage of the mass, our assumption about the compound biological effectiveness of BPA for high-grade meningioma—which was assumed to be equal to that of glioblastoma—might have been an underestimation; the real value might be higher than that for glioblastoma. If we can apply BNCT for high-grade meningioma as the initial radiotherapy or at least at the first recurrence, rather than at such advanced stages, more favorable results than those described in our study might be obtained, such as avoiding systemic metastasis or out-of-field recurrence.

Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: Miyatake, Kawabata, Ono. Acquisition of data: Miyatake, Kawabata, Hiramatsu. Analysis and interpretation of data: Miyatake, Kawabata, Hiramatsu. Drafting the article: Miyatake, Kawabata. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Miyatake. Study supervision: Miyatake, Kuroiwa, Ono.

References

1. Barendsen GW: RBE-LET relationships for different types of lethal radiation damage in mammalian cells: comparison with DNA dsb and an interpretation of differences in radiosensitivity. **Int J Radiat Biol 66:**433–436, 1994
2. Boskos C, Feuvret L, Noel G, Habrand JL, Pommier P, Alapetite C, et al: Combined proton and photon conformal radiotherapy for intracranial atypical and malignant meningioma. **Int J Radiat Oncol Biol Phys 75:**399–406, 2009
3. Broerse JJ, Barendsen GW, van Kersen GR: Survival of cultured human cells after irradiation with fast neutrons of dif-

ferent energies in hypoxic and oxygenated conditions. **Int J Radiat Biol Relat Stud Phys Chem Med 13:**559–572, 1968
4. Chamberlain MC: The role of chemotherapy and targeted therapy in the treatment of intracranial meningioma. **Curr Opin Oncol 24:**666–671, 2012
5. Chamberlain MC, Glantz MJ: Cerebrospinal fluid-disseminated meningioma. **Cancer 103:**1427–1430, 2005
6. Chan AW, Bernstein KD, Adams JA, Parambi RJ, Loeffler JS: Dose escalation with proton radiation therapy for high-grade meningiomas. **Technol Cancer Res Treat 11:**607–614, 2012
7. Coderre JA, Morris GM: The radiation biology of boron neutron capture therapy. **Radiat Res 151:**1–18, 1999
8. Combs SE, Hartmann C, Nikoghosyan A, Jäkel O, Karger CP, Haberer T, et al: Carbon ion radiation therapy for high-risk meningiomas. **Radiother Oncol 95:**54–59, 2010
9. Enam SA, Abdulrauf S, Mehta B, Malik GM, Mahmood A: Metastasis in meningioma. **Acta Neurochir (Wien) 138:**1172–1178, 1996
10. Farr LE, Sweet WH, Robertson JS, Foster CG, Locksley HB, Sutherland DL, et al: Neutron capture therapy with boron in the treatment of glioblastoma multiforme. **Am J Roentgenol Radium Ther Nucl Med 71:**279–293, 1954
11. 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 102:**471–475, 2011
12. Gonzalez J, Kumar AJ, Conrad CA, Levin VA: Effect of bevacizumab on radiation necrosis of the brain. **Int J Radiat Oncol Biol Phys 67:**323–326, 2007
13. Hakim R, Alexander E III, Loeffler JS, Shrieve DC, Wen P, Fallon MP, et al: Results of linear accelerator-based radiosurgery for intracranial meningiomas. **Neurosurgery 42:**446–454, 1998
14. Hug EB, Devries A, Thornton AF, Munzenride JE, Pardo FS, Hedley-Whyte ET, et al: Management of atypical and malignant meningiomas: role of high-dose, 3D-conformal radiation therapy. **J Neurooncol 48:**151–160, 2000
15. Imahori Y, Ueda S, Ohmori Y, Kusuki T, Ono K, Fujii R, et al: Fluorine-18-labeled fluoroboronophenylalanine PET in patients with glioma. **J Nucl Med 39:**325–333, 1998
16. Imahori Y, Ueda S, Ohmori Y, Sakae K, Kusuki T, Kobayashi T, et al: Positron emission tomography-based boron neutron capture therapy using boronophenylalanine for high-grade gliomas: part I. **Clin Cancer Res 4:**1825–1832, 1998
17. Jääskeläinen J, Haltia M, Servo A: Atypical and anaplastic meningiomas: radiology, surgery, radiotherapy, and outcome. **Surg Neurol 25:**233–242, 1986
18. Levin VA, Bidaut L, Hou P, Kumar AJ, Wefel JS, Bekele BN, 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 79:**1487–1495, 2011 (Erratum in **Int J Radiat Oncol Biol Phys 84:**6, 2012)
19. Locher G: Biological effects and therapeutic possibilities of neutrons. **Am J Roentgenol Radium Ther 36:**1–13, 1936
20. Mahmood A, Caccamo DV, Tomecek FJ, Malik GM: Atypical and malignant meningiomas: a clinicopathological review. **Neurosurgery 33:**955–963, 1993
21. Miyatake S, Kawabata S, Kajimoto Y, Aoki A, Yokoyama K, Yamada M, 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 103:**1000–1009, 2005
22. Miyatake S, Kawabata S, Nonoguchi N, Yokoyama K, Kuroiwa T, Matsui H, et al: Pseudoprogression in boron neutron capture therapy for malignant gliomas and meningiomas. **Neuro Oncol 11:**430–436, 2009
23. Miyatake S, Tamura Y, Kawabata S, Iida K, Kuroiwa T, Ono K: Boron neutron capture therapy for malignant tumors related to meningiomas. **Neurosurgery 61:**82–91, 2007
24. Morris GM, Coderre JA, Hopewell JW, Micca PL, Fisher C: Boron neutron capture irradiation of the rat spinal cord: effects of variable doses of borocaptate sodium. **Radiother Oncol 39:**253–259, 1996
25. Morris GM, Coderre JA, Micca PL, Fisher CD, Capala J, Hopewell JW: Central nervous system tolerance to boron neutron capture therapy with p-boronophenylalanine. **Br J Cancer 76:**1623–1629, 1997
26. Noël G, Habrand JL, Mammar H, Haie-Meder C, Pontvert D, Dederke S, et al: Highly conformal therapy using proton component in the management of meningiomas. Preliminary experience of the Centre de Protonthérapie d'Orsay. **Strahlenther Onkol 178:**480–485, 2002
27. Ojemann SG, Sneed PK, Larson DA, Gutin PH, Berger MS, Verhey L, et al: Radiosurgery for malignant meningioma: results in 22 patients. **J Neurosurg 93 (Suppl 3):**62–67, 2000
28. Palma L, Celli P, Franco C, Cervoni L, Cantore G: Long-term prognosis for atypical and malignant meningiomas: a study of 71 surgical cases. **J Neurosurg 86:**793–800, 1997
29. Pollock BE, Stafford SL, Link MJ, Garces YI, Foote RL: Stereotactic radiosurgery of World Health Organization grade II and III intracranial meningiomas: treatment results on the basis of a 22-year experience. **Cancer 118:**1048–1054, 2012
30. Rieken S, Habermehl D, Haberer T, Jaekel O, Debus J, Combs SE: Proton and carbon ion radiotherapy for primary brain tumors delivered with active raster scanning at the Heidelberg Ion Therapy Center (HIT): early treatment results and study concepts. **Radiat Oncol 7:**41, 2012
31. Stafford SL, Pollock BE, Foote RL, Link MJ, Gorman DA, Schomberg PJ, et al: Meningioma radiosurgery: tumor control, outcomes, and complications among 190 consecutive patients. **Neurosurgery 49:**1029–1038, 2001
32. Tamura Y, Miyatake S, Nonoguchi N, Miyata S, Yokoyama K, Doi A, et al: Boron neutron capture therapy for recurrent malignant meningioma. Case report. **J Neurosurg 105:**898–903, 2006
33. Weber DC, Schneider R, Goitein G, Koch T, Ares C, Geismar JH, et al: Spot scanning-based proton therapy for intracranial meningioma: long-term results from the Paul Scherrer Institute. **Int J Radiat Oncol Biol Phys 83:**865–871, 2012

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Address correspondence to: Shin-Ichi Miyatake, M.D., Department of Neurosurgery, Osaka Medical College, 2-7 Daigaku-machi, Takatsuki City, Osaka 569-8686, Japan. email: neu070@poh.osaka-med.ac.jp.

腫瘍細胞選択的粒子線治療「ホウ素中性子捕捉療法」と抗血管新生薬による症候性脳放射線壊死の治療

宮武 伸一[1)]

1) 大阪医科大学医学部脳神経外科

Cell-selective Particle Radiation, Boron Neutron Capture Therapy and Treatment of Symptomatic Radiation Necrosis in the Brain by Anti-angiogenic Agent

Shin-Ichi Miyatake, M.D., Ph.D.[1)]

1) Department of Neurosurgery, Osaka Medical College

Boron neutron capture therapy (BNCT) has been advocated as a novel particle radiation therapy for malignant tumors that targets tumor cells biologically. Since 2002, we have applied this unique radiotherapy for 133 malignant gliomas and malignant meningiomas at our institution. In addition, we recently applied anti-angiogenic agents aggressively for intractable symptomatic radiation necrosis in the brain.

Here is our latest comprehensive data regarding these unique treatments, including those I presented at the 32nd annual meeting of the Japanese Neurosurgical Congress, along with some new findings.

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Key words : bevacizumab, boron neutron capture therapy (BNCT), positron emission tomography (PET), radiation necrosis

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はじめに

Boron neutron capture therapy (以下 BNCT) は原理上腫瘍に対する細胞選択的照射が可能な唯一の放射線治療法である．ホウ素 (^{10}B) 化合物を投与し，その後，熱中性子もしくは熱外中性子を照射する．ホウ素化合物自体には細胞毒性はなく，また中性子の殺細胞効果もきわめて小さいが，ホウ素同位体^{10}B 原子核は中性子を捕獲し，きわめて線エネルギー付与（粒子が 1μm 運動する間に周囲に付与するエネルギー：keV/μm）の高いヘリウム原子核（α粒子）とリチウム反跳核をそれぞれ，9μm と 4μm という，細胞 1 個に相当する距離に放出し，その細胞を破壊する細胞選択的な粒子線治療ともいえる (Fig. 1)[3)]．すなわち殺細胞効果はホウ素中性子捕獲反応の生じた細胞に限局され，隣接する細胞には影響を及ぼさない．そこで，ホウ素化合物を腫瘍に選択的に集積できれば，腫瘍選択的な細胞破壊が可能となる．

本稿では，まず BNCT 時にその適応決定，線量 simulation に用いる F-BPA-PET を紹介し，次いで悪性神経膠腫に対する治療効果，悪性髄膜腫に対する治療効果，F-BPA-PET による治療効果の判定や放射線壊死，pseudoprogression の鑑別を紹介する．さらには原子炉に代わる新規中性子源として開発してきた小型加速器による治験を紹介する．最後に高線量放射線治療の宿命ともいえ

連絡先：宮武伸一，〒569-8686 高槻市大学町 2-7 大阪医科大学医学部脳神経外科
Address reprint requests to: Shin-Ichi Miyatake, M.D., Ph.D., Department of Neurosurgery, Osaka Medical College, 2-7 Daigaku-machi, Takatsuki-shi, Osaka 569-8686, Japan

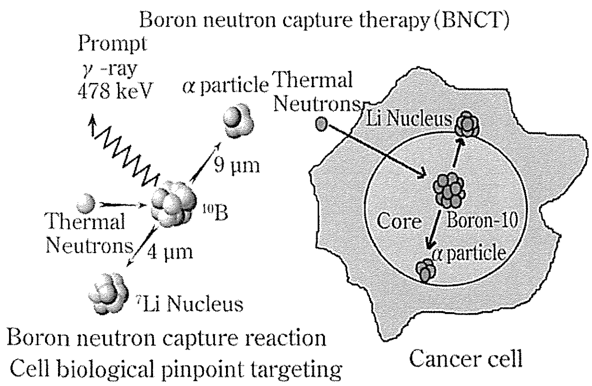

Fig. 1 Principle of BNCT

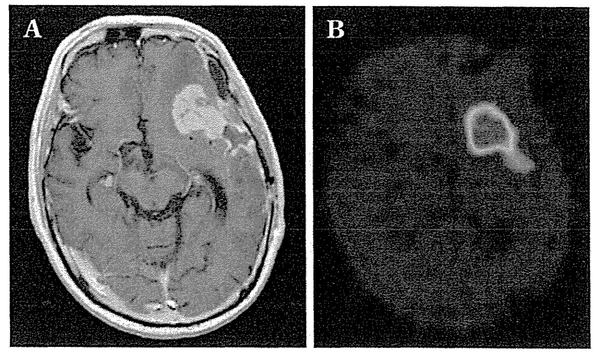

Fig. 2 Typical F-BPA-PET findings in glioblastoma multiforme (GBM)
A : T1-Gd enhanced MRI revealed a left frontal mass. B : F-BPA-PET imaging showed marked BPA accumulation not only in the enhanced area but also in the surrounding brain. The lesion/normal brain ratio of the tracer uptake in this case was 7.1.

る，脳放射線壊死に対する抗血管新生薬による治療法とその薬事申請への行程を紹介する．

F-BPA-PET

BNCT における治療用化合物 BPA（boronophenylalanine）を用いた PET 検査を中性子照射に先立って行う．BPA は文字通りホウ素化した phenylalanine であり，腫瘍において亢進したアミノ酸代謝を利用し，腫瘍内に能動的かつ選択的に集積される．フッ素ラベルした BPA をトレーサとして利用することにより，PET により腫瘍内および脳内 BPA 濃度が推測され，治療の適応決定および照射線量が simulation できる．**Fig. 2** に BPA-PET による BPA の取り込みを示す．この症例では左前頭葉部腫瘍は反対側正常脳に比べて，7.1 倍のトレーサの集積を示している．この PET が示す情報は大きく，2 つの情報が存在する．1 つは 7.1 倍という数字は，同一部位に腫瘍細胞と正常細胞が存在すれば（浸潤部領域にそのような situation が想像できる），腫瘍細胞は正常細胞の 7.1 倍の粒子線を吸収することを示す．もう 1 つの情報は，造影 MRI に比較して，その外側にもトレーサの集積を認めることより，造影域より外側に浸潤している細胞にも targeting できていることを物語っている[10]．

悪性神経膠腫に対する BNCT の効果

悪性黒色腫とともに最も初期より BNCT が適応されてきた疾患が悪性神経膠腫であった．われわれは再発悪性神経膠腫に BNCT を適応し，すべての症例で画像上顕著な効果を認めた[7)10]．また，新規診断膠芽腫にも積極的に BNCT を適応し，化学療法なしに良好な成績を収めている[8]．この経験をもとに，現在 BNCT 後に追加 X 線外照射および temozolomide を併用した，新規診断膠芽腫に対する多施設共同研究を厚生労働科学研究費のサポートをいただき，展開中である．

初発膠芽腫に対する BNCT の効果および問題点を示す症例を **Fig. 3** として提示する．左側脳室三角部近傍の膠芽腫である．手術による部分摘出の後，BNCT を施行した．BNCT 施行前，施行 8 カ月後の頭部 MRI および脊髄 MRI を A，B，C として提示している．BNCT は良好な局所制御を示しているが，脊髄髄腔内播種をきたし，この症例を亡くしている．われわれの BNCT の経験では，このように局所制御は比較的良好であるが，およそ半分の症例は髄腔内播種で亡くしている．今後の課題と考えている．

すでに放射線治療歴を有する再発悪性神経膠腫に対しても，本治療法は細胞選択性を有するので，積極的な照射を行ってきた．再発神経膠腫に対する RPA 分類を用いて[2]，BNCT の成績と既存治療法の成績を比較すると，予後不良群でその生存期間中央値を有意に延長している[13]．しかしながら，たとえば **Fig. 2** に示した症例では，病変と正常脳のトレーサの集積比が 7.1 倍と高値を示すが，逆に考えると正常脳は腫瘍の 1/7.1 の粒子線を被曝する．再発例の場合にはすでに許容線量限界に近い放射線治療が施行されているので，BNCT といえども，脳放射線壊死が問題となる．この点に関しては後述の抗血管新生療法を展開している．

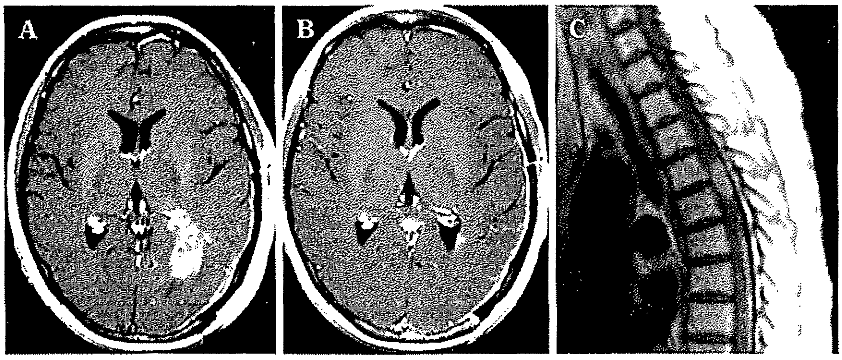

Fig. 3 Periodic Gd-enhanced MRI findings of a GBM case treated by BNCT. A newly diagnosed GBM case in which the left trigonal lesion was treated by BNCT.

A : Brain MRI, prior to BNCT. B : Brain MRI, 8 months after BNCT. C : Spinal MRI, 8 months after BNCT, showing CSF dissemination of the lesion at the spinal cord.

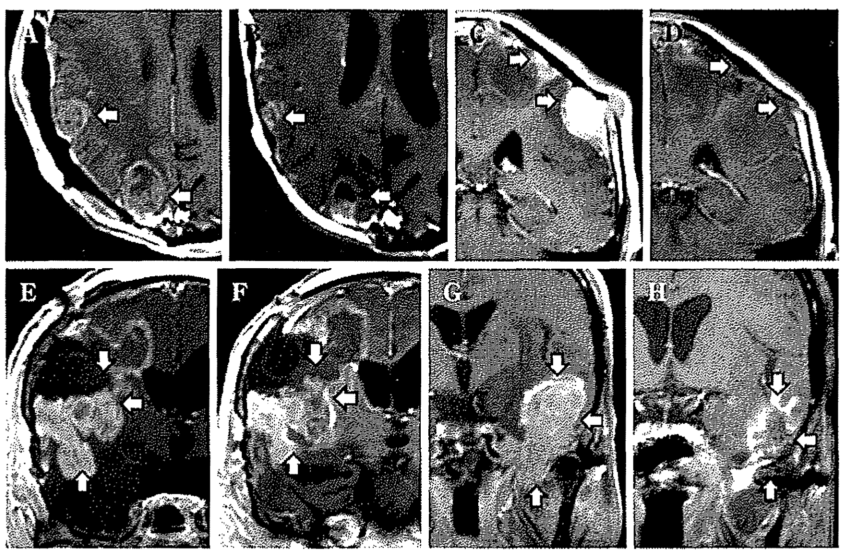

Fig. 4 Typical MRI changes of malignant meningiomas treated by BNCT

A, B : Prior to BNCT and 3 months after BNCT of a anaplastic meningioma.
C, D : Prior to BNCT and 4 months after BNCT of a anaplastic meningioma.
E, F : Prior to BNCT and 5 months after BNCT of an anaplastic meningioma.
G, H : Prior to BNCT and 4 months after BNCT of a rhabdoid meningioma.

高グレード髄膜腫に対する BNCT の効果

高グレード髄膜腫（high grade meningioma：HGM）は手術，定位放射線治療を行っても，その予後は悪い[6)18)]．ことに WHO grade 3 に属する anaplastic meningioma の予後は悪い．われわれは世界に先駆けて，これら HGM に対しても積極的に BNCT を適応してきた[11)19)]．Fig. 4 に anaplastic meningioma 3 例，rhabdoid meningioma 1 例の BNCT 前後の MRI を示す．この 4 例以外でもすべての症例で画像上顕著な腫瘍縮小効果を経験している．われわれの施設に紹介をいただく症例はすべて，複数回の手術，X 線外照射，定位放射線治療等が施行され，それでも制御不能な治療不応症例であるが，良好な局所制御を認めている．2011 年 9 月までに治療を終え，その後 1 年以上の経過を観察しえた 20 例では，局所再発は 4 例で認めたのみであるが，多くの症例を BNCT 後に失っ