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

SHIN-ICHI MIYATAKE, M.D., SHINJI KAWABATA, M.D., YOSHIHANA KAJIMOTO, M.D., ATSUSHI AOKI, M.D., KUNIO YOKOYAMA, M.D., MAKOTO YAMADA, M.D., TOSHIHIKO KUROIWA, M.D., MOTOMU TSUJI, M.D., YOSHI IMAHORI, M.D., MITSUHIRO KIKIHARA, PH.D., YOSHIHIKO SAKURAI, PH.D., SHIN-ICHIRO MASUNAGA, M.D., KENJI NAGATA, M.D., AKIRA MARUHASHI, PH.D., AND KOJI ONO, M.D.

Departments of Neurosurgery and Surgical Pathology, Osaka Medical College, Takatsuki Osaka; Department of Neurosurgery, Kyoto Prefectural University of Medicine, Kyoto; Department of Agriculture, Osaka Prefectural University, Sakai, Osaka; and Division of Medical Physics and Radiation Oncology, Research Laboratory, Research Reactor Institute, Kyoto University, Kumorari, Osaka, Japan

Object. To improve the effectiveness of boron neutron capture therapy (BNCT) for malignant gliomas, the authors used epithermal rather than thermal neutrons for deep penetration and two boron compounds—sodium borocaptate (BSH) and boronophenylalanine (BPA)—with different accumulation mechanisms to increase the boron level in tumors while compensating for each other’s faults.

Methods. Thirteen patients, 10 of whom harbored a glioblastoma multiforme (GBM), one a gliosarcoma, one an anaplastic astrocytoma, and one an anaplastic oligoastrocytoma, were treated using this modified BNCT between January 2002 and December 2003. Postoperatively, neuroimaging revealed that only one patient with a GBM had no lesion enhancement postoperatively. The patients underwent 11B-BPA positron emission tomography, if available, to assess the accumulation and distribution of BPA before neutron radiotherapy. The neutron fluence rate was estimated using the Simulation Environments for Radiotherapy Applications dose-planning system before irradiation. The patients’ volume assessments were performed using magnetic resonance (MR) imaging or computerized tomography (CT) scanning. Improvements in the disease as seen on neuroimages were assessed between 2 and 7 days after irradiation to determine the initial effects of BNCT; its maximal effects were also analyzed on serial neuroimages.

The mean tumor volume before BNCT was 42.3 cm³. Regardless of the pre-BNCT tumor volume, in every patient harboring an assessable lesion, improvements on MR or CT images were recognized both at the initial assessment (range of volume reduction rate 17.4–71%, mean rate 46.4%) and at follow-up assessments (range of volume reduction rates 30.3–87.6%, mean rate 58.5%). More than 50% of the contrast-enhanced lesions disappeared in eight of the 12 patients during the follow-up period.

Conclusions. This modified BNCT produced a good improvement in malignant gliomas, as seen on neuroimages.

Key Words • glioma • boron neutron capture therapy • boronophenylalanine • sodium borocaptate • positron emission tomography scanning

Boron neutron capture therapy is a targeted approach to radiotherapy that significantly increases the therapeutic ratio relative to conventional radiotherapeutic modalities. Boron neutron capture therapy is a binary approach: a 10B-labeled compound delivers high concentrations of boron-10 to the targeted 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 the tissues. The short range (< 10 μm) of the α and 7Li particles released from the 10B(n,α) 7Li neutron capture reaction makes the microdistribution of boron-10 critically important in the therapy. These particles represent high linear energy transfer radiation. Their characteristics contribute to strong tumoricidal activity with negligible damage to normal tissue. Therefore, if sufficient quantities of boron compounds can be made to accumulate selectively in tumor tissues, BNCT becomes an ideal radiotherapy.

It is important to note that a previous version of BNCT had many problems: a lack of neutron penetration, especially in cases of deep-seated tumors; an insufficient contrast in the boron concentration between tumor and normal tissues;
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an absolute lack of boron in tumor tissues; and an uncertain estimation of the neutron flux captured by the $^{10}$B atoms in tumor cells. We modified several points of the technique to resolve these problems and applied this modified BNCT to 13 patients with malignant gliomas between January 2002 and December 2003. We previously reported the effectiveness of BNCT in two cases. In the current paper we wish to introduce the modifications we have made and our revised clinical regimen, and to demonstrate the effectiveness of our modified BNCT in 13 consecutive cases, especially with regard to imaging studies.

Clinical Material and Methods

Patient Population

Between January 2002 and December 2003, 25 patients with malignant gliomas were admitted to our department for BNCT. Thirteen patients (10 harboring a GBM, one a gliosarcoma, one an anaplastic astrocytoma, and one an anaplastic oligoastrocytoma) underwent this treatment, as listed in Table 1. Five tumors were newly diagnosed as malignant gliomas and eight were identified as recurrent lesions after a previous operation and some adjuvant therapy. Some of the 13 patients underwent diagnostic studies and surgery at Osaka Medical College and others were surgically treated at other hospitals and transferred to Osaka Medical College for BNCT. Aside from these 13 patients, others were excluded for various reasons: three for CSF dissemination of the disease on presentation, four because the tumor was located too deep with relation to the brain surface (> 6 cm), three because there was tumor extension to the opposite hemisphere, and two because of limited BPA uptake in $^{18}$F-BPA PET scans, as described later in this paper.

Clinical Regimen of the Modified BNCT

This project was approved by the Ethical Committee of Osaka Medical College and by the BNCT Committee of KURRI. Individual cases were discussed and selected by the latter committee. Some candidates were not approved, as mentioned in the previous section. Our clinical regimen of modified BNCT is shown in Fig. 1. For the new cases, a craniotomy was performed to remove as much of the tumor as possible. After histological confirmation of the disease, residual tumors were assessed using neuroimages. For cases of recurrent disease, the growing mass was confirmed by a review of follow-up images with a washout interval of at least 2 months after adjuvant treatments. Some recurrent tumors were confirmed histologically at surgery and others were diagnosed based on findings on $^{207}$Th single photon emission tomography images. The patients underwent $^{18}$F-BPA PET, if available, to assess the distribution of BPA and to estimate the boron concentration in tumors before neutron radiotherapy, as described later in this paper. The L/N ratio of BPA uptake can be estimated from this study and dose planning was made according to this L/N ratio, as described later. The PET study was omitted in four patients: there was no enhanced mass in one patient, a poor preoperative condition in one patient, and no access to the PET scanner could be secured for two patients. Figure 2 shows representative data for this PET study. The neutron flux was also estimated using a computer workstation equipped with SERA dose planning software (Idaho National Engineering and Environmental Laboratory, Idaho Falls, ID) before the radiation was delivered. Twelve hours before neutron radiotherapy, the patients were administered 5 g of BSH intravenously over a 1-hour period at the Osaka Medical College, and then transferred to the KURRI. Patients were positioned for neutron radiotherapy in the reactor room and 250 mg/kg of BPA was administered intravenously for 1 hour before the radiation treatment. Blood was sampled every 2 to 3 hours after BSH administration until neutron radiotherapy was completed, and the boron concentration in the blood was monitored. The boron concentration in the blood from BSH during neutron radiotherapy was estimated based on the measured $^{10}$B concentration and the time relationship. From our previous experience with BNCT, which was performed using craniotomy, we hypothesized that boron concentrations in tumor and blood contributed from BSH were equal just before neutron radiotherapy. Boron concentrations from BPA in the tumor and in normal brain tissue were also estimated based on the L/N ratio of $^{18}$F-BPA on PET scans. Judging from the boron concentrations contributed from each boron compound, the neutron fluence rate simulated by SERA, and factors of relative biological effectiveness of the neutron beam and compound described previously, the total dose delivered to the tumor and normal brain could be estimated. The duration of neutron radiotherapy was determined so as not to deliver more than 13 Gy-Eq to the normal brain and as much as possible to the contrast-enhanced tumor in newly diagnosed cases. For cases of recurrent tumor the duration of radiotherapy was determined in each case according to the previous radiation dose and the irradiated field. Here, the Gray equivalent represents a biologically equivalent x-ray dose that can deliver equivalent effects to that of a total BNCT radiation dose. Neutron radiotherapy was principally performed without craniotomy and without anesthesia. After treatment, the doses given were reestimated precisely. If the dose for a tumor (contrast-enhanced area) was less than 30 Gy-Eq, the amount by which the dosage was short was added by stereotactic radiosurgery to a limited area after BNCT. Using this criterion, only one patient (Case 4) underwent stereotactic radiosurgery 1 month after BNCT.

### TABLE 1

**Characteristics of 13 patients with malignant gliomas**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs.)</th>
<th>Sex</th>
<th>Histological Diagnosis</th>
<th>Tumor Diagnosis</th>
<th>Radiotherapy Before BNCT (Gy)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>61, M</td>
<td>GBM</td>
<td>rec</td>
<td>conv</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>29, F</td>
<td>GBM</td>
<td>rec</td>
<td>conv</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>74, F</td>
<td>AA</td>
<td>new</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>51, F</td>
<td>GBM</td>
<td>new</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>73, M</td>
<td>GBM</td>
<td>new</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>30, M</td>
<td>AO</td>
<td>rec</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>56, M</td>
<td>GS</td>
<td>new</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>62, M</td>
<td>GBM</td>
<td>rec</td>
<td>conv</td>
<td>60</td>
</tr>
<tr>
<td>9</td>
<td>44, F</td>
<td>GBM</td>
<td>new</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>48, M</td>
<td>GBM</td>
<td>rec</td>
<td>conv</td>
<td>80</td>
</tr>
<tr>
<td>11</td>
<td>59, M</td>
<td>GBM</td>
<td>rec</td>
<td>conv</td>
<td>30</td>
</tr>
<tr>
<td>12</td>
<td>50, F</td>
<td>GBM</td>
<td>rec</td>
<td>conv</td>
<td>60</td>
</tr>
<tr>
<td>13</td>
<td>61, F</td>
<td>GBM</td>
<td>rec</td>
<td>conv</td>
<td>20</td>
</tr>
</tbody>
</table>

* AA = anaplastic astrocytoma; AO = anaplastic oligoastrocytoma; conv = conventional; GS = gliosarcoma; rec = recurrent; RS = radiosurgery.
Assessment of Effectiveness

The effectiveness of this treatment was volumetrically assessed by performing a serial neuroimaging analysis. Magnetic resonance and CT imaging were performed using slice thicknesses of 7.5 and 10 mm, respectively. The images were analyzed using a commercial software package (Scion Image, version Beta 4.0.2; Scion Corp., Frederick, MD). The contrast-enhanced area was measured in each slice and recorded in square millimeters. Then the value of the area was multiplied by the thickness of each slice (7.5 for MR imaging and 10 for CT scanning) to obtain the volume. The percentage of reduction was calculated in the following manner:

\[ \frac{1}{H} \times 100 = \frac{\text{summation of the enhanced volume in each assessment}}{\text{summation of the enhanced volume obtained on the image just prior to the BNCT}} \times 100. \]

The initial effects were evaluated on MR or CT images obtained 2 to 7 days after BNCT. Computerized tomography scanning was adopted for this assessment only in Case 3 because pre-BNCT MR imaging was not available. The maximal effects were also determined on the most effective images during the follow-up periods. Generally, follow-up images were obtained every 1 or 2 months after the initial observation periods.

Histological Analysis After BNCT

Craniotomy was repeated after BNCT in five patients (Cases 4–7 and 12; Table 1) because of disease progression seen on neuroimages after transient shrinkage of the tumors. Sampling of the enhanced lesion was guided by a neuronavigation system (Stealth-station; Medtronic, Minneapolis, MN). Specimens were subjected to a histological analysis in which we used H & E staining and applied an LI based on the reaction to anti-Ki-67 monoclonal antibody.

Results

Parameters of BNCT in Each Patient

The parameters of BNCT in each patient are listed in Table 2. Tumor size before BNCT varied from 0 to 107.6 cm³. Nine of the 13 patients underwent 18F-BPA PET examination. The L/N ratios of 18F-BPA in patients harboring a GBM ranged from 2.7 to 7.8. The duration of neutron radiotherapy lasted 60 to 120 minutes. During this period the concentrations of BSH and BPA in tumor tissue, estimated by repeated venous sampling and based on the L/N ratio on PET scans, varied from 17 to 40 ppm and from 33.6 to 99 ppm, respectively. If 18F-BPA PET scans were not available.
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(Cases 3, 4, 7, and 9), the BPA values were calculated from a putative L/N ratio of 3.5. It is unclear why there was a difference in BSH concentration in blood, which should have been equal to the BSH concentration in tumor tissue. Presumably the difference in the speculated BPA concentration in the tumor tissue can be ascribed to the difference in the L/N ratio of tumor tissue, because the boron concentration in blood derived from BPA was approximately 12 ppm almost constantly (data not shown). The minimal tumor doses for contrast-enhanced lesions ranged from 11.4 to 38.4 Gy-Eq. Maximal brain doses were 3.7 to 13.6 Gy-Eq. In Case 4, to decrease the maximal dose to the normal brain by less than 13 Gy, the dose for the deepest part of tumor at the trigone was only 23.8 Gy-Eq. We therefore added stereotactic radiosurgery to the treatment plan for this portion of the lesion only, with a marginal dose of 15 Gy delivered 1 month after BNCT, as described earlier.

Antiedema Effects

As shown in results we have previously published, BNCT resulted in a marked and rapid decrease in brain edema caused by a tumor without the necessity of dehydrating or steroid medications. As a representative case, a fluid-attenuated inversion-recovery image obtained in Case 12 is shown in Fig. 5. Antiedema effects were recognized in all most all cases in this series.

Initial Effects

As Table 3 shows, reductions in tumor volume were identified in all 12 patients who harbored a lesion that could be assessed on neuroimages and received this treatment. The percentage of reduction rates ranged from 17.4 to 71% of the initial tumor seen on neuroimages.

Maximal Effects

Maximal reductions in the size of the tumor ranging from 30.3 to 87.6% were obtained 2 to 227 days after BNCT. More than 50% of contrast-enhanced lesions disappeared in eight of 12 patients during the follow-up period.

Histological Analysis Before and After BNCT

We identified enlargement of enhanced areas on neuroimages in five patients during the follow-up period and reexplored these areas by performing a craniotomy. Histological analyses showed recurrent tumor in two of these patients (Cases 6 and 7, data not shown). Interestingly, the recurrent mass in Case 7 displayed only a sarcomatous feature and no glioma component was observed (data not shown; in preparation for publication). In the other three patients (Cases 4, 5, and 12), necrosis was identified after BNCT. In Case 4, we performed a repeated craniotomy 5 months after the BNCT. Figure 6B and B’ depicts H & E–stained tissue in this case before and after BNCT. Eight of 12 biopsy samples obtained at repeated craniotomy displayed only necrosis without viable tumor cells, and four of the 12 exhibited some viable cells among the necrotic tis-
sue. After BNCT, however, only 0.5% of the cells demonstrated Ki-67 positivity, as opposed to 12% at the initial craniotomy. This patient’s tumor was well controlled in the brain, and no deterioration was observed during the follow-up period. Nevertheless, the patient died 9 months after BNCT as a result of CSF dissemination of the tumor. One patient (Case 5) moved his head during his first BNCT session and had to undergo BNCT again 1 month later (see Table 2). In this case, there was similar Ki-67 positivity, 25% before and 0.8% after BNCT. There was a tendency in both Cases 4 and 5 for neuronlike cells to be preserved just around the necrotic area after BNCT (data not shown; in preparation for publication). In one patient (Case 12) an enlargement of the contrast-enhanced mass and edema was found on neuroimages 9 months after BNCT, although when the mass was resected at a repeated craniotomy, the tissue was almost completely necrotic.

Adverse Effects of BNCT

All patients exhibited alopecia. Apart from this adverse effect, generalized convulsive seizure occurred in one patient (Case 8). No acute brain swelling or consciousness disturbance occurred in our patient series. As described earlier, rather than producing acute brain swelling, BNCT decreased brain edema rapidly immediately after treatment. In three patients (Cases 4, 5, and 12) there was an enlargement of the contrast-enhanced mass, but for the most part this represented necrosis, which was proven by repeated craniotomy. The necrosis seemed to be related to additional radiosurgery in Case 4, repeated BNCT in Case 5, and previous photon-based fractionated radiotherapy in Case 12.

Discussion

Since the 1950s, BNCT has been used to treat high-grade gliomas; however, the results have not been satisfactory. Disappointing outcomes of early trials were attributed to two primary factors: inadequate tumor specificity of the boron compounds that were used, and insufficient penetration by the thermal neutrons. To overcome these factors and obtain satisfactory results, we modified the treatment in three ways. First, we used an epithermal rather than a thermal beam to improve the distribution of thermal neutrons in deep sites. With the proximity of the KURRI, an epithermal beam has recently become available for the treatment of high-grade gliomas. This is the first trial in Japan in which an epithermal beam has been applied to the treatment of brain tumors.

Second, we used both of the two boron compounds currently available worldwide for BNCT: BSH and BPA. Each of these compounds reaches or accumulates in different subpopulations of tumor cells in a different fashion. Sodium borocaptate is not delivered into the normal brain through the blood–brain barrier, and the concentration of

Fig. 3. Cases 3, 4, and 8. Representative cases of improvement. A: Images obtained just prior to BNCT. B: Images demonstrating the initial effect of therapy estimated within 1 week. C: Images revealing the most improvement, obtained during the follow-up period.
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TABLE 3

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Lesion Volume Pre-BNCT (cm³)</th>
<th>Lesion Volumes in cm³ (days after BNCT, % reduction)</th>
<th>Survival</th>
<th>Time to Death (mos)</th>
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<tr>
<td></td>
<td></td>
<td>Initial Effect</td>
<td>Maximum Effect</td>
<td>From Diagnosis</td>
</tr>
<tr>
<td>1</td>
<td>55.2</td>
<td>20.3 (2, 63.2%)</td>
<td>20.3 (2, 63.2%)</td>
<td>D</td>
</tr>
<tr>
<td>2</td>
<td>88.1</td>
<td>62.6 (2, 29.4%)</td>
<td>56.4 (49, 36.0%)</td>
<td>DC</td>
</tr>
<tr>
<td>3</td>
<td>29.1</td>
<td>11.3 (7, 61.3%)</td>
<td>3.6 (14, 87.6%)</td>
<td>DC</td>
</tr>
<tr>
<td>4</td>
<td>16.1</td>
<td>11.5 (2, 46.1%)</td>
<td>4.22 (34, 80.3%)</td>
<td>DC</td>
</tr>
<tr>
<td>5</td>
<td>42.1</td>
<td>12.2 (7, 71.0%)</td>
<td>12.2 (7, 71.0%)</td>
<td>DC</td>
</tr>
<tr>
<td>6</td>
<td>107.6</td>
<td>88.9 (7, 17.4%)</td>
<td>74.0 (49, 31.2%)</td>
<td>D</td>
</tr>
<tr>
<td>7</td>
<td>2.2</td>
<td>0.82 (7, 62.9%)</td>
<td>0.71 (59, 68.0%)</td>
<td>D</td>
</tr>
<tr>
<td>8</td>
<td>32.3</td>
<td>18.4 (7, 43.0%)</td>
<td>8.8 (52, 52.6%)</td>
<td>D</td>
</tr>
<tr>
<td>10</td>
<td>39.5</td>
<td>17.5 (7, 55.7%)</td>
<td>17.5 (7, 55.7%)</td>
<td>DC</td>
</tr>
<tr>
<td>11</td>
<td>26.5</td>
<td>8.0 (7, 30.3%)</td>
<td>8.0 (7, 30.3%)</td>
<td>D</td>
</tr>
<tr>
<td>12</td>
<td>64.3</td>
<td>26.0 (7, 40.5%)</td>
<td>26.0 (7, 40.5%)</td>
<td>A</td>
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<tr>
<td>13</td>
<td>3.6</td>
<td>2.31 (7, 35.8%)</td>
<td>0.53 (227, 85.4%)</td>
<td>A</td>
</tr>
</tbody>
</table>

* A = alive; D = died; DC = died of CSF dissemination; DO = died of other cause.

Fig. 4. Cases 6 and 7. Representative cases of treatment failure. A: Images obtained just prior to BNCT. B: Images obtained 2 months after BNCT. C: Images obtained 4.5 and 6 months after BNCT.

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this compound in tumor tissue is related to both the vasculature of the tissue and the concentration of BSH in the blood. Boronophenylalanine preferentially accumulates in the cell subpopulation that is actively proliferating; however, some of this compound inevitably accumulates in normal tissue. Therefore, the simultaneous use of both compounds ensures that the disadvantages of one compound are cancelled by the other.10 Third, we used 18F-BPA PET to estimate concentrations of BPA in the tissues. This readily gave us an accurate assessment of BPA accumulation and distribution before irradiation, that is, without craniotomy, as one of us previously reported.10,11,22 With these improvements, we were able to apply BNCT without the need for craniotomy and with a reasonable estimation of the absorbed dose.

In this series, although the number of cases was very lim-
ited, definitive antitumor effects on malignant gliomas were observed on neuroimages regardless of the pre-BNCT tumor size in cases of both new and recurrent tumors. In an analysis of a large series, Barker and associates\(^1\) reported using conventional fractionated photon-based radiotherapy, a neuroimaging improvement (> 50% reduction in the size of contrast-enhanced lesions) was obtained in only 24% of GBM cases and the improvement depended on the size of the tumor before treatment. These authors also reported that the neuroimaging improvements were related to longer patient survival times. Chanana and colleagues\(^7\) reported the results of a Phase I/II study of BNCT in which epithermal neutrons and BPA were used in patients with GBMs. Because their study involved dose escalation, it is difficult to make a simple comparison between their results and ours. Nevertheless, Chanana and colleagues reported that follow-up neuroimages documented improvement in only nine of 37 cases. By comparison, our current results are relatively good. Although the exact reason for this discrepancy is unclear, it is noted that those authors did not measure the BPA concentration in each patient; in our study, we used not only BPA but also BSH as boron source compounds. The use of both compounds theoretically increased the absolute boron concentration and improved its microdistribution in tumor tissues.

The histological analysis of samples obtained at repeated craniotomy after BNCT showed marked tumor necrosis, as stated in Results. This treatment produced anti-DNA synthesis effects, which was shown by the Ki-67 LI analysis. Interestingly, neuronlike cells around the necrotic area were preserved, which reflects the specific tumoricidal activity of this treatment. Moreover, an MR spectroscopy analysis focusing on the boundary zone of the tumor and normal brain revealed a decrease in chorine activity and stable N-acetyl aspartate activity after BNCT compared with findings before BNCT. The former represents tumor activity and the latter represents neuron activity.\(^{24,25}\) This observation coincides with the aforementioned histological analysis (manuscript in preparation).

We have described the potent effects of this treatment; however, as shown in Table 3, 10 of our patients did not survive. Two of the 10 died of other causes, such as pneumonia, although good neuroimaging had revealed responses to the treatment. Four of our patients died as a result of local...
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Fig. 6. Case 4. Interesting findings obtained at repeated craniotomy. A and A': Magnetic resonance images obtained prior to the first and second craniotomy, respectively. The remaining enhanced lesion at the left trigone (A) shrank rapidly after BNCT; however, it enlarged again 3 months after the intervention (A'). B and B': Photomicrographs of the surgical specimen obtained from the first and second craniotomies, respectively, demonstrating typical pathological findings for GBM (B) and marked necrosis with somewhat damaged tumor tissue (B'). H & E. C and C': Photomicrographs demonstrating Ki-67 in tissue obtained at the first and second craniotomies, respectively. Note that the LI changed from 12% (C) to 0.5% (C'). Original magnifications × 40 (B and B') and × 80 (C and C').

We witnessed two additional cases of local recurrence, as shown in Fig. 4. In Case 6, the original tumor extended very deeply and invades the corpus callosum before the initial BNCT. The patient was treated with repeated BNCT after a 1-month interval. In total, we applied 24.9 Gy-Eq to the deepest part of the contrast-enhanced mass. The primary mass was well controlled during the follow-up period, as shown in Fig. 4; however, the tumor that had invaded the corpus callosum grew anteriorly during this period. We attributed this local recurrence to the absolute lack of absorbed doses in the deepest part of the tumor. The curative dose of BNCT for malignant gliomas has yet to be determined. We therefore settled on a putative curative dose of 30 Gy-Eq based on previous results in which fast neutron radiation was used to treat malignant gliomas, as stated in Clinical Material and Methods. In Case 7, the original mass, recognized just prior to BNCT, lay above the inferior sagittal sinus; this lesion disappeared during the follow-up period. A new enhanced lesion appeared just below the inferior sagittal sinus, however, as shown in Fig. 4. During BNCT, we applied 32.6 Gy-Eq to the deepest part of the enhanced mass recognized on the pre-BNCT MR imaging. This dose was greater than the putative curative dose. There are two possibilities for this treatment failure in Case 6: the putative curative dose of 30 Gy-Eq may have been lower than the true curative dose or delivery of 32.6 Gy-Eq was an overestimation. For the latter possibility, there may have
been an uneven distribution of boron compounds. It may be that not enough BSH was delivered into nonenhancing infiltrative tumors that display a high intensity on T2-weighted MR images. Likewise, not enough BPA may have been delivered to peripheral invading tumor cells, compared with the center of the enhanced mass, as Smith and colleagues reported.

In this series, we treated eight recurrent cases. For the prevention of radiation injury, we could deliver a limited dose with BNCT for patients with recurrent tumors who previously received conventional radiotherapy. The purpose of radiation treatment for recurrent cases was palliation of the disease. Most cases of tumor recurrence were introduced to our institute because the patient’s disease could not be controlled with conventional radiotherapy and chemotherapy. In all recurrent cases treated in this series neuroimaging revealed improvements in the disease and a decrease in peritumoral edema. In some patients treated by BNCT there were improvements in neurological symptoms such as aphasia. Activities of the patients’ daily living were not disturbed by this treatment. Necrosis probably caused by radiation was observed in one patient (Case 12); however, this patient underwent necroscopy and has been fine on a course of medication. Although the end point of this treatment in new cases should be cure of the disease, this has not yet occurred. To reach this end, we should estimate the boron concentration more precisely in tumor tissue and in adjacent normal brain tissue on the cellular level in humans. Also, it may be useful to develop another method to administer boron compounds, such as long-term infusion of BPA, or intracarotid injection of the compounds to obtain more preferable results by BNCT.

Again we have modified our clinical protocols and will present the results of their application in the near future. In some cases of recurrent tumor surgery and other treatments were performed in different fashions at other institutions before the patient was transferred to our clinic. This study was therefore not a controlled prospective randomized trial. Nevertheless, we are able to show the effectiveness of this treatment even with a limited number of cases, although we believe that prospective randomized trials will be necessary to evaluate this treatment more scientifically.

Conclusions

In this paper we introduced the clinical regimen of our modified BNCT for malignant gliomas. This treatment elicited good clinical responses as shown on neuroimages, in which a decrease in peritumoral edema is found without neurological sequelae or a decrease in activities of daily living.

Acknowledgments

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Address reprint requests 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.