BORON NEUTRON CAPTURE THERAPY IN THE TREATMENT OF LOCALLY RECURRENT HEAD AND NECK CANCER

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Purpose: Head and neck carcinomas that recur locally after conventional irradiation pose a difficult therapeutic problem. We evaluated safety and efficacy of boron neutron capture therapy (BNCT) in the treatment of such cancers.

Methods and Materials: Twelve patients with inoperable, recurred, locally advanced (rT3, rT4, or rN2) head and neck cancer were treated with BNCT in a prospective, single-center Phase I-II study. Prior treatments consisted of surgery and conventionally fractionated photon irradiation to a cumulative dose of 56–74 Gy administered with or without concomitant chemotherapy. Tumor responses were assessed using the RECIST (Response Evaluation Criteria in Solid Tumors) criteria and adverse effects using the National Cancer Institute common toxicity grading v3.0. Intravenously administered boronophenylalanine-fructose (BPA-F, 400 mg/kg) was used as the boron carrier. Each patient was scheduled to be treated twice with BNCT.

Results: Ten patients received BNCT twice; 2 were treated once. Ten (83%) patients responded to BNCT, and 2 (17%) had tumor growth stabilization for 5.5 and 7.6 months. The median duration of response was 12.1 months; six responses were ongoing at the time of analysis or death (range, 4.9–19.2 months). Four (33%) patients were alive without recurrence with a median follow-up of 14.0 months (range, 12.8–19.2 months). The most common acute adverse effects were mucositis, fatigue, and local pain; 2 patients had a severe (Grade 3) late adverse effect (xerostomia, 1; dysphagia, 1).

Conclusions: Boron neutron capture therapy is effective and safe in the treatment of inoperable, locally advanced head and neck carcinomas that recur at previously irradiated sites. © 2007 Elsevier Inc.

Boron neutron capture therapy, Radiotherapy, Head and neck cancer, Positron emission tomography, Boronophenylalanine.

INTRODUCTION

Approximately 700,000 new cases of head and neck cancer are diagnosed worldwide annually (1). The primary treatment usually consists of surgery and radiation therapy administered with or without chemotherapy, but despite therapy, many cancers recur. Some locoregional recurrences can be managed successfully, but a majority of patients with an inoperable locoregional tumor recurrence succumb to the disease within a few months after recurrence (2). Few therapeutic options besides palliative chemotherapy are available for patients whose cancer is considered inoperable and recurs at an previously irradiated site.

Boron neutron capture therapy (BNCT) is based on the nuclear capture reaction that occurs when nonradioactive boron (10B) is irradiated with neutrons of thermal energy to yield high energy α particles (4He2+) and recoiling lithium (7Li).
The effect of $\alpha$ and $^7\text{Li}$ is primarily limited to boron-containing cells, because $\alpha$ and $^7\text{Li}$ have path lengths of approximately one cell diameter in tissue. The success of BNCT is dependent on a selective uptake of sufficient amounts of $^{10}\text{B}$ into cancer cells as compared with normal tissues. Preferential uptake of boron into cancerous tissue is achieved using boron carriers such as a derivative of phenylalanine, boronophenylalanine (BPA), or sodium borocaptate. After administration of BPA or sodium borocaptate by an intravenous infusion, the tumor site is irradiated with neutrons, the source of which is currently a nuclear reactor. Neutron beams with energy ($E_n$) in the epithermal range ($0.5 \text{ eV} < E_n < 10 \text{ keV}$) have usually been used in clinical trials (3–7).

High radiation doses may be selectively delivered to cancer cells using BNCT without causing excessive radiation damage to normal tissues provided that cancer tissue accumulates substantially more boron than the adjacent normal tissues. Hypothetically, doses as high as 60–70 Gy (radiobiologically weighted) may be delivered to $^{10}\text{B}$ accumulating cancer within approximately 1 h (7), whereas such doses are usually administered over 6–7 weeks when conventionally fractionated photon radiation therapy is used. A few uncontrolled clinical trials have evaluated BNCT, administered usually only once, in the treatment of glioblastoma after brain surgery (4–7). In these studies, the median survival times have been 13–15 months after BNCT. These survival times are similar to those achieved with brain surgery, postoperative radiation, and chemotherapy (8).

Efficacy and tolerability of BNCT in the treatment of head and neck cancer is not known. To our knowledge, this is the first report of a prospective registered clinical trial that evaluates BNCT as treatment of human cancer located outside of the central nervous system.

METHODS AND MATERIALS

Study objectives

Twelve patients diagnosed with locally recurrent inoperable head and neck carcinoma were entered into this prospective, Phase I-II, noncomparative, open-label, single-center study. The study was registered with an identifier number NCT00114790 at http://www.clinicaltrials.gov. The primary study objectives included evaluation of safety and treatment response to BPA-mediated BNCT, and the secondary objective assessment of the time to cancer progression and overall survival.

Patients

Study participants were required to have inoperable, recurrent, histologically confirmed head and neck cancer. Such patients were eligible provided that they had the World Health Organization performance status 3 or less, prior conventional radiotherapy administered had been given to the site of the recurrent tumor, the white blood cell count was greater than 2,500/mm$^3$, blood platelet count greater than 75,000/mm$^3$, and serum creatinine less than 180 $\mu$mol/L. Whenever available, positron emission tomography (PET) was carried out using fluorine-18 ($^{18}\text{F}$)-labeled L-BPA ($^{18}\text{F}$-L-BPA) as the tracer to estimate tumor BPA accumulation. We required that at least 2.5 times more $^{18}\text{F}$-L-BPA accumulated in the tumor than in the corresponding contralateral normal tissue.

We excluded patients who had an effective standard treatment option available, metastatic disease outside of the head and neck region, expected survival less than 3 months, concomitant systemic chemotherapy or concurrent experimental anticancer therapy, a time interval less than 3 months from prior radiation therapy, patients who had untreated or treated severe congestive heart failure or renal failure, and patients who had a cardiac pacemaker or other metal implants that might interfere with magnetic resonance imaging (MRI). We also excluded restless patients who were unable to lie in a cast for 30–60 min, pregnant women, and those who were younger than 18.

Study participants provided a written informed consent prior to initiation of the study procedures. The study was approved by an institutional Ethics Committee and the National Agency for Medicines, Finland. The investigators conducted the trial in accordance with the Declaration of Helsinki.

PET

Positron emission tomography was carried out using a GE Advance PET Scanner (General Electric Medical Systems, Milwaukee, WI) operated in two-dimensional mode using $^{18}\text{F}$-fluoro-L-BPA as the tracer (9). The intravenously injected $^{18}\text{F}$-fluoro-L-BPA dosage ranged typically between 160 and 240 MBq. Tumor-to-normal tissue ratios were evaluated from static emission scans obtained 20–40 min from injection.

Radiation dose planning and BNCT delivery

Each patient was scheduled to receive two BNCT treatments administered 3 to 5 weeks apart. Computed tomography, contrast-enhanced T1-weighted MRI, and PET images were coregistered (aligned) with each other. Computed tomography was used to construct a three-dimensional model of the head and neck, and MRI and PET were used to define the target volume. The three-dimensional Monte Carlo software package SERA (INEEL/MSU, Idaho Falls/Bozeman, ID) was used for dose planning.

The tissue compositions for transport computations were defined according to the ICRU Report 46 (10). The weighted total dose ($D_w$) was defined as the sum of the physical dose components ($D_p$) multiplied by weighting factors ($w_i$) of each dose component in a tissue as $D_w = w_gD_g + w_BDB + w_NDN + w_{fast_n}D_{fast_n}$, where $D_g$ is the gamma dose, $D_B$ the boron dose, $D_N$ the nitrogen dose, and $D_{fast_n}$ the fast neutron dose. The radiobiologic weighting factors and the weighted total dose were defined as for intracranial tumors treated with BNCT (7, 11). The weighting factor for boron dose was taken as 3.8 in the target and tumor, 2.5 in the mucosal membranes, and 1.3 in other normal tissues. When reporting weighted doses, the annotation (W) is added after the dose for clarity. Both physical doses and weighted doses were used as the basis of dose planning.

The doses in the tumor, the target volume, and in the sensitive tissues were computed individually as a function of the average boron concentration in the whole blood during irradiation. For the boron concentration, tumor-to-whole-blood ratio of 3.5:1 and the normal tissue-to-whole-blood ratio of 1:1 were assumed based on studies performed for brain tumors, because few data are available regarding L-BPA accumulation in head and neck cancer. A 2:1 mucosal membrane-to-blood boron concentration was assumed.

The clinical target volume (CTV) included the gross tumor volume present in pretreatment MRI with approximately a 1.5 cm margin. No further margin was added to the planning target volume around the CTV. The CTV was irradiated from two portals in all cases using either an 11-cm or a 14-cm diameter circular neutron beam aperture. All macroscopic tumors were included in the
CTV, but no attempt was made to irradiate subclinical neck node metastases.

Maximum doses allowed in dose planning were determined for critical anatomic structures. The mucosal membrane absorbed physical dose was used as the dose-limiting variable. This was limited to less than 6 Gy for each of the BNCT treatments. The average planning target volume normal tissue dose was limited to less than 4 Gy (W) per treatment in the first 3 patients entered into the study, to less than 7 Gy (W) in the following 4 patients, and to less than 10 Gy (W) per treatment in the first 3 patients entered into the study, to less than 6 Gy for each of the BNCT treatments. The average whole-blood boron concentration during irradiation was based on kinetic models (13).

L-BPA, purchased from Interpharma Praha (Prague, Czech Republic), was used as the boron carrier agent. To increase solubility, L-BPA was complexed with fructose to form L-BPA-F at the hospital Pharmacy to form L-BPA-F solution, which was administered at a concentration of 30 g L-BPA/L and pH of 7.6 (7). Intravenous drochlorine 10 mg was administered orally before L-BPA-F infusion. None of the patients received concomitant systemic cancer therapy.

Ten to 15 mg of dexamethasone was administered daily after completion of L-BPA-F infusion to alleviate radiation-associated edema. The dose was tapered down within 3–4 weeks. Cetirizine hydrochlorine 10 mg was administered orally before L-BPA-F infusion. None of the patients received concomitant systemic cancer therapy.

Three patients (Patients 5, 6, 12; Table 1) received cancer chemotherapy (capecitabine with or without oxaliplatin, or docetaxel) after BNCT. The remaining patients who had disease progression received best supportive care.

### Evaluation of response and adverse effects

The follow-up visits took place at 4-week to 12-week intervals after BNCT. Computed tomography or MRI was performed at 1, 3, 6, and 12 months after irradiation. Treatment response was evaluated using the RECIST (Response Evaluation Criteria in Solid Tumors) criteria (14). Adverse effects were evaluated according to the National Cancer Institute common toxicity grading form v3.0.

### Statistical analysis

Assuming a response rate of 25% and that this rate is constant for all patients, the probability of all patients failing treatment is less than 0.05 when 12 patients are entered to the study. Confidence intervals for the response rate were calculated using normal approximation.

### Table 1. Patient and tumor characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/ Gender</th>
<th>WHO PS*</th>
<th>Site of primary tumor</th>
<th>Histologic type</th>
<th>Tumor-node-metastasis (TNM)‡</th>
<th>Largest tumor diameter (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>53/M</td>
<td>1</td>
<td>Gum</td>
<td>SCC</td>
<td>60 Gy, 2 Gy/fx</td>
<td>No rT4N0M0 6.5</td>
</tr>
<tr>
<td>02</td>
<td>73/M</td>
<td>1</td>
<td>Oropharynx</td>
<td>SCC</td>
<td>60 Gy, 2 Gy/fx</td>
<td>No rT2N0M0 3.5</td>
</tr>
<tr>
<td>03</td>
<td>37/M</td>
<td>2</td>
<td>Tongue</td>
<td>SCC</td>
<td>56 Gy, 2 Gy/fx</td>
<td>No rT2N2M0 3.1</td>
</tr>
<tr>
<td>04</td>
<td>54/F</td>
<td>2</td>
<td>Not specified†</td>
<td>SCC</td>
<td>60 Gy, 2 Gy/fx</td>
<td>No rT0N2M0 2.5</td>
</tr>
<tr>
<td>05</td>
<td>67/F</td>
<td>1</td>
<td>Nasopharynx</td>
<td>SCC</td>
<td>68 Gy, 2 Gy/fx</td>
<td>Cisplatin+5-FU rT1N2M0 5.5</td>
</tr>
<tr>
<td>06</td>
<td>73/F</td>
<td>2</td>
<td>Nasopharynx</td>
<td>SCC</td>
<td>50 Gy, 2 Gy/fx</td>
<td>Cisplatin+5-FU rT3N0M0 6.0</td>
</tr>
<tr>
<td>07</td>
<td>46/F</td>
<td>1</td>
<td>Nasopharynx</td>
<td>Adenocystic carcinoma</td>
<td>60 Gy, 2 Gy/fx</td>
<td>No rT4N0M0 4.7</td>
</tr>
<tr>
<td>08</td>
<td>64/M</td>
<td>1</td>
<td>Cheek mucosa</td>
<td>SCC</td>
<td>60 Gy, 2 Gy/fx</td>
<td>No rT4N0M0 3.0</td>
</tr>
<tr>
<td>09</td>
<td>64/F</td>
<td>2</td>
<td>Maxillary sinus</td>
<td>Transitional cell carcinoma</td>
<td>66 Gy, 2 Gy/fx</td>
<td>No rT3N0M0 4.7</td>
</tr>
<tr>
<td>10</td>
<td>79/M</td>
<td>1</td>
<td>Nasopharynx</td>
<td>SCC</td>
<td>59 Gy, 1.8 Gy/fx</td>
<td>No rT3N0M0 1.5</td>
</tr>
<tr>
<td>11</td>
<td>68/M</td>
<td>2</td>
<td>Gum</td>
<td>SCC</td>
<td>54 Gy, 2 Gy/fx</td>
<td>No rT4N0M0 3.0</td>
</tr>
<tr>
<td>12</td>
<td>45/F</td>
<td>3</td>
<td>Tongue</td>
<td>SCC</td>
<td>60 Gy, 2 Gy/fx</td>
<td>Cisplatin rT4N2M0 8.4</td>
</tr>
</tbody>
</table>

**Abbreviations:** M = male; F = female; SCC = squamous cell carcinoma; fx = fraction.

* Performance status as defined according to the World Health Organization.

† Tumor-node-metastasis (TNM) classification was done according to International Union Against Cancer (UICC), 6th edition (2002).

‡ A neck metastasis with no detectable primary tumor was present.
**Role of the funding source**

The sponsor of the study (Boneca Corporation Ltd., Hus, Finland) had no role in study design, data analysis, data interpretation, or writing of the report. A trial nurse employed by the sponsor helped the investigators in data collection. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**RESULTS**

**Patient accrual and characteristics**

Twelve patients were accrued between December 1, 2003, and December 31, 2005 (Table 1). These patients were not consecutive; 7 further patients with inoperable, locoregionally recurred head and neck carcinoma were treated during this time with BNCT outside of the study (Fig. 1). The reasons for their exclusion from the protocol were either ineligibility (n = 3) or the trial was not active because of regulatory reasons (n = 4). Two of the 12 patients received only one BNCT because of progression of cancer (n = 1) or patient request (n = 1). The median size of the gross tumor volume before administering BNCT was 87 cm$^3$ (range, 16–517 cm$^3$) and that of the initial planning target volume 233 cm$^3$ (range, 88–987 cm$^3$). Six patients underwent PET scan before BNCT using $^{18}$F-L-BPA as the tracer. The tumor-to-background ratios of the standardized uptake values ranged from 2.5 to 6.3 (median, 3.6) suggesting approximately fourfold accumulation of BPA in the tumors as compared with the corresponding normal tissues.

**Radiation dose delivered**

The median blood boron concentration at the time of neutron irradiation of the first portal was 20.9 µg/g (range, 13.6–26.5 µg/g) and 17.5 µg/g (range, 11.7–22.3 µg/g) when the second portal was irradiated. The median average tumor dose delivered to the gross tumor volume during the first scheduled BNCT was 21 Gy (W) (range, 14–29 Gy [W]) and during the second BNCT treatment 20 Gy (W) (range, 15–24 Gy [W], Table 2). An average of 91% of these tumor doses resulted from the boron neutron capture reactions, 5% from gamma dose, 3% from nitrogen neutron capture reactions, and 1% from fast neutron dose. The median average tumor cumulative physical radiation dose from both BNCT treatments was 12 Gy (range, 6–16 Gy).

The median average planning target volume doses during the first BNCT were 21 Gy (W) (range, 15–25 Gy [W]) and during the second BNCT 20 Gy (W) (range, 15–23 Gy [W]). The highest median normal tissue doses occurred in the...
buccal mucosa, oropharyngeal mucosa, and in the maxillary sinus, and were 11 Gy (W), 9 Gy (W), and 8 Gy (W), respectively, as calculated per one BNCT.

Tumor response and survival

All patients were evaluable for response to BNCT. Ten (83%; 95% CI, 62–100%) patients responded to BNCT (Fig. 2–5). Seven (58%; 95% CI, 30–86%) patients achieved a complete response, 3 (25%) a partial response, and 2 (17%) had stabilized disease for 5.5 and 7.6 months. At the time of analysis, four of the seven complete responses were ongoing with a median duration of 14.0 months (range, 12.8–19.2 months; Table 2). The median duration of the partial responses was 6.8 months (range, 1.3–7.5 months).

Six (50%) patients had either disappearance or marked relief of tumor pain after BNCT, dysphagia was substantially relieved in 4 (33%) cases, and 4 patients had less trismus after BNCT.

The median time to disease progression was 9.8 months, and the median overall survival time 13.5 months. Five (41%) patients are alive 12.8–19.2 months after treatment initiation, and 4 of these patients are alive without disease recurrence.

Treatment safety

The most frequent severe acute adverse effects were radiation mucositis, fatigue, and oral or neck pain (Table 3). One patient was diagnosed with Grade 2 osteoradionecrosis of the mandible. However, persisting mucositis resulted in later than the scheduled administration of the second BNCT in all but 1 of the patients (Table 2). Late severe adverse effects, defined as by their presence more than 3 months after the date

Fig. 2. (Left) Buccal squamous cell carcinoma that recurred after conventional radiation therapy (60 Gy, Patient 8, Table 1). (Right) Clinical complete response 1 month after the first boron neutron capture therapy (BNCT) treatment. The response is ongoing 14 months after BNCT.

Fig. 3. (Left) A magnetic resonance image showing recurred transitional cell carcinoma in the left maxillary sinus (white arrows) with subcutaneous infiltration and growth into the left orbita (Patient 9, Table 1). (Right) Complete response after boron neutron capture therapy.
of the second BNCT, were uncommon; 1 patient had Grade 3 xerostomia and 1 had Grade 3 dysphagia (Table 4).

DISCUSSION

Most patients who are diagnosed with inoperable, locoregionally recurrent head and neck carcinoma at a previously irradiated site succumb to the disease within a few weeks or months. Chemotherapy and further conventional radiation therapy may be considered, but are usually not curative (15, 16). In the present series, we treated patients who had recurrent inoperable head and neck cancer using BNCT. Most patients responded despite prior conventional radiation therapy in history, and most responses lasted for several months. Four (33%) patients were alive without cancer recurrence after a follow-up time exceeding 1 year, suggesting that some patients treated with BNCT may achieve a durable treatment response.

The safety and efficacy of BNCT in the treatment of non–brain tumors has not been evaluated in formal prospective clinical trials. The few case reports available suggest that BNCT may be effective in the treatment of head and neck cancer (17–19), which are in line with those of the present study and the early reports presented in October 2006 at the 12th International Congress on Neutron Capture Therapy, Takamatsu, Japan (20, 21). We treated 7 further patients with inoperable, locally recurrent head and neck carcinoma who could not participate in the current trial and who had conventional radiation therapy in history at the FiR 1 BNCT facility between the starting date and the closing date of the trial (Fig. 1). Five of these 7 patients responded to BNCT (2 died early); 1 of these 5 patients has a partial remission ongoing at 10 months and another 1 a complete remission ongoing at 24 months after BNCT. These findings also suggest that BNCT is effective for locally advanced head and neck carcinoma.

Fig. 4. (Left) Bilateral recurrence of cancer of the tongue causing rapidly progressive, massive edema of the head and neck; presentation on the date of boron neutron capture therapy (BNCT) (Patient 12, Table 1). (Right) Presentation 4 months after the second BNCT. Persistent tumor growth is present in the neck, but most edema has subsided.

Fig. 5. (Left) Recurrent cancer of the tongue that grows in the left oropharynx and hypopharynx before boron neutron capture therapy (BNCT) (Patient 3, Table 1). (Right) Complete tumor response 10 months after BNCT. The patient is alive without recurrence 19 months after administering BNCT.
BNCT for head and neck cancer ● L. KANKAANRANTA et al.

Table 3. Acute adverse effects recorded *

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>None n (%)</th>
<th>Grade 1 or 2 n (%)</th>
<th>Grade 3 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucositis</td>
<td>1 (8)</td>
<td>6 (50)</td>
<td>5 (42)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (17)</td>
<td>6 (50)</td>
<td>4 (33)</td>
</tr>
<tr>
<td>Oral/neck pain</td>
<td>4 (33)</td>
<td>3 (25)</td>
<td>5 (42)</td>
</tr>
<tr>
<td>Periodontal disease</td>
<td>5 (42)</td>
<td>7 (58)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Taste alteration</td>
<td>5 (42)</td>
<td>7 (58)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>5 (42)</td>
<td>7 (58)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>6 (50)</td>
<td>4 (33)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Xerostomia</td>
<td>7 (58)</td>
<td>4 (33)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Myositis</td>
<td>7 (58)</td>
<td>5 (42)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Trismus</td>
<td>8 (67)</td>
<td>4 (33)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Tumor pain</td>
<td>9 (67)</td>
<td>2 (17)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Skin fibrosis</td>
<td>9 (67)</td>
<td>3 (25)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>9 (67)</td>
<td>2 (17)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>9 (67)</td>
<td>0 (0)</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Otitis</td>
<td>10 (83)</td>
<td>2 (17)</td>
<td>0 (0)</td>
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<tr>
<td>Radiation dermatitis</td>
<td>10 (83)</td>
<td>2 (17)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>10 (83)</td>
<td>2 (17)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Septicemia</td>
<td>10 (83)</td>
<td>0 (0)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Osteoradionecrosis</td>
<td>11 (92)</td>
<td>1 (8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>11 (92)</td>
<td>1 (8)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

* Adverse effects recorded within the first 3 months of follow-up as calculated from the date of the first boron neutron capture therapy.

† One septicemia was Graded as 4 in severity.

Boron neutron capture therapy was associated with similar toxicities as conventional photon radiation therapy. The numbers of patients treated and the relatively short follow-up times available do not allow full evaluation of adverse effects of BNCT in the treatment of head and neck cancer, but the data suggest that the method is safe enough to be assessed in larger studies. We administered BNCT twice and after prior photon radiation therapy, which may have increased the frequency of adverse effects. Despite this, BNCT was moderately well tolerated.

The present study has some limitations. The number of patients treated was relatively small and the follow-up time of the patients still alive short. We based our dose calculations on the data obtained from studies on brain tumors, because the patients still alive short. We based our dose calculations (22). Undoubtedly this creates uncertainty in the dose calculations and emphasizes the need to carry out and finance boron delivery agent distribution studies in this patient population.

Availability of BNCT is limited to few centers worldwide (3), because sufficient numbers of epithermal neutrons can only be obtained from a nuclear reactor. However, compact accelerator-based neutron generators, compatible with installment in hospital environments, are under development. These may allow more widespread use of the technique.

We conclude that BNCT is a novel method to treat locally recurrent, inoperable, and previously irradiated head-and-neck cancer. We are evaluating BNCT for patients who have inoperable, locally advanced head and neck cancer in a larger prospective Phase II trial. Eventually, BNCT may need to be evaluated in a randomized trial against the best supportive care, repeated conventional radiation therapy, or chemotherapy in this patient population.

REFERENCES