FIRST CLINICAL CASE OF BORON NEUTRON CAPTURE THERAPY FOR HEAD AND NECK MALIGNANCIES USING $^{18}$F-BPA PET

Teruhito Aihara, MD,¹ Junichi Hiratsuka, MD,² Norimasa Morita, MD,² Masako Uno, MD,¹ Yoshinori Sakurai, PhD,³ Akira Maruhashi, PhD,³ Koji Ono, MD,³ Tamotsu Harada, MD¹

¹ Departments of Otolaryngology and Head and Neck Surgery, Kawasaki Medical School, Kurashiki, Japan
Matsushima 577, Kurashiki 701-0192 Japan. E-mail: aiteru@med.email.ne.jp
² Radiation Oncology, Kawasaki Medical School, Kurashiki, Japan
³ Radiation Oncology Research Laboratory, Research Reactor Institute, Kyoto University, Osaka, Japan

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Abstract: Background. We investigated the application of boron neutron capture therapy (BNCT) to suitable cancers other than glioblastoma and melanoma. Head and neck malignancies were consequently selected as adaptable cancers. We reported the clinical results of our first case treated and discussed several advantages to the application of BNCT to head and neck tumors.

Methods. The patient was a 48-year-old woman with recurrent submandibular gland cancer. We confirmed the p-boronophenylalanine (BPA)-accumulating capacity of the tumor by fluorine-18-labeled p-boronophenylalanine positron emission tomography ($^{18}$F-BPA PET) before BNCT. The tumor/normal tissue boron concentration ratio was 2.9. The patient underwent a preirradiation CT scan for treatment planning performed using the “SERA” software program. The tumor was irradiated at the Kyoto University Research Reactor with epithermal neutrons 5 MW for 90 minutes. The tumor dose and normal tissue dose calculated ranged from 20.0 to 25.2 Gy and from 3.2 to 5.8 Gy, respectively.

Results. To date there has been continuous complete regression in the tumor and no acute and chronic complications for 1.5 years.

Conclusions. Although only 1 patient has shown complete regression and additional long-term follow-up should be required to assess this treatment, we believe that head and neck tumors are suitable for BNCT and that such excellent results will have a great impact on patients in the near future. ©2006 Wiley Periodicals, Inc. Head Neck 28: 850–855, 2006

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Mishima¹ first proposed employing boron neutron capture therapy (BNCT) for malignant melanomas using the specific melanin synthesis activity of melanoma cells. For that purpose, p-boronophenylalanine (BPA) was reevaluated by his group. In 1987, based on experimental studies in many research fields,²,³ they successfully treated a patient who had metastatic melanoma with BNCT.⁴ Since then, 22 patients have been treated.⁵ One of us (J. H.) has participated in clinical trials as a radiation oncologist from the beginning. We had expected that BNCT would be applied to an increasing number of melanoma patients, but
the number has been less than expected. This is because the frequency of patients with melanoma is very low in Japan and because considerable progress has been made in the surgical field. We investigated other cancers for which BNCT would be suitable, and head and neck tumors were consequently selected as adaptable cancers. Our experimental data from hamsters suggested that there was high boron accumulation into neck tumors with the use of BPA. Kato et al. began BNCT using both BSH (Na₂B₁₂H₁₁SH) and BPA for recurrent parotid gland carcinoma for the first time and reported excellent preliminary results. On the basis of the encouraging results of their pioneering clinical trial, our many years’ experience with melanoma BNCT and the trend toward emphasizing the quality of life after treatment, we also began treating our patients with BNCT using BPA alone. We waited for a case that would fulfill the following 4 points in applying our BNCT to a patient with a head and neck tumor for the first time: (1) there was no currently available conventional therapy to control the tumor; (2) the tumor was not very far from the skin surface (< 5 cm), because it must be possible to administer curative doses to the target by using an epithermal neutron beam; (3) the tumor/normal tissue ratio in boron concentration was > 2.5 using fluorine-18-labeled p-boronophenylalanine positron emission tomography (¹⁸F-BPA PET); and (4) consent to perform BNCT was obtained from the patient and the family. In the present work, we report the clinical results of our first case treated with BPA alone using ¹⁸F-BPA PET and discuss several advantages to the application of BNCT to head and neck malignancies.

CASE REPORT

Patient. The patient was a 48-year-old woman who presented at our hospital in March 2003 with swelling of the right mandibular region. A 5.5-cm hard mass was palpated in the right mandibular region, and several nodules were found in the right neck in the initial examination. On CT scans at admission, a 5.0- × 3.5-cm tumor containing calcification was noted in the right submandibular gland. In submandibular cytology by needle puncture and aspiration, the tumor was classified as class V (epithelial malignant cell: positive). Tumor resection and right radical neck lymph node dissection were carried out in April 2003 based on a diagnosis of T2N2bM0 stage IVA submandibular gland cancer. On postoperative pathologic examination, the cancer was determined to be a mucoepidermoid carcinoma (high-grade malignancy). She was given 5-fluorouracil [5-FU], 300 mg/day, immediately after the operation, to control a possible distant metastasis. In September 2003, a thumb-sized subcutaneous tumor was noted on the right neck in spite of adjuvant chemotherapy after surgery, and it was confirmed by biopsy that the tumor was a local recurrent cancer (Figure 1A). Neck CT scans detected an irregularly contrasted tumor measuring 3 × 3 cm in the center of the right neck (Figure 1B). The deepest point from the skin surface was 4 cm. Radiological examinations revealed no distant metastases. As the tumor showed rapid growth, she was given additional chemotherapy, but it was ineffective, and in addition, she started suffering from severe neck pain and stiffness. She asked for BNCT of the recurrent lesion rather than reoperation. With the approval of the Medical Ethics Committee (Kawasaki Medical School, Kyoto University and the Nuclear Safety Bureau of the Japanese Government), we confirmed the BPA accumulating capacity of the tumor by ¹⁸F-BPA PET before BNCT. The tumor/normal tissue boron concentration ratio (T/N ratio) was 2.9, as mentioned below. BNCT was carried out in October 2003.

¹⁸F-BPA PET Study. The accumulation of BPA to the tumor and surrounding normal tissue was imaged and quantified by a ¹⁸F-BPA PET study before BNCT. She was injected intravenously with 168 MBq of ¹⁸F-BPA during a 40-second period. Emission scan imaging was carried out in several regions of interest (ROIs) including the tumor and the family. In the present work, we report the clinical results of our first case treated with BPA alone using ¹⁸F-BPA PET and discuss several advantages to the application of BNCT to head and neck malignancies.
tion (a 30-minute interval from the end of BPA administration) (the $^{10}$B concentration in the blood was measured by prompt $\gamma$-ray spectrometry); (2) final setting of the patient on the irradiation port with attachment of thermo-luminescence dosimeters and gold wires on the skin surface of the radiation field for dosimetry (we placed a gelatin sheet, 5-mm thickness, on the skin of the radiation field because the irradiation dose at the tumor surface was enhanced); (3) epithermal neutron irradiation at the Kyoto University Reactor (KUR) with a reactor power of 5 MW (the irradiation field was large enough to cover the target area for the neutron beam, 12 cm $\times$12 cm; (4) neutron flux measurement using gold wire for 15 minutes, after the start of irradiation; and (5) optimization of the neutron dose based on the measured blood $^{10}$B concentration and neutron flux. These procedures generally were the same as those of BNCT for malignant melanoma.9

The patient underwent a preirradiation CT scan for treatment planning that was performed with the SERA10 software program. The SERA-calculated distribution was normalized using the thermal and epithermal neutron fluences measured by gold wire analysis at the patient’s skin surface. Using the normalized data for the thermal neutron fluences, fast neutron and $\gamma$-ray physical doses, and compound biological effectiveness (CBE)- and relative biological effectiveness (RBE)-weighted doses, $E_{\text{Total}}$ (Gy-Eq), were calculated by the following equations6:

$$E_{\text{Total}} = E_{\text{Thermal}} + E_{\text{Fast}} + E_{\gamma},$$

$$E_{B_{10}} = (C_{\text{BPA}} \times CBE_{\text{BPA}}) \times 7.43 \times 10^{-14} \times \Phi_{\text{Thermal}},$$

$$E_{\text{Thermal}} = N \times \text{RBE}_{\text{Thermal}} \times 6.78 \times 10^{-14} \times \Phi_{\text{Thermal}},$$

$$E_{\text{Fast}} = \text{RBE}_{\text{Fast}} \times D_{\text{Fast}},$$

$$E_{\gamma} = \text{RBE}_{\gamma} \times D_{\gamma},$$

where $D$ is the physical absorbed dose (Gy), $\Phi_{\text{Thermal}}$ is the neutron fluence ($\text{cm}^{-2}$), $N$ is the $^{14}\text{N}$ concentration ($\%$), where $^{14}\text{N} = 2\%$, $C$ is the $^{10}\text{B}$ concentration (ppm), RBE$_{\text{Thermal}} = 3.0$, RBE$_{\text{Fast}} = 3.0$, RBE$_{\gamma} = 1.0$, CBE$_{\text{BPA}} = 3.8$ for tumor, CBE$_{\text{BPA}} = 2.5$ for normal skin, and CBE$_{\text{BPA}} = 1.35$ for normal tissue.

The pharmacokinetics of boron in blood are well characterized and predictable. In our case, we assumed that the mean value of $^{10}$B concentration in the blood during the irradiation was 12 ppm, based on the boron concentration values of blood at the time of just finished BPA-drip and just before irradiation. The mean value of the $^{10}$B
concentrations of both the blood and the normal tissue were equal to each other. The $^{10}$B concentration in the tumor was estimated by multiplying the normal tissue value by a factor of the T/N ratio ($12 \times 2.9 = 34.8$ ppm). The thermal neutron and epithermal neutron fluxes at the patient’s skin surface were $1.07 \times 10^8$ cm$^{-2}$/s and $1.07 \times 10^8$ cm$^{-2}$/s, respectively.

We determined that the irradiation time based on the condition that 20 Gy-eq was given at the deepest point of the tumor. The tumor was irradiated with epithermal neutrons 5 MW for 90 minutes. The tumor dose and normal tissue dose calculated ranged from 20.0 to 25.2 Gy and from 3.2 to 5.8 Gy, respectively. Figure 2 shows the dose distribution using SERA.

The next day, irradiation erythema and edema appeared at the irradiated area but did not change into erosion. The edema was successfully treated with steroids. Mild acute reactions were seen in the mucosal lining of the oral cavity and oropharynx, but they were all self-limiting and required only symptomatic intervention (grade 2 of the Radiation Therapy Oncology Group [RTOG] scoring system). It appears from both clinical observation and studies in experimental animal systems that BPA concentrates not only in the tumor but also in rapidly dividing normal tissue such as the skin and mucosa of the oral cavity.$^{11}$ Ten days after treatment, the erythema and edema gradually disappeared with decreased tumor size. Approximately 2 months later, almost complete regression was obtained without further treatment. To date, there has been continuous complete regression in the tumor, and no chronic complications such as skin ulcers and xerostomia have occurred for 1.5 years. The patient’s previous symptoms also completely disappeared. No neurological side effects, such as transient palsy and radiation myelitis, were seen in the neck spinal cord. Figure 3

![Figure 2](image1.png)

**FIGURE 2.** Dose distribution calculated by SERA for tumor (A) and normal tissue (B). We placed a gelatin sheet (5-mm thickness) on the skin of the radiation field because the irradiation dose at the tumor surface was enhanced. The tumor outline was drawn round the red twofold dotted line. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

![Figure 3](image2.png)

**FIGURE 3.** (A) Local appearance 12 months after boron neutron capture therapy (BNCT) suggests that the tumor has completely disappeared. (B) The tumor region was cicatrized on CT performed 12 months after the irradiation. (C) fluorine-18-labeled p-boronophenylalanine positron emission tomography ($^{18}$F-BPA PET) was performed after 12 months, and no accumulation of BPA in the lesion was noted. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
shows the clinical appearance of the tumor 12 months after BNCT. No recurrence and no residual tumor were proven by either CT scan or BPA-PET findings.

**DISCUSSION**

One of the most critical points for clinical safety, therapeutic efficacy, and specificity of BNCT is higher incorporation of $^{10}$B into tumor cells than into normal tissue. Originally, p-BPA was developed based on the reasoning that because the biosynthesis of melanin requires tyrosine as a precursor, the boronated form of this amino acid might be selectively taken up by melanoma cells. Since 1987, Mishima et al have succeeded in treating human melanoma lesions with BNCT using p-BPA, and in both in vitro and in vivo research, it has been proven that BPA highly accumulates in melanoma cells. It has also been demonstrated that BPA is selectively taken up by several tumor types in animal or human models. Coderre et al suggested that there are mechanisms of BPA uptake that are independent of melanin synthesis, and that the accumulation of BPA in rapidly growing animal tumors (including melanoma) could be due to a metabolic demand for the amino acids needed for protein synthesis. Nonpigmented tumor cells such as mouse squamous cell carcinoma (SCC VII) have also shown a certain level of boron accumulation, although at a much lower level than that by melanotic melanoma (unpublished data). Ishiwata et al reported that $^{18}$F-BPA is taken up in high levels by tumors without melanogenesis, such as amelanotic melanoma and mammary carcinoma with PET, that tumor uptake of the tracer at an earlier time might correlate with the amino acid transport system and/or the amino acid demand of tumor tissues in general, and that the selectivity for melanomas was enhanced at a later time. We also think that BPA passes as not only a tyrosine analogue for melanin synthesis, but also as an amino acid analogue for protein synthesis. We believe that this T/N ratio (2.9) was high because the tumor had rapid growth and a high metabolic demand for the amino acids needed for protein synthesis. Chandra et al reported that there was no significant difference in boron delivery to subcellular compartments between $^{18}$F-BPA and nonfluorinated BPA based on quantitative subcellular observations using the SIMS-based imaging technique of iron microscopy.

The tumor response of conventional radiotherapy depends on several factors, including tumor size, differentiation, and histopathology. Actually, the tumor response to irradiation is changeable even in the same pathologic group of squamous cell head and neck cancers. Conventional radiotherapy for unresectable salivary gland malignancies has not proved a successful strategy, but neutron radiation therapy has led to a superior outcome. The literature has revealed a 67% local control rate for 309 patients treated with neutrons but only 26% for those treated with conventional photon radiotherapy. The greater density of ionizations along the tracks of high linear energy transfer (LET) particles as neutrons results in an increased biological effect compared with the same physical dose of low LET radiation as photons. Usually, this is called relative biological effectiveness (RBE), which is the ratio of the absorbed dose of a reference source of radiation (eg, x-rays) to that of the test radiation that produces the same biological effect. In addition, from the radiation biological point of view, high LET radiation has a lower oxygen enhancement ratio (OER) than low LET radiation. There is evidence that a significant proportion of human cancers contain hypoxic cells which are thought to be radio-resistant. Recently, worldwide clinical trials with proton-beam radiotherapy, which has a superior dose distribution, have been carried out. We think that BNCT is a novel radiotherapy that has the advantages of both the high LET radiation of the neutron beam and the superior dose distribution of the proton beam. In addition, with BNCT using $^{18}$F-BPA PET it is possible to predict the therapeutic efficacy or response by estimating the T/N boron concentration ratio. Tumors with a T/N ratio of $>2.5$ are expected to respond well to BNCT, even in the case of mucoepidermoid carcinomas or malignant melanomas, which are thought to be radio-resistant tumors. In contrast, a T/N ratio of $<2.5$ for a tumor appears to be a contraindication for BNCT.

There are several advantages in applying BNCT to head and neck tumors. First, the head and neck have many important physiological and cosmetic functions. Treatment of the patient with a head and neck malignancy has a great influence on his/her quality of life after treatment. Second, as head and neck malignancies exist superficially and are not very far from the skin surface, it is possible to administer curative doses to the target by using an epithermal neutron beam. Third, there are a great many patients with head and
neck tumors that cannot be controlled by conventional cancer therapy. The good response in our first case appears to have been due to the fact that the lesion was not very far from the skin surface and that the T/N ratio (2.9) was relatively high. We are going to try BNCT for 20 patients with recurrent head and neck cancer and then compare those clinical results with those of conventional salvage therapy (phase II study).

Although we have had only 1 patient who has shown complete regression and additional long-term follow-up should be required to assess this treatment, we believe that head and neck tumors are suitable for BNCT and that excellent results will have a great impact on patients in the near future.

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REFERENCES