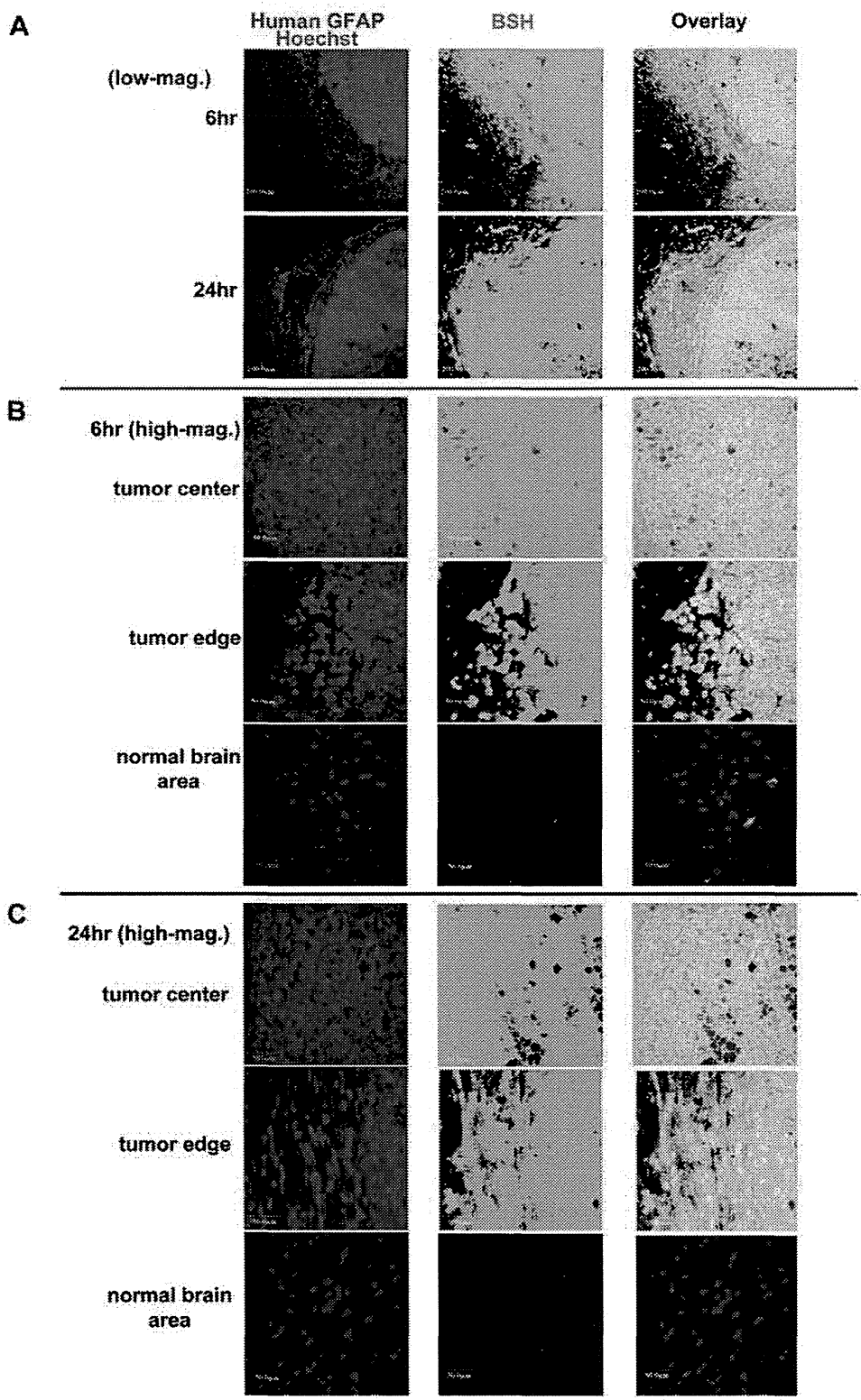

Fig. 4. Confocal imaging showing immunohistochemistry of BSH in mouse brain tumor model with injection into mouse tail vain 4-A: Confocal imaging of brain tumor slices at low magnification showing human-specific detected GFAP (brain tumor area: red), BSH (green), nucleus (blue) 6 or 24 h after mouse tail vein injection of 8BSH-11R. Scale bar = 200 μm 4-B, C: Immunohistochemistry imaging of the tumor core area (tumor center), tumor border zone (tumor edge) and normal brain area (normal brain) showing human GFAP (red), BSH (green) and nucleus (blue). Scale bar = 50 μm. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

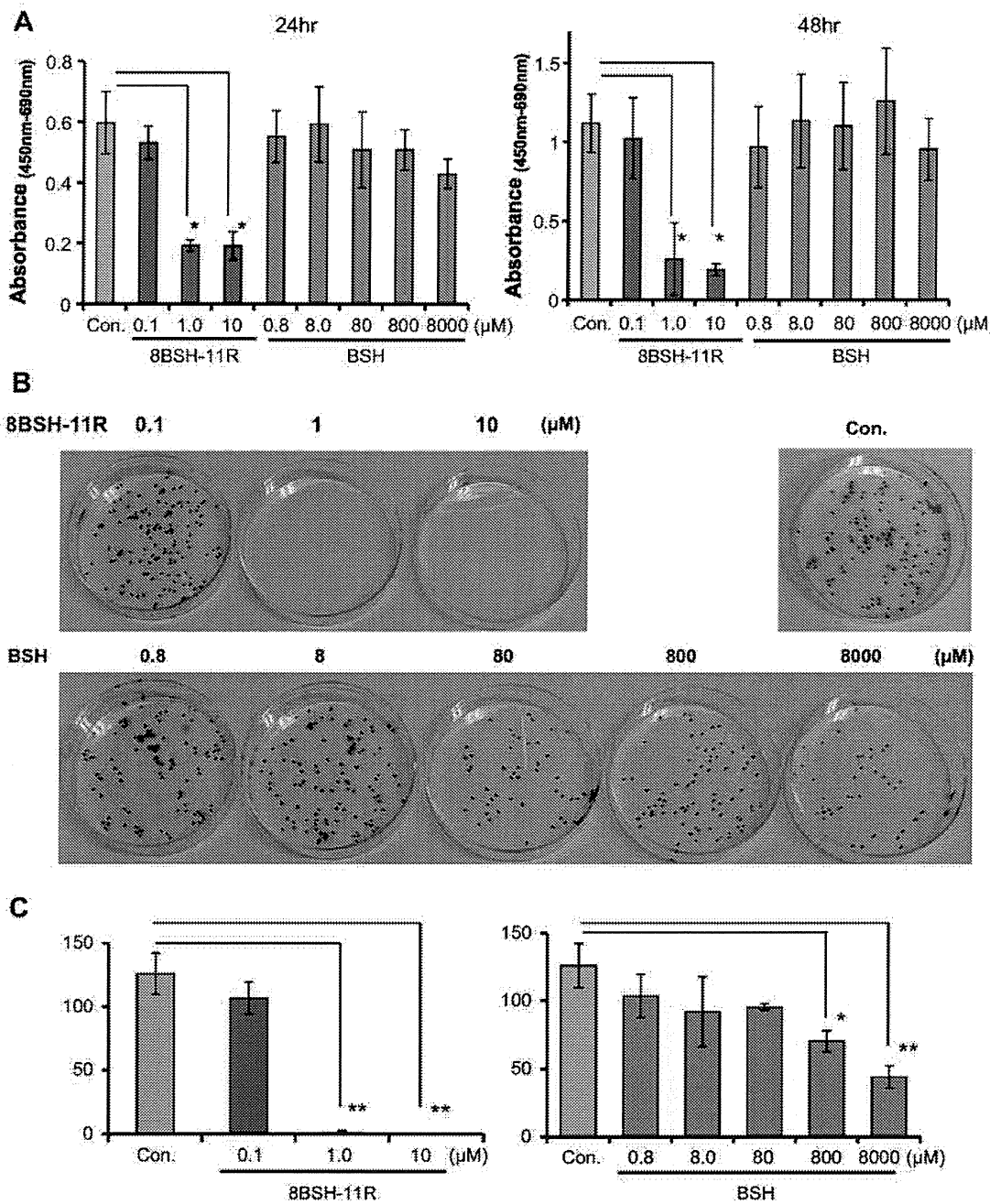

Fig. 5. Cell proliferation results with administration of BSH or 8BSH-11R after neutron irradiation by nuclear reactor 5-A: WST-1 assay showing early-stage damage of BNCT to malignant glioma cells (U87 delta EGFR) 24 and 48 h after neutron irradiation at each different BSH or 8BSH-11R concentration. All data were measured at the absorbance 450 nm-690 nm. $^{*}p < 0.01$ 5-B, C: Colony formation assay results showing late-stage damage of BNCT to glioblastoma cells with different doses of BSH or 8BSH-11R. $^{*}p < 0.05$, $^{**}p < 0.01$.

4. Discussion

The nuclear reaction effectiveness of BNCT is a very limited area with alpha decay that induces alpha particles and lithium-7 nuclei and induces specific cell death through the double strand break of DNA [3,25]. BNCT is not only next-generation therapy but also one of the most anticipated treatments in the short-term against various malignant refractory tumors [28]. One of the most difficult problems in BNCT to develop the next stage for clinical use is to develop new and useful boron compounds beyond the present boron agent, BSH. A clinical trial with high-dose BPA (900 mg/kg) in BNCT against glioblastoma patients in Sweden showed no survival improvement compared to standard therapy [29]. However, the combination use of BPA (700 mg/kg) and BSH (100 mg/kg) in BNCT against glioblastoma patients with additional X-ray irradiation therapy induced a very good outcome by the Osaka Medical University group, Japan [2]. The combined use of BSH and BPA is the key to BNCT success in glioblastoma therapy. BPA can pass through the blood brain barrier (BBB) and accumulate in the tumor [5]. BPA is taken up into cells through L-type amino acid transporter 1 (LAT-

1), which can transport neutral amino acids with a relatively bulky aromatic side chain (e.g. phenylalanine and tyrosine) [30–32] LAT-1 highly expresses many malignant tumor cell lines including glioma cells and a few normal organs (e.g. brain and placenta). On the other hand, BSH is an anionic boron cluster, but cannot enter cells by itself. Regarding the anti-cancer effect of BNCT, extracellular boron localization in cancer cells is less effective than intracellular boron; however, there is no clear evidence or simulations about the relationship between boron localization and nuclear energy transfer on a cellular level. In our simulation results, the cell membrane localization of 1ppm boron showed only 1/30–1/1000 times energy deposition in the nucleus with neuron irradiation. This showed a very clear direction to innovate a new boron compound from BSH. We consider that the combined use of BSH and BPA is essential for glioblastoma treatment from Japanese BNCT clinical data and the next plan to improve the survival outcome will depend on the improvement of BSH. Several reports about boron delivery systems (BDS) have shown the good effectiveness to develop intra-cellular transducible BSH, but this peptide BDS is reported for the original in BNCT research [23,24,33–36]. BSH, CPPs and BSH-CPPs were not toxic and were very safe in clinical use [11,37]. The 8BSH-11R-administrated group with neutron irradiation showed a very strong tumor killing effect compared to the BSH-administrated group. Regarding effectiveness in the brain tumor model, 8BSH-11R localized specifically in the tumor area and inside malignant glioma cells and long-term accumulation in the tumor was maintained (Fig. 4). Interestingly, 8BSH-11R did not show uptake into the normal brain area for enhanced permeability and retention (EPR) effects.

Delivering multiple boron clusters into cells by CPP is economical, safe and effective in respect of medical treatment because one CPP can carry many BSHs while maintaining a high of boron ratio of one boron molecule in the cell; that is using, the peptide dendrimer it is expected that the cell will be destroyed by concentrated boron clusters with a sufficient effect of BNCT, when a small amount of the peptide dendrimer is carried into cells. Since a well-defined peptide dendrimer can be prepared with simple SPPS and organic synthesis, this peptide dendrimer is expected to be used in the application of medical treatment that differs from the drug delivery of dendrimers reported by other groups [38–43].

This is the original paper on a new boron compound with a peptide delivery system *in vitro* and *in vivo*. Some papers have pointed out the toxicity of BDS with liposomes, whereas, the peptide delivery system with CPPs is very safe and is anticipated to be used for clinical applications. In this study, we used 11R, the polyarginine domain and TAT as CPP for BDS, aiming for clinical application in BNCT [36]. Several reports have pointed out that DDS with CPP transduction therapy needs repeated administration to maintain a continuous long-term effect *in vivo* in cancer treatment [44]. Considering that BNCT is usually only once treatment, this application of BDS is ideal for the development of CPP therapy [45]. Our results showed that the malignant glioma cells in the 8BSH-11R group had inhibited tumor growth with a very low concentration of BSH-peptide administration compared to the clinical use of BSH with neutron radiation. The ingenious use of BSH in BNCT, such as its combination with CPPs, offers a new direction for new BDS (Table 3). Recently, many functional peptides have been reported for tumor targeting, low-pH sensitive peptide (pH Low Insertion Peptide: pHLIP), hypoxia region stable domain (oxygen degradation domain: ODD) and many tumor surface receptor targeting peptides [46–48]. We can apply these peptides with important functions against various cancers to deliver boron peptide. Hence, this new boron compound with functional peptide use will contribute to enhancing safe and effective BNCT as a next-generation major cancer therapy.

Table 3
A chart of BSH-fused peptide plan from present BSH compound to next generation of BSH-peptides.

	BSH compound	Peptide vector	Advantages & disadvantages
Present BSH	BSH	No	No BBB passage, No uptake into cell High boron content
1st generation BSH-peptide	BSH-11R	11R (CPP)	Intracellular transduction with CPP Low boron content
2nd generation BSH-peptide	(BSH)n-11R	11R (CPP) Lys dendritic domain	Intracellular transduction High boron content No targeting function
3rd generation BSH-peptide	Target-peptide-(BSH)n-poly-Arg	Tumor-targeting domain Lys dendritic domain 11R or not	Intracellular transduction High boron content Targeting function

5. Conclusion

We made multi-linked mercaptoundecahydrododecaborate (BSH) fused cell-penetrating peptide, 11R and became successful for introducing safely into malignant glioma *in vitro* and *in vivo*. Intracellular boron compounds fused CPP showed strong tumor growth inhibition with neutron irradiation and.

BSH-peptide has potential to be the core boron agent in future boron neutron capture therapy.

Competing financial interests

The authors declare no competing financial interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.biomaterials.2013.12.055.

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NEURO-ONCOLOGY

Bevacizumab treatment of symptomatic pseudoprogression after boron neutron capture therapy for recurrent malignant gliomas. Report of 2 cases

Shin-Ichi Miyatake, Motomasa Furuse, Shinji Kawabata, Takashi Maruyama, Toshihiro Kumabe, Toshihiko Kuroiwa, and Koji Ono

Department of Neurosurgery, Osaka Medical College, Takatsuki, Osaka, Japan (S.-I.M., M.F., S.K., T.K.); Department of Neurosurgery, Tokyo Women's Medical College, Shinjuku, Tokyo, Japan (T.M.); Department of Neurosurgery, Tohoku University, Sendai, Miyagi, Japan (T.K.); Radiation Oncology and Particle Radiation Oncology Research Center, Research Reactor Institute, Kyoto University, Kumatori, Osaka, Japan (K.O.)

Background. Bevacizumab, an anti–vascular endothelial growth factor antibody, has been used for the treatment of radiation necrosis. Thus far, however, there has been no definitive report on its use for the treatment of symptomatic pseudoprogression. Here we report 2 cases of successful treatment with bevacizumab for symptomatic pseudoprogression after boron neutron capture therapy (BNCT) was applied for recurrent malignant gliomas.

Methods. Two recurrent malignant gliomas received BNCT. Both cases were treated with intravenous administration of bevacizumab at the deterioration that seemed to be symptomatic pseudoprogression.

Results. The first case was recurrent glioblastoma multiforme and the second was recurrent anaplastic oligoastrocytoma. Both cases recurred after standard chemoradiotherapy and were referred to our institute for BNCT, which is tumor-selective particle radiation. Just prior to neutron irradiation, PET with an amino acid tracer was applied in each case to confirm tumor recurrence. Both cases showed deterioration in symptoms, as well as on MRI, at intervals of 4 months and 2 months, respectively, after BNCT. For the first case, a second PET was applied in order to confirm no increase in tracer uptake. We diagnosed both cases as symptomatic pseudoprogression and started the intravenous administration of 5 mg/kg bevacizumab biweekly with 6 cycles. Both cases responded well to this, showing rapid and dramatic improvement in neuroimaging and clinical symptoms. No tumor progression was observed 8 months after BNCT.

Conclusions. Bevacizumab showed marked effects on symptomatic pseudoprogression after BNCT. BNCT combined with bevacizumab may prolong the survival of patients with recurrent malignant gliomas.

Keywords: bevacizumab, boron neutron capture therapy, malignant gliomas, pseudoprogression.

With the advent of temozolomide (TMZ), concomitant chemoradiation and maintenance chemotherapy with TMZ have become the worldwide standard treatment for malignant gliomas (MGs), especially glioblastoma multiforme (GBM).[1] In GBM treatments, pseudoprogression (psPD) can be encountered with a relatively high frequency, especially in O^6-DNA methylguanine-methyltransferase (MGMT) promoter methylated cases,[2] and intensive treatment might be the primary factor in psPD, as Brandsma et al reported.[3] Boron neutron capture therapy (BNCT) is biochemically targeted radiation based on the nuclear capture and fission reactions that occur when nonradioactive boron-10, which is a constituent of natural elemental boron, is irradiated with low-energy thermal neutrons to yield high linear energy transfer alpha particles and recoiling lithium-7 nuclei. Because these particles are released within a very short range, such as 9 μm, the cytotoxic effects are confined within boron-10–containing cells.[4] Boron-10–containing compounds can be accumulated selectively into tumor cells by several mechanisms. For example,

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Corresponding Author: Shin-Ichi Miyatake, MD, PhD, Department of Neurosurgery, Osaka Medical College, 2-7 Daigaku-machi, Takatsuki City, Osaka 569-8686, Japan (neu070@poh.osaka-med.ac.jp).

boronophenylalanine (BPA) is selectively and preferentially accumulated into tumor cells via the augmented metabolism of amino acids in comparison with normal cells. We applied BNCT aggressively to newly diagnosed and recurrent MGs.[5–7] We previously reported a high incidence of psPD after BNCT, not only in MGs but also in malignant meningiomas.[8] However, it is difficult for us to estimate precisely the psPD occurrence rate after BNCT, because many cases were followed up after BNCT by physicians in charge in many towns in Japan. Nevertheless, we have the impression that psPD might occur more frequently by BNCT than by X-ray treatment and that the rate of psPD after BNCT might be higher in recurrent cases than in newly diagnosed cases.

Bevacizumab, an anti–vascular endothelial growth factor (VEGF) antibody, has been used for the treatment of symptomatic radiation necrosis (RN).[9,10] It is difficult to definitively distinguish RN from psPD. We therefore applied intravenous administration of bevacizumab to cases we highly suspected to be symptomatic psPD encountered after BNCT for recurrent MGs. Here we report 2 successfully treated cases of symptomatic psPD after BNCT with bevacizumab.

Case Presentation

Case 1

A 56-year-old male experienced speech disturbance and consequently retired from his job. First he received a craniotomy in April 2008 with a diagnosis of gemistocytic astrocytoma followed by fractionated X-ray treatment (total 50 Gy) and repetitive chemotherapy with nitrosourea. In April 2011, a recurrent lesion appeared with gadolinium (Gd) enhancement on MRI. Re-craniotomy revealed GBM histologically. After surgery, the enhanced lesion gradually grew, and sensory aphasia was aggravated despite the repeated administration of TMZ. Also, carbon 11–labeled methionine PET (C-Met-PET) showed high uptake of the tracer beyond the Gd-enhanced lesion. The patient was then referred to our institute for BNCT. Upon referral, MRI showed a small ringlike enhanced lesion having satellite-enhanced dots in the left temporal lobe, with a relatively large volume of fluid-attenuated inversion recovery (FLAIR) at high intensity, as shown in Fig. 1A and D. A simultaneous fluorine 18–labeled (F)-BPA-PET image showed marked tracer uptake in the left temporo-parietal region, as shown in Fig. 2A, with a 5.5 lesion/normal (L/N) brain ratio of the tracer, indicating that the lesion was a highly malignant tumor.

We administered BNCT to our patient according to our recent protocol for recurrent MGs and malignant meningiomas. Briefly, only BPA was administered in the 2 h (200 mg/kg/h) just prior to neutron irradiation and then during neutron irradiation (100 mg/kg/h). The irradiation time was decided by simulation not to exceed 12.0 Gy-Eq (Gray-equivalent) for the peak brain dose. Using BNCT, we estimated maximum brain dose, maximum tumor dose, and minimum tumor dose as 10.8, 110, and 82.3 Gy-Eq, respectively. Here, Gy-Eq corresponds to the biologically equivalent X-ray dose that would have equivalent effects on

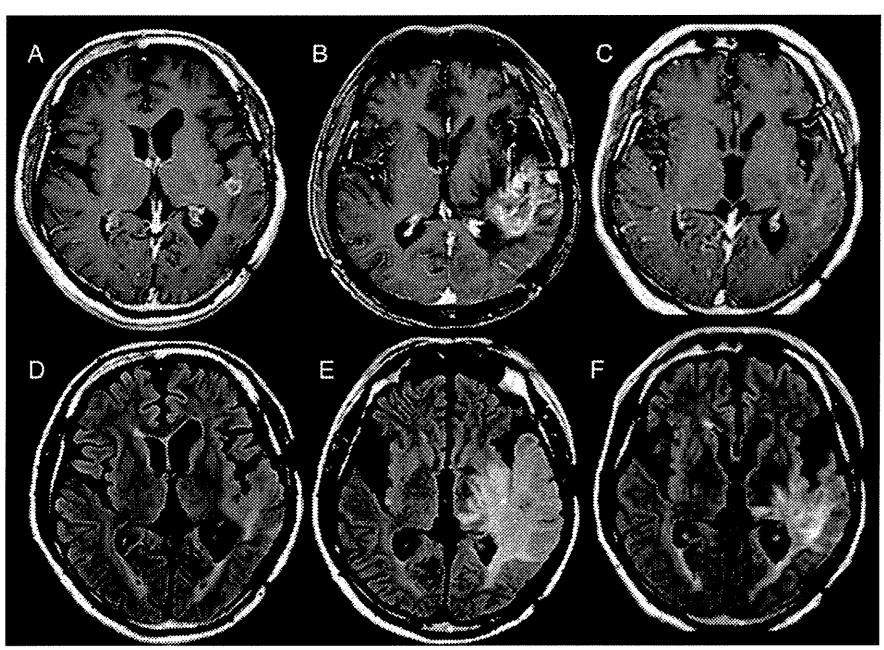

Fig. 1. Periodic MRI changes in case 1. (A–C) Gd-enhanced T1-weighted MRI. (D–F) FLAIR MRI. (A and D) Just prior to BNCT; (B and E) 4 months after BNCT; (C and F) 7 months after BNCT (3 cycles after initial bevacizumab treatment).

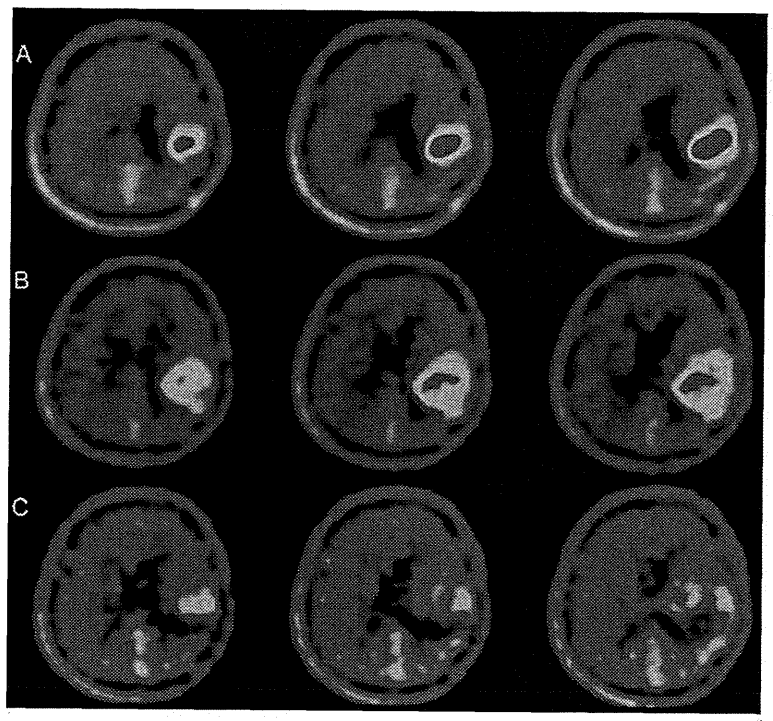

Fig. 2. F-BPA-PET in case 1, prior to BNCT and at aggravation as well as in follow-up with the patient in good condition. (A) Prior to BNCT; (B) 4 months after BNCT (at aggravation); (C) 8 months after BNCT.

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

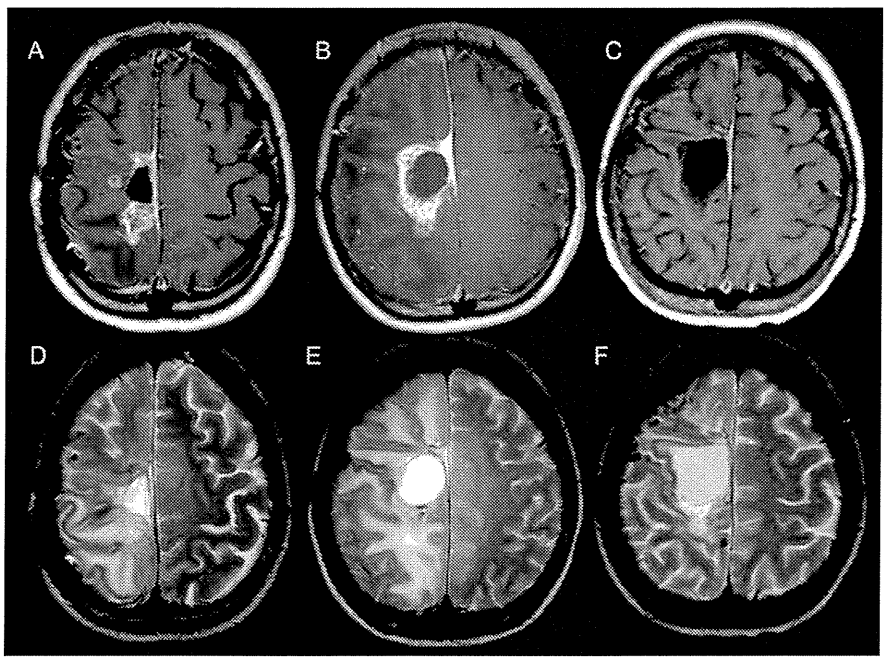

Fig. 3. Periodic MRI changes in case 2. (A–C) Gd-enhanced T1-weighted MRI. (D–F) T2-weighted MRI. (A and D) Just prior to BNCT; (B and E) 2 months after BNCT; (C and F) 6 months after BNCT (4 cycles after initial bevacizumab treatment).

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.

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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: $\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.

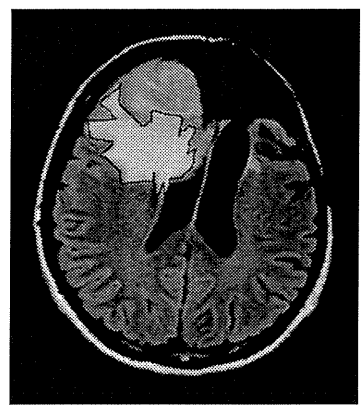

Figure 1. The area of hyperintensity was manually outlined on each FLAIR MR image (black line).

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

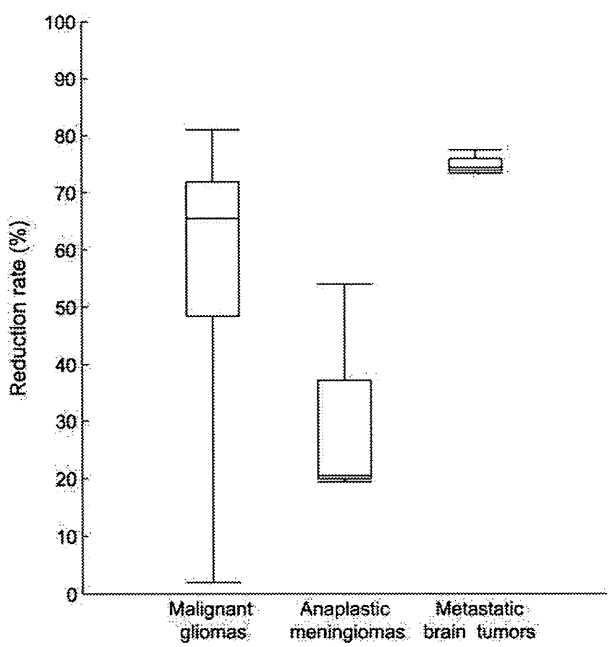

Figure 2. Box plots demonstrating reduction rates of perilesional edema in each tumor pathology.

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/

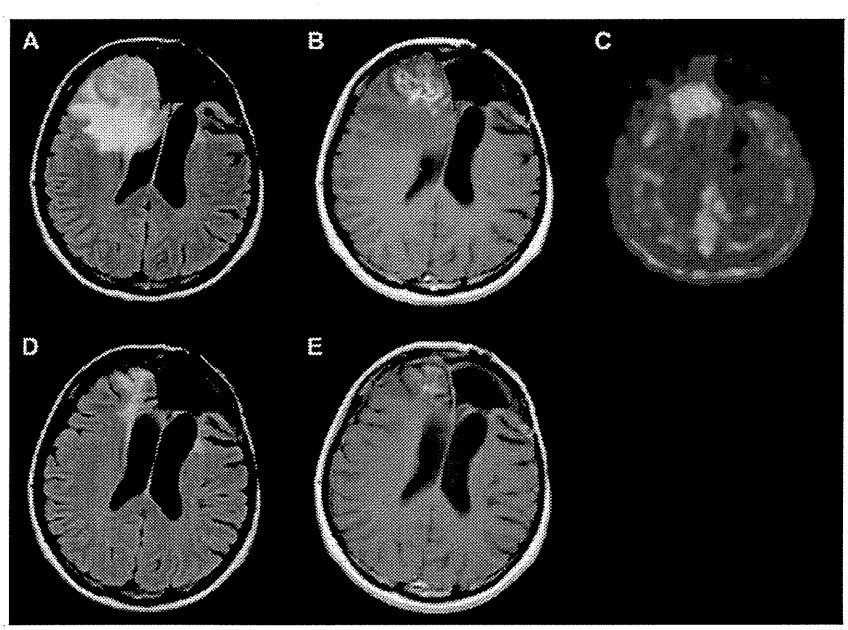

Figure 3. A 27-year-old woman (Case 8) with a left frontal anaplastic astrocytoma was treated with BNCT and X-ray radiotherapy after surgical resection. The patient had a convulsion due to enlarged perilesional edema 4 years later. MR images showed a heterogeneous enhancement with the massive perilesional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

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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

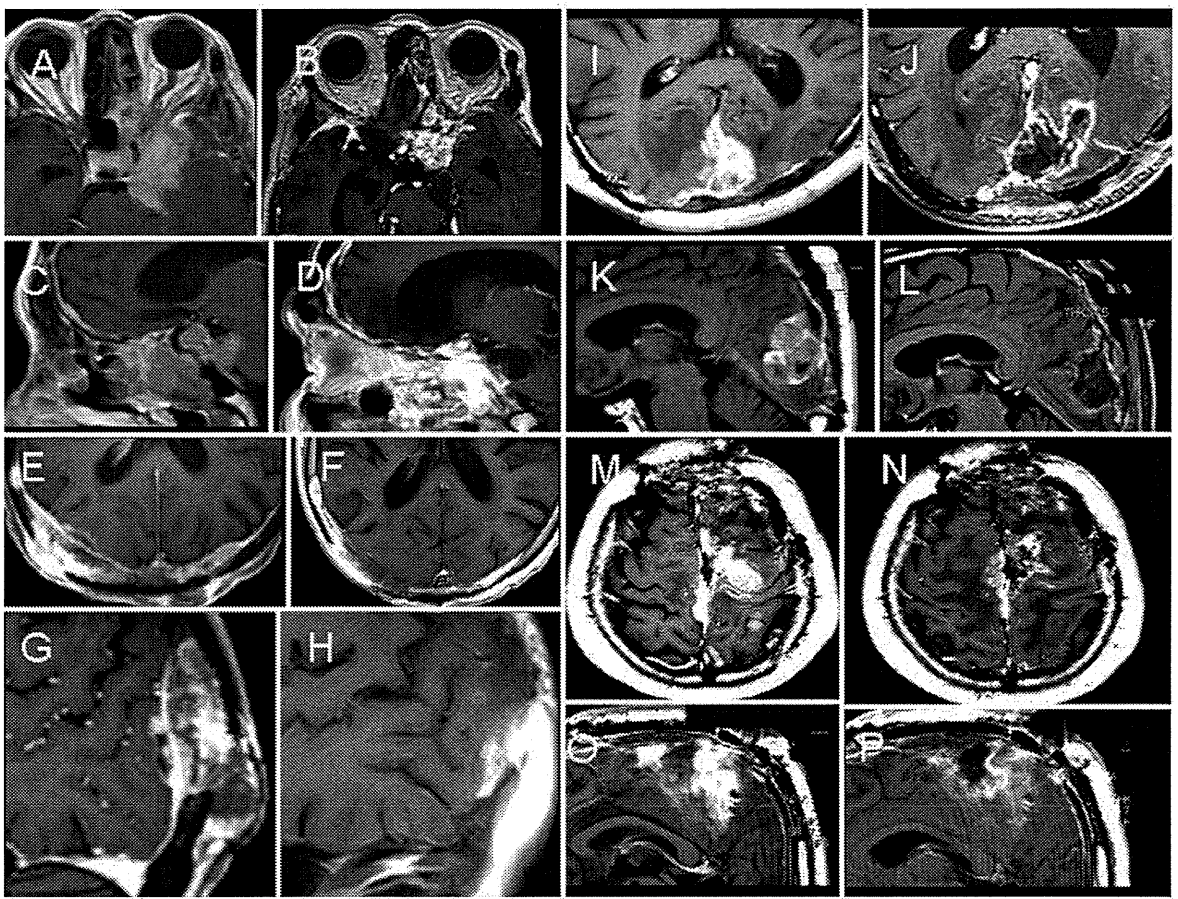

FIG. 1. Representative tumor shrinkage after BNCT demonstrated on axial (A, B, E, F, I, J, M and N) and sagittal (C, D, G, H, K, L, O, and P) Gd-enhanced MR images. Each case shows marked tumor volume reduction after BNCT. **A–D:** Case 17. Images of an anaplastic meningioma before (A and C) and 10 months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

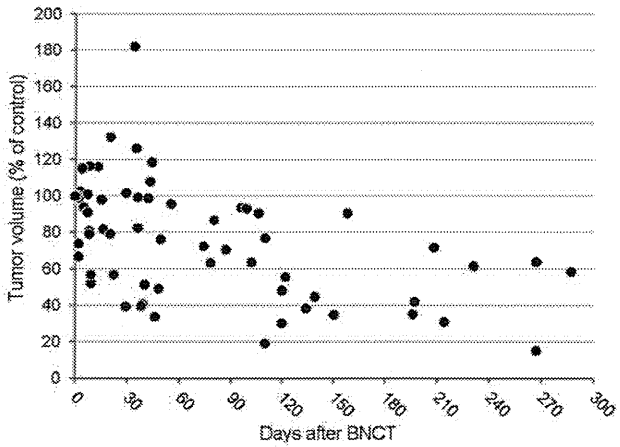

FIG. 2. Scatterplot of the relationship of tumor volume relative to the elapsed time (days) after BNCT. Day 0 means the date of the treatment, and the value (100%) plotted on Day 0 was actually acquired 1–3 weeks before treatment. All the values obtained from each patient from BNCT to relapse were plotted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

Case No.	Longevity (mos)		Systemic Metastasis	Dissemination	Symptomatic Radiation Necrosis	Local Recurrence		Cause of Death
	From Diagnosis	From BNCT				Out of Field	In Field	
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.