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Boron neutron capture therapy of brain tumors: clinical trials at the Finnish facility using boronophenylalanine

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Summary

Two clinical trials are currently running at the Finnish dedicated boron neutron capture therapy (BNCT) facility. Between May 1999 and December 2001, 18 patients with supratentorial glioblastoma were treated with boronophenylalanine (BPA)-based BNCT within a context of a prospective clinical trial (protocol P-01). All patients underwent prior surgery, but none had received conventional radiotherapy or cancer chemotherapy before BNCT. BPA-fructose was given as 2-h infusion at BPA-dosages ranging from 290 to 400 mg/kg prior to neutron beam irradiation, which was given as a single fraction from two fields. The average planning target volume dose ranged from 30 to 61 Gy (W), and the average normal brain dose from 3 to 6 Gy (W). The treatment was generally well tolerated, and none of the patients have died during the first months following BNCT. The estimated 1-year overall survival is 61%. In another trial (protocol P-03), three patients with recurring or progressing glioblastoma following surgery and conventional cranial radiotherapy to 50–60 Gy, were treated with BPA-based BNCT using the BPA dosage of 290 mg/kg. The average planning target dose in these patients was 25–29 Gy (W), and the average whole brain dose 2–3 Gy (W). All three patients tolerated brain reirradiation with BNCT, and none died during the first three months following BNCT. We conclude that BPA-based BNCT has been relatively well tolerated both in previously irradiated and unirradiated glioblastoma patients. Efficacy comparisons with conventional photon radiation are difficult due to patient selection and confounding factors such as other treatments given, but the results support continuation of clinical research on BPA-based BNCT.

Introduction

The first patient was treated with boron neutron capture therapy (BNCT) at the Finnish Research Reactor (FiR 1) in May 1999. The reactor is located within the Helsinki metropolitan area (about one million inhabitants) at Otaniemi, Espoo, about 6 km from the largest hospital of Finland, the Helsinki University Central Hospital. The FiR 1 reactor, a light-water moderated 250 kW Triga Mark II nuclear research reactor, was taken in use in 1962. It functioned as a training and research reactor for neutron activation analysis, isotope production, and neutron physics until the mid-1990s. In 1996, an epithermal neutron beam was

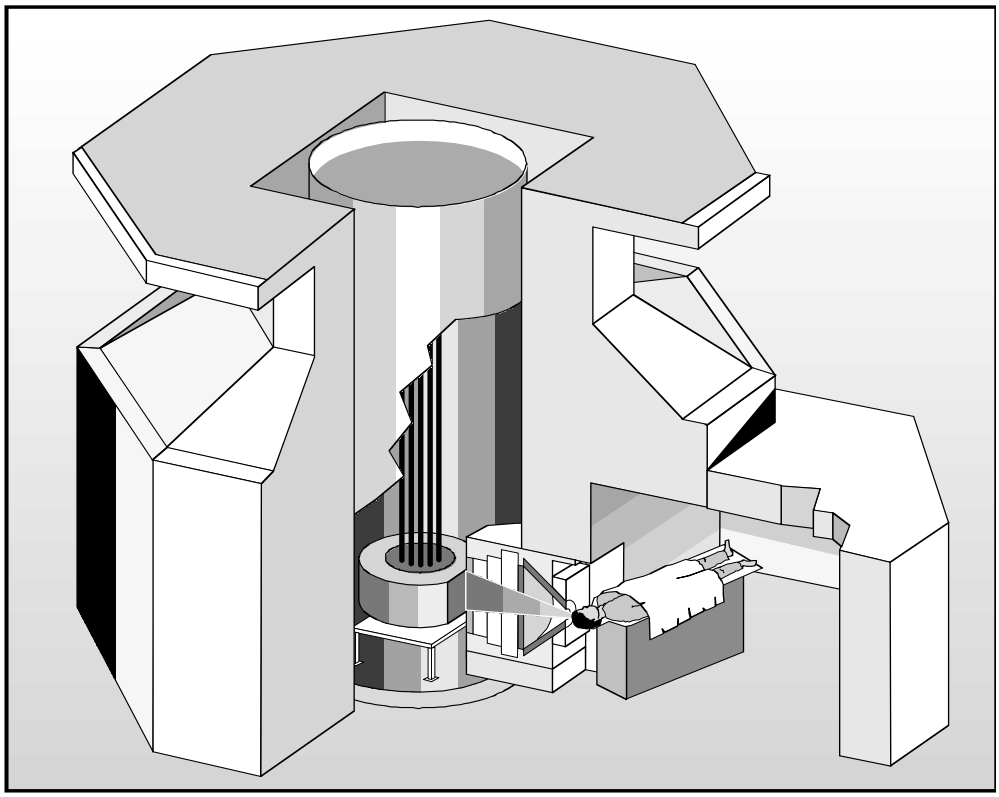


Figure 1. Schematic drawing of the BNCT facility at Fir 1.

constructed based on a new neutron moderator material Fluental™ developed at VTT (Technical Research Centre of Finland) [1,2]. After successful demonstration of a high purity epithermal beam, the patient irradiation room was constructed by cutting partly into the concrete shielding of the reactor (Figure 1). The Fluental™ moderator was shortened to create at that time the highest intensity and best purity epithermal neutron beam for BNCT. The whole reactor building was renovated including construction of irradiation simulation and monitoring rooms, and a laboratory for boron analysis, creating a dedicated clinical BNCT facility at the reactor site [3].

Patients are treated in a collaboration with the Helsinki University Central Hospital, VTT, and the NC-Treatment Ltd. The Finnish BNCT multispeciality team consists of radiation therapists and clinical oncologists, neurologists, neurosurgeons, radiologists, pathologists, radiation physicists, chemists, pharmacists, nurses, and the nuclear reactor facility personnel. The BNCT facility has been licensed for clinical use and is being surveyed by Finnish Nuclear and Radiation Safety Authority (STUK). The FiR 1 neutron beam is particularly well suited for BNCT because of its low hydrogen-recoil and incident gamma doses, and its high intensity and penetrating neutron spectrum characteristics [4].

To improve patient safety and to further characterize the properties of the FiR 1 neutron beam, beagle dogs were irradiated with the FiR 1 beam before starting the current clinical trials. The beagles were irradiated using escalating neutron doses without the ^{10}B carrier compound L-boronophenylalanine-fructose (L-BPA-F), but one dose group was infused with 700 mg L-BPA/kg body weight. In these experiments the relative biological efficiency (RBE) of the FiR 1 beam as compared with a conventional Linac 6 MV photon beam turned out to be about 1.25 in the dog brain [5]. Glioblastoma multiforme was chosen as the first tumor type to be treated, because treatment results achieved with conventional therapies are uniformly poor in this disease. Moreover, the pioneering work on

BPA-based BNCT performed at other BNCT facilities, notably at the Brookhaven National Laboratory, had already produced preclinical and clinical data that further improves safety of irradiations and formed a basis for further development of clinical BNCT [6,7]. In this paper we describe the methodology used by the Finnish BNCT consortium in clinical BNCT trials, and describe shortly the first clinical results obtained at the Finnish BNCT facility. Since BNCT is considered as an experimental form of radiation therapy, all our patients have been treated within the context of clinical research protocols approved by an institutional ethical committee, and a written informed consent was obtained from all patients.

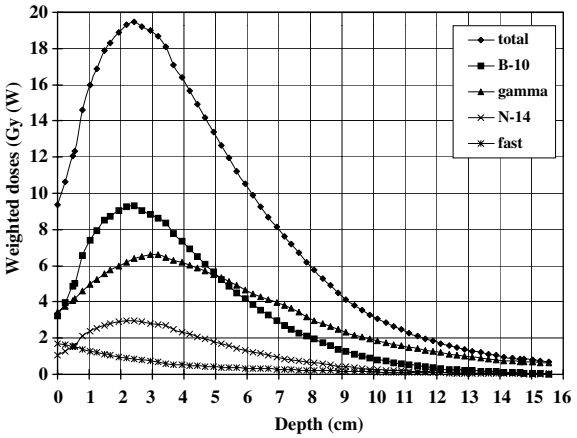


Figure 2. Modeled weighted dose rates to the normal brain in the central axis of a circular 14 cm diameter beam in a patient head. Boron concentration is 13 ppm.

Patients and methods

The neutron beam

The neutron beam obtained from FiR 1 is moderated using Fluental™, which is composed of 69% aluminumfluoride, 30% aluminum, and 1% lithium fluoride. Circular collimator apertures of 8, 11, 14, 17, and 20 cm in diameter are available for clinical use. The measured thermal (<0.5 eV), epithermal (0.5 eV–10 keV), and fast neutron (>10 keV) fluence rates are 8.1×10^7, 1.1×10^9, and 3.4×10^7 neutrons/cm^2/s, respectively, at the exit plane using a 14 cm diameter collimator at 250 kW power [8]. The undesired fast neutron dose per epithermal fluence is 2 Gy/10^{13} cm^{-2} and the corresponding gamma contamination 0.5 Gy/10^{13} cm^{-2} [2]. The in-depth dose characteristics of the epithermal neutron beam are shown in Figure 2. The beam monitoring instrumentation includes three neutron sensitive fission counters and one gamma-sensitive ionization chamber positioned in the neutron beam second to the moderator substance [9]. The instrument readings are monitored with a computer program and back-up hardware counters to ensure the beam stability during irradiation. The main purpose of the monitoring system is to provide a dosimetric link with the patient dose during the treatment. The fission chamber count rates have been calibrated to the induced thermal neutron fluence rate and to the absorbed dose rate at reference conditions in a tissue substitute phantom. A computational model for the neutron beam has been constructed, and the model has been verified by several measurement campaigns [10]. The model accurately produces neutron and gamma fields both in free beams and in phantoms. Based on this model, a source description for the treatment planning code has been created.

Boronophenylalanine-fructose

Prior to clinical studies, different synthetic batches of L-BPA were investigated [11]. For clinical studies L-BPA was purchased from Katchem Ltd. (Prague, Czech Republic). L-BPA was complexed under aseptic conditions with fructose to form L-BPA-F at the pharmacy of the Helsinki University Central Hospital. The L-BPA-F solution was prepared at a concentration of 30 g L-BPA/L by combining L-BPA with 10% molar excess of fructose in water. The final pH of the L-BPA-F solution was adjusted to 7.6 and tested for pyrogens before use. The infused amount of L-BPA varied between 290 and 400 mg/kg given at a constant rate over 2 h intravenously before irradiation (Table 2). L-BPA-F solution was infused at the BNCT facility, and irradiation with the neutron beam started about 45 min after completion of infusion.

Blood samples for monitoring whole blood boron concentration were taken immediately before starting L-BPA-F infusion, and thereafter at about 20 min intervals during L-BPA-F infusion, following infusion, after treating the first portal with epithermal neutron irradiation, and the last one or two samples were taken after completion of irradiation. The blood samples were analyzed for blood boron concentration using inductively coupled plasma-atomic emission spectrometry (ICP-AES) as described elsewhere [12]. Estimation of

the average whole blood boron concentration during irradiation was based on kinetic models [13].

Radiation dose planning

Conventional cranial imaging for BNCT dose planning was done 1–3 weeks before BNCT delivery with a 1.5T Magnetom Vision MRI imager. Gadolinium-DTPA was used as a contrast agent. MRI detectable markers were placed on the skin before MRI to mark the reference points for head positioning, and their locations were tattooed on the skin. The MRIs taken before craniotomy and 1–2 days after craniotomy were not used for dose planning, but were examined for additional information regarding tumor localization, tumor volume, and presence of edema.

The 3D Monte Carlo software packages BNCT_Rtpe and/or SERA (INEEL/MSU, Idaho Falls/Bozeman, USA) were used in the BNCT dose planning. Contrast enhanced T1-weighted MR images were used to construct a computed 3D model of the patient's head. The tissue compositions for transport computations were defined according to the ICRU Report 46 [14]. The weighted total dose (D_W) was defined as the sum of physical dose components (D_i) multiplied by weighting factors (w_i) of each dose component in a tissue

$$D_W = w_g D_g + w_B D_B + w_N D_N + w_{fast\_n} D_{fast\_n},$$

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 [15]. The weighting factor for boron dose w_B was taken as 3.8 in the target and the tumor, and 1.3 in the normal brain. Weighting factors w_N and w_{fast_n} were taken as 3.2, and w_g was considered to be 1.0 in the target, the tumor, and the normal brain [16,17]. The fluence-to-kerma conversions of the weighted nitrogen and the weighted fast neutron doses were calculated using a nitrogen concentration of 1.84 wt % and a hydrogen concentration of 10.57 wt %, assuming the brain tissue to be composed of equal proportions of the white and gray matter [18]. The unit for the physical dose components is Gy and for the weighted dose Gy (W).

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 brain-to-whole blood ratio of 1 : 1 were assumed. The computational head model consisted of the skin, the skull, the brain, the target volume, and the tumor regions in protocol P-01. In addition to these structures, the sinuses were also outlined in protocol P-03. When computing the average brain dose, the entire brain and the tumor site were included in the computation volume. The target volume was defined to consist of the enhancing tumor present in MRI, the surrounding edema, plus a 1–2 cm margin in the brain tissue in three dimensions. Two fields were irradiated in all cases, and an attempt was made to exclude the contralateral hemisphere from the target volume whenever possible. Maximum doses allowed in dose planning were determined for different anatomical structures.

Patient positioning

Patient positioning simulation for irradiation was carried out one day preceding irradiation. The beam entry and exit coordinates were provided by the dose planning program. The entry and exit coordinates given by the dose planning program were transformed in a Microsoft Excel program to a positioning coordinate system with the help of three detectable reference markers, which were placed on the patient's skin before carrying out the dose planning MRI. Patient positioning was performed in the treatment simulation room located next to the nuclear reactor. The computed beam exit and entry points were first localized and marked on the skin. After finding the optimal head position relative to the beam aperture, head and body vacuum immobilizers were shaped to secure maintained head and body position during neutron beam irradiation. The patient positioning system included a custom-made treatment coach equipped with electrical controls for the couch table position in three dimensions (Te-Pa Medical Oy, Lappeenranta, Finland), a beam aperture simulator, and a total of nine crosshair lasers. The crosshair laser system was fixed to the center of the beam aperture, and provided an identical coordinate system for head positioning both in the simulation room and in the irradiation room.

Irradiation and monitoring of the irradiation dose

Following BPA-F infusion, the patient was placed in the preshaped vacuum immobilizers on the treatment couch. The correctness of the head position for treatment was verified using positioning lasers first in the simulator and then at the irradiation site immediately before irradiation. All treatments were given as one single fraction. The irradiation time of the first field ranged

from 15.2 to 40.2 min (median, 29.6 min), patient repositioning between the fields took about 20 min, and irradiation of the second field lasted from 14.5 to 37.2 min (median, 21.5 min). Hence, the irradiation procedure typically lasted for about 1 h. Apertures of 11 or 14 cm in diameter were used in all irradiations. During neutron beam irradiation, the patient position was monitored with two television cameras. Pulse and blood oxygen level were monitored during irradiation. Vital signs were recorded before irradiation, and at 2-h intervals following irradiation for 8 h.

The nominal irradiation time computed with a dose planning program was adjusted based on the whole blood boron concentrations measured at the reactor site with ICP-AES. The blood boron analysis results were available about 10 min after sampling. The average blood boron concentration during each neutron irradiation was estimated based on kinetic models and preirradiation blood boron concentration data. Two kinetic models, an open two-compartment model and a biexponential fit are currently in use in the Finnish BNCT-trials (Figure 3). These models estimate the clearance of boron from the blood after BPA-F infusion of 290 mg BPA/kg body weight with accuracy of about 1 ppm or less during the first and second radiation fields [13]. Recently, a more capable kinetic model was developed [19]. The target beam monitor counts were set based on the corrected irradiation times. The irradiation was terminated by a reactor scram when the set beam monitor counts were reached.

Absorbed gamma doses were measured using *in vivo* thermoluminescence dosimeters (TLD) placed in the ipsilateral ear canal, at the fixation point ventral to the contralateral ear, at the base of the nose, and on the skin over the 7th cervical vertebra, the thyroid, the sternum, and on the umbilicus. Thermal neutron fluences were measured with Mn(n, γ) activation foils/wires placed on the beam entry points, in the ipsilateral ear canal, and at the base of the nose.

Patient follow-up

After neutron beam irradiation, the patients were followed up at the Department of Oncology, Helsinki University Central Hospital for about 2–3 days for possible acute radiation-related adverse effects. Dexamethasone was routinely prescribed to prevent radiation-related edema, and all patients also received antiepileptic medication. Neurological status and adverse effects were recorded using structured forms. Brain MRI examinations were scheduled to be performed 1, 3, 6, 9, 12, 18, and 24 months after irradiation using gadolinium-DTPA as a contrast agent, and clinical follow-up visits were performed at 1–3 month intervals during the first post-irradiation year.

Protocols

Protocol P-01

P-01 is a prospective, nonrandomized, phase I to II study focusing on feasibility of giving BNCT as primary radiotherapy to patients with newly diagnosed glioblastoma multiforme. Eighteen glioblastoma patients have been enrolled between May 1999 and December 2001. Eleven patients were male and the median age was 55.5 (ranging 31–67). The median time interval from surgery to BNCT was 31.5 days (ranging from 15 to 43 days). The inclusion and exclusion criteria are presented in Table 1. BPA is given intravenously complexed with fructose as 30 g BPA/L aqueous solution over 2 h, and the BPA-F dosage given

Table 1. P-01 protocol inclusion and exclusion criteria (BNCT as primary treatment for glioblastoma following surgery)

Inclusion criteria
Histologically confirmed glioblastoma multiforme
Supratentorial location
Age 18–75
Karnofsky's performance status 70% or higher
Adequate antiepileptic medication
Written informed consent is obtained and the patient is able to understand the nature of the trial
Exclusion criteria
Radiation tolerance of the optic chiasma or the basal ganglia is estimated to be exceeded in dose planning, or an adequate dose is not considered to be achieved in the deep-seated parts of the target
Less than 30% of the tumor has been removed at surgery based on comparison of the preoperative MRI and a postoperative MRI taken no longer than 72 h after craniotomy
Over 6 week time interval from craniotomy to BNCT
Prior cranial radiation therapy, cancer immunotherapy, chemotherapy or gene therapy
Serious cardiac insufficiency, liver or renal disease, or infection
Presence of a cardiac pacemaker, or metallic prostheses or implants in the head and neck area that prohibit MRI
Pregnancy or breast feeding
Phenylketonuria
Dexamethason is contraindicated

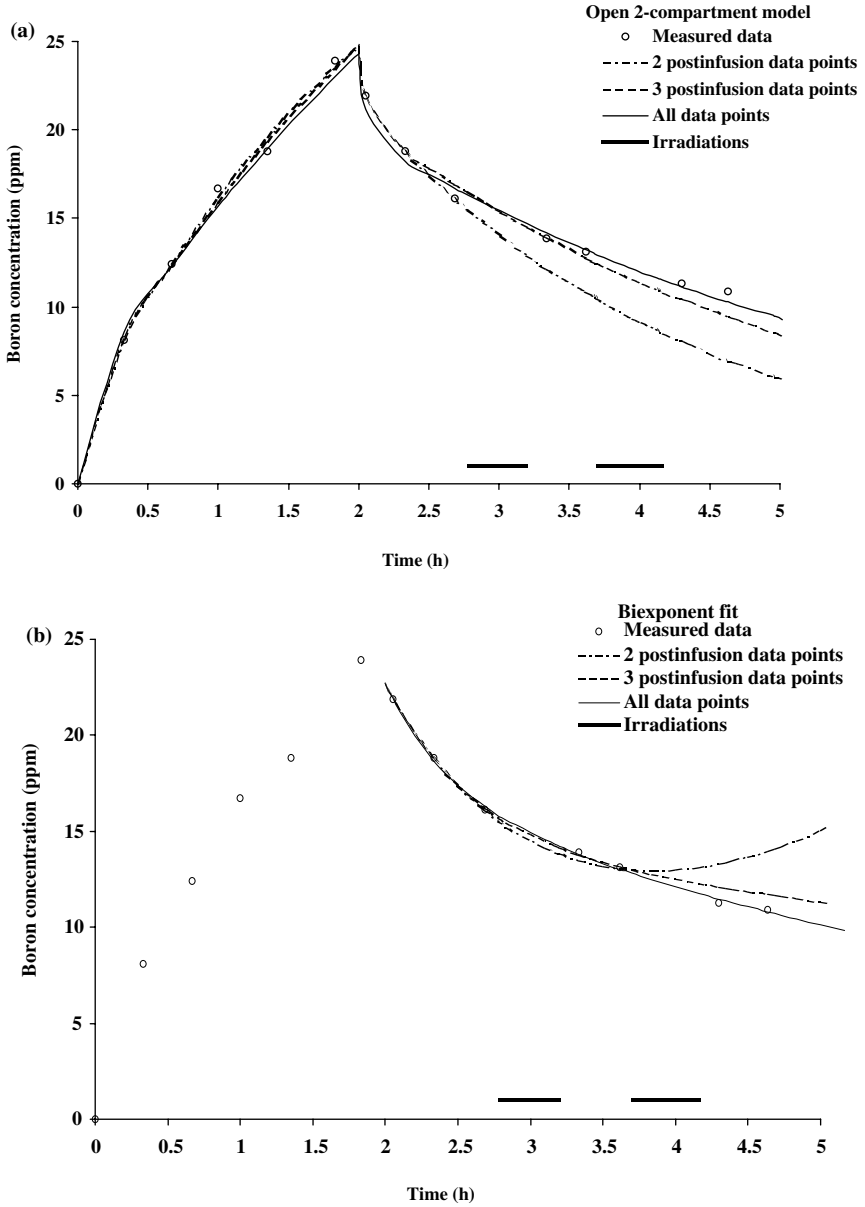


Figure 3. (a) ^{10}B concentration time-behavior based on an open 2-compartment model and blood boron concentration data from a patient infused with 290 mg BPA/kg body weight. The measured data points are expressed as circles. The results are obtained using data available before the first irradiation field (chain curve, 2 postinfusion data points used for fitting), before the second irradiation field (broken curve, 3 postinfusion data points used for fitting), and when all data points are available for fitting (solid curve). (b) A similar analysis using a bi-exponential function fitting instead of the 2-compartment model. Chain curve, 2 postinfusion data points used for fitting; broken curve, 3 postinfusion data points used for fitting; solid line, all data points available for fitting.

varied between 290 and 400 mg BPA/kg body weight. Blood hematology and chemistry are monitored before irradiation, 1 day after irradiation, and at the 1- and 3-month follow-up visits.

The BNCT_Rtpe dose planning program was used. The protocol limits the maximum average weighted dose to the normal brain as 7 Gy (W). The BPA dosages, the average weighted planning target volume (PTV)

Table 2. BPA dosages, and the average weighted doses in 18 glioblastoma patients treated in the P-01 protocol

Case	Gender/ age	BPA dosage (mg/kg)	Average planning target volume dose (range) (Gy (W))	Average normal brain dose (range) (Gy (W))	Normal brain peak dose (Gy(W))
1	F/63	290	30 (12–43)	3 (0–9)	8.1
2	F/50	290	36 (15–55)	5 (2–10)	9.3
3	M/59	290	44 (16–69)	5 (1–12)	12.0
4	F/60	290	48 (16–79)	5 (0–14)	13.5
5	M/47	290	45 (18–65)	5 (1–13)	12.3
6	M/48	290	49 (21–68)	5 (1–13)	12.3
7	M/67	290	45 (18–68)	5 (1–13)	11.9
8	M/66	290	49 (18–78)	5 (1–13)	12.4
9	F/52	290	47 (15–72)	5 (1–13)	10.8
10	F/44	290	54 (24–74)	6 (1–14)	12.7
11	M/57	290	50 (24–72)	5 (0–14)	13.0
12	F/49	290	50 (17–75)	6 (1–14)	13.7
13	M/31	330	43 (14–75)	5 (1–13)	12.4
14	M/54	360	45 (17–70)	5 (1–12)	11.1
15	M/64	360	54 (28–74)	4 (1–12)	12.0
16	M/60	360	48 (17–71)	5 (1–12)	12.1
17	M/39	400	42 (17–64)	5 (1–12)	11.3
18	F/57	400	61 (32–84)	5 (1–13)	12.0

Table 3. The normal brain maximum (peak) physical doses delivered (protocol P-01)

Case	Physical boron dose (Gy)	Physical gamma dose (Gy)	Physical nitrogen dose (Gy)	Physical fast neutron dose (Gy)	Total physical dose (Gy)
1	2.7	2.9	0.5	0.1	6.2
2	3.0	3.5	0.5	0.1	7.1
3	4.5	3.9	0.6	0.2	9.2
4	5.1	4.4	0.7	0.2	10.4
5	4.2	4.3	0.7	0.2	9.4
6	4.4	4.3	0.7	0.2	9.6
7	4.4	3.9	0.6	0.2	9.1
8	5.1	3.7	0.6	0.2	9.6
9	3.8	3.7	0.6	0.2	8.3
10	4.6	4.2	0.7	0.2	9.7
11	4.7	4.4	0.7	0.2	10.0
12	4.9	4.7	0.7	0.2	10.5
13	4.8	4.0	0.6	0.2	9.6
14	4.6	3.2	0.5	0.2	8.5
15	5.0	3.6	0.6	0.1	9.3
16	4.9	3.8	0.6	0.1	9.4
17	4.2	3.9	0.6	0.1	8.8
18	5.5	3.1	0.5	0.1	9.2

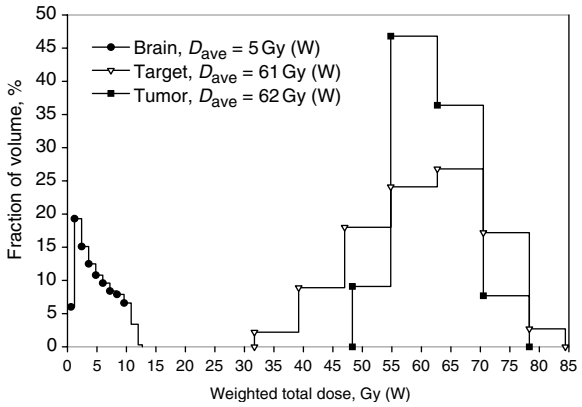
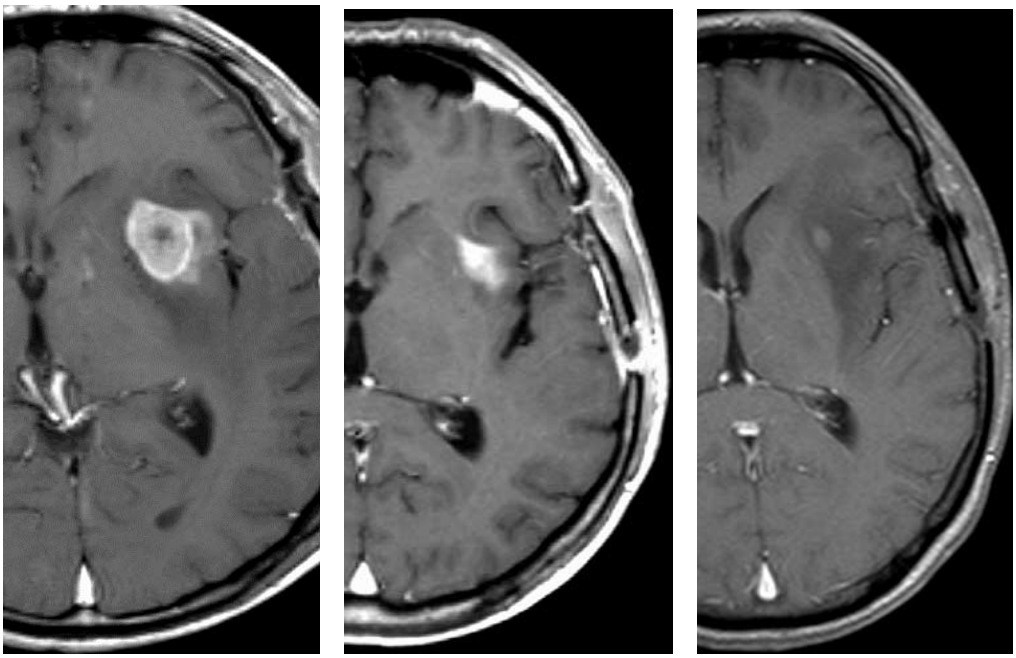


Figure 4. An example of a dose–volume histogram showing the computed weighted doses in the normal brain, the target, and the tumor (patient 18 in Table 2).

doses, and the average weighted doses to the normal brain are shown in Table 2 for the 18 patients treated. The average PTV doses were first increased in the first 12 cases while keeping the BPA-F dosage constant at 290 mg BPA/kg, following which we gradually increased the BPA-F dosage from 290 to 400 mg BPA/kg body weight in patients 13–18. The average weighted dose to the normal brain has remained at about 5 Gy (W). The normal brain weighted peak doses were less than 14 Gy (W) (Table 2), and the normal brain physical (unweighted) peak doses less than 11 Gy (Table 3). An example of a computed dose–volume histogram is shown in Figure 4. The protocol may accrue a maximum of 20 patients.

The BPA-F infusion was well tolerated, and BNCT-related acute toxicity has been acceptable. The only serious (Grade 3 or 4) toxicity related to BNCT consists of acute abdominal pain leading to laparotomy in one case. Transient dysphasia lasting for a few days was observed in six patients, transient amnesia in three, and six patients had an epileptic fit within the first week following BNCT. None of the patients have died during the first months following BNCT. The 6-month overall survival is 100% (5 patients have been followed up for less than 6 months), and estimated 1-year survival 61%. Most patients received further cancer treatments following recurrence. Since follow-up is still incomplete, overall toxicity, time to progression, and overall survival results will be presented in a more detail in a future report. An example of treatment result following BNCT is shown in Figure 5.



Before BNCT 1 month after BNCT 3 months after BNCT

Figure 5. An example of irradiation result in a 39-year-old man with histologically confirmed glioblastoma multiforme. Left panel: A transaxial MRI scan taken 10 days after brain surgery showing an enhancing tumor in the left insular lobe. Middle panel: An MRI taken one month following BPA-based BNCT suggesting tumor response (the patient used dexamethason 6 mg/day). Right panel: An MRI three months following BNCT (the patient has been without corticosteroids for about 1.5 months).

Protocol P-03

P-03 is a prospective, nonrandomized, phase I study. The main purpose of the study is to find out whether BPA-based BNCT is feasible in patients with recurrent or progressing glioblastoma who have received prior cranial conventional external beam radiotherapy. The primary end-point is treatment-related toxicity. The secondary end-points include progression-free survival (PFS), overall survival, and quality of life. The protocol was opened in February 2001, and three patients have been treated since. The patient eligibility criteria are given in Table 4.

Therapy consists of tumor biopsy or debulking surgery to confirm histological diagnosis of recurrent/progressing glioblastoma and to remove some tumor tissue. Patients receive a 2-h intravenous infusion of BPA-F that delivers 290 mg BPA/kg body weight before neutron beam irradiation. BNCT is given as a single fraction usually through two portals. The brain peak dose as computed to the maximum volume of 1 cm^3 is limited to less than 8 Gy (W), average normal brain dose to $\leq$6 Gy (W), and the minimum planned tumor dose must be $\geq$17 Gy (W) (requires a favorable tumor location). In the 3–6 first patients treated the normal brain peak dose will be limited to a maximum of 7 Gy (W) (ranging 5.0–7.0 Gy (W)). The SERA dose planning program will be used. The protocol will accrue a maximum of 22 patients.

The BPA dosages, average weighted PTV doses, and average weighted doses to the normal brain are shown in Table 5. In the first three treated patients, the therapy was well tolerated, and no serious short-term toxicity was encountered. Two patients have died of progressing glioblastoma 5 and 7 months after giving BNCT, but the third patient is alive at 12+ months. The small number of patients treated precludes making firm conclusions, but taking into account the very poor outcome of patients with recurring/progressing glioblastoma after full-dose conventional radiotherapy and the relatively good tolerability of BNCT in the first patients, the protocol will remain open and continues to accrue more patients.

Table 4. Protocol P-03 inclusion and exclusion criteria (recurrent or persisting glioblastoma following external photon irradiation)

Inclusion criteria
Histologically confirmed supratentorial glioblastoma
Recurrent or progressing glioblastoma after surgery and radiotherapy
The total prior radiation therapy dose given is 50–60 Gy
Conventional fractionation schemes have been used (conventional: 1.8–2.0 Gy/day, 5 days per week, weekly dose 9–10 Gy)
Recurrence/progression has been confirmed by serial MRI scans *and* a biopsy, or debulking reoperation
The WHO performance status ≤ 2
WBC $>2{,}500/mm^3$, platelets $>75{,}000/mm^3$, serum creatinine $<180\,\mu mol/l$
An informed consent is obtained
Exclusion criteria
Age <18
Glioblastoma that infiltrates the brain stem or the optic tracts
A minimum gross tumor dose of 17 Gy (W) is not obtained in dose-planning
Less than 6 months has elapsed from the last date of conventional photon irradiation
Less than 4 weeks has elapsed from the last cancer chemotherapy dose prior to giving BNCT
More than approximately one-third of the total brain volume has been within the 90% isodose
Gliomas where the enhancing tumor volume is larger than two-third of the volume of one hemisphere in the MRI examination preceding BNCT
More than one radiotherapy course has been given to the brain tumor
Untreated congestive heart failure or renal failure
Uncontrolled brain edema despite use of corticosteroids
A cardiac pacemaker or unremovable metal implants present in the head and neck region that will interfere with MRI-based dose-planning
Restlessness or inability to lie in a cast for 30–60 min
Clinical follow-up after therapy cannot be arranged
Pregnancy
The patient is not able to understand the treatment options
The patient is not willing to participate in the follow-up schedule

Table 5. BPA dosages, and average weighted doses given in 3 patients with recurrent/progressing glioblastoma (P-03 protocol)

Case	Gender/ age	BPA-F dosage (mg/kg)	Average planning target volume dose (range) (Gy (W))	Average normal brain dose (range) (Gy (W))	Normal brain peak dose (Gy(W))
1	M/65	290	29 (14–39)	2 (0–7)	6.5
2	M/52	290	25 (8–39)	3 (0–7)	7.1
3	M/42	290	25 (8–41)	3 (0–8)	7.0

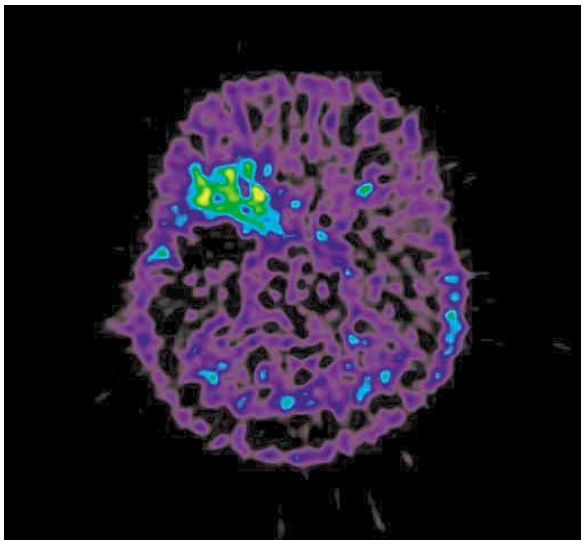


Figure 6. ^{18}F-BPA PET image of a patient with recurrent anaplastic meningeoma on the right sphenoidal wing. The tumor-to-brain ^{18}F-BPA uptake ratio was 2.5–3.5 suggesting potential feasibility of BNCT for treating this tumor.

Future protocols

Protocols under development include a protocol where BNCT is given shortly preceding stereotactically guided, conformal fixed-field photon radiotherapy, and another protocol where patients with different histological types of brain tumor are selected for BNCT based on *in vivo* measured uptake of ^{18}F-labeled L-BPA (L[^{18}F]FBPA) in positron emission tomography (PET) (Figure 6).

Discussion

The median survival of glioblastoma patients is less than 12 months with conventional therapy, which usually consists of surgery and radiotherapy. The purpose of protocol P-01 was to study the safety and tolerability of BPA-based BNCT using gradually escalating doses of irradiation and BPA. The results suggest that BPA-based BNCT can be safely given with the doses used, and that the technique is feasible. However, the small patient number treated and the short follow-up preclude making comparisons regarding efficacy of BPA-based BNCT with conventional radiation therapy. The extent and the quality of primary and secondary surgery, patient selection, and concomitant and

subsequent other therapies also confound such comparisons. Yet, the absence of serious adverse effects and the relatively favorable 1-year overall survival figure of 61% warrant further study on BPA-based BNCT.

Neither the optimal epithermal neutron irradiation technique nor the preferred method of delivering the boron carrier compound have been established, and refinements in either or both of these components of BPA-based BNCT may result in a clinical benefit. Since the toxicity of BPA-based BNCT has been acceptable when BPA doses up to 400 mg/kg has been infused within 2 h prior to irradiation, still higher BPA doses might be studied in future protocols. However, recent studies performed in the rat 9L gliosarcoma model suggest that longer than 2-h infusion times are needed to increase the boron concentration in the infiltrating tumor cells outside the main tumor mass, otherwise the infiltrating tumor cells may remain underdosed [20]. These findings suggest that the 2-h infusion time may not be optimal and that infusion times of 6 h or longer need to be addressed in other protocols (Capala et al., in this issue). Blood–brain barrier disrupting agents may enhance entry of BPA into the central nervous system, and might further improve the clinical efficiency of BNCT [21], whereas the benefits of split-dose delivery remain to be shown [22]. Since combination therapies have proved superior to single modality therapy in the treatment of many types of human cancer, BNCT also needs to be assessed in combinations with targeted photon radiotherapy, radiation sensitizers and protectors, signal transduction inhibitors, and anti-angiogenic agents as well as with conventional cancer chemotherapy in future clinical trials.

So far, the dose planning of the Finnish BNCT treatments has been based on the estimated boron concentration in the target volume obtained from reported kinetic studies, and measured blood boron concentrations and on-line kinetic models. One of the ongoing research projects in Finland is to assess directly the macroscopic spatial and temporal distribution of ^{10}B within the brain and the tumor using magnetic resonance spectroscopy (MRS) and PET technologies. Techniques such as ^{18}F-BPA PET [23–25] and MRS [26] may turn out to be valuable in identifying tumors of different histological types that accumulate BPA more than the surrounding brain tissue, may aid in optimizing boron compound administration, dosimetry, and dose planning, and may help in understanding the treatment results.

Protocol P-03 was designed to assess the feasibility and efficacy of BPA-based BNCT in patients with glioblastoma that has recurred or progressed following full dose conventional photon radiotherapy. The outcome of such patients is bleak. The median progression-free survival of these patients is only about 3 months even when treated with modern chemotherapy agents such as temozolomide [27], and there is no curative therapy available. Although the clinical data is scarce, some recovery from initial irradiation appears to take place in the central nervous system. This was demonstrated in a study where rhesus monkeys were reirradiated 2 years after the first radiation therapy course to the cervical spinal cord. The ED_{50} value for myeloparesis of a single course of irradiation turned out to be 76 Gy, whereas the extrapolated ED_{50} for an initial dose of 44 Gy plus a varying retreatment dose was over 110 Gy [28]. In the rat spinal cord model, recovery from the initial dose has been 5–50% [29]. In line with these data, toxicity related to photon reirradiation in humans has been considered as acceptable, when the time interval between the two irradiations has been at least one year and only a part of the brain has been within the target volume [30].

The risk of brain necrosis has been estimated to be about 5% within 5 years of follow-up (TD 5/5) when 60 Gy has been delivered to about one-third of the total brain volume, or when 50 Gy has been given to two-thirds of the brain volume [31]. Assuming 20% recovery within $\geq$6 months following radiation, only 12 Gy conventional radiotherapy can be given after a full dose of 60 Gy given in 6 weeks at the TD 5/5 risk level. However, when calculating from the biological effective dose (BED) formula and using the α/β of 3 Gy for late reacting tissues, 12 Gy given as 2 Gy daily fractions relates to about 6.4 Gy single dose. When the normal brain peak dose (peak volume 1 cm^3) is limited to 6.4 Gy (W), a single fraction average tumor dose as high as 20–35 Gy (W) may still be given with BPA-mediated BNCT with the currently used BPA-F protocol at the Otaniemi BNCT facility for brain tumors that do not infiltrate into the deep-seated brain structures. Unlike the 12 Gy photon dose given with conventional fractionation, such a single dose of 20–35 Gy (W) might have significant clinical effects. Therefore, a fairly large dose might still be delivered to such tumors with BNCT, where only a relatively small volume of the normal brain (<5%) receives the maximum radiation dose when modern BNCT protocols are used [29]. In line with this we encountered limited

toxicity from BNCT in the first three patients irradiated with glioblastoma recurring after 50–60 Gy photon irradiation. The survival times of these patients are not disappointing, and warrant continuation of the P-03 protocol.

At present, the optimal way of giving BNCT is still not known. Importantly, in the absence of randomized clinical trials, it is not known whether BNCT is more or less effective than conventional photon radiation in the treatment of malignant brain tumors. Since BNCT capacity is limited worldwide, phase I to II trials should preferably be carried out in a coordinated manner to refine the technique, and randomized comparisons to standard photon therapy may need to be carried out by international cooperative groups. Such international collaborative efforts might resolve the major open questions within a reasonably short time period.

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References

1. Auterinen I, Hiismäki P: Epithermal BNCT neutron beam design for a Triga II reactor. In: Soloway H, Barth RF (eds) Advances in Neutron Capture Therapy. Proceedings of the 5th International Symposium on Neutron Capture Therapy. Plenum Press, New York, 1993, pp 81–84
2. Auterinen I, Hiismäki P, Kotiluoto P, Rosenberg RJ, Salmenhaara S, Seppälä T, Serén T, Tanner V, Aschan C, Kortesniemi M, Kosunen A, Lampinen J, Savolainen S, Toivonen M, Välimäki P: Metamorphosis of a 35 years old Triga reactor into a modern BNCT facility. In: Hawthorne MF, Shelly K, Wiersema RJ (eds) Frontiers in Neutron Capture Therapy, Vol 1. Plenum Press, New York, 2001, pp 267–275
3. Savolainen S, Auterinen I, Kallio M, Kärkkäinen M, Kosunen, A, Aschan C, Benczik J, Färkkilä M, Hiismäki P, Kaita K, Kulvik M, Ryynänen P, Seppälä T, Seren T, Tanner V, Toivonen M, Vähätalo J, Ylä-Mella H: The Finnish boron neutron capture therapy program – an overview on scientific projects. In: Larsson B, Crawford J, Weinreich R (eds) Advances in Neutron Capture Therapy, International Congress Series 1132, Vol I, Medicine and Physics. Elsevier Science B, Amsterdam, 1997, pp 342–347
4. Wheeler FJ, Nigg DW, Capala J, Watkins PR, Vroegindeweij C, Auterinen I, Seppala T, Bleuel D: Boron neutron capture therapy (BNCT): implications of neutron beam and boron compound characteristics. Med Phys 26: 1237–1244, 1999
5. Benczik J: Relative biological effectiveness of reactor produced epithermal neutrons for the canine brain. Thesis, University of Helsinki, 2000
6. Chanana AD, Capala J, Chadha M, Coderre JA, Diaz AZ, Elowitz EH, Iwai J, Joel DD, Liu HB, Ma R, Pendzick N, Peress NS, Shady MS, Slatkin DN, Tyson GW, Wielopolski L: Boron neutron capture therapy for glioblastoma multiforme: interim results from the phase I/II dose-escalation studies. Neurosurgery 44: 1182–1192, 1999
7. Diaz AZ, Coderre JA, Chanana AD, Ma R: Boron neutron capture therapy for malignant gliomas. Ann Med 32: 81–85, 2000
8. Seren T, Kortesniemi M, Aschan C, Seppälä T, Lampinen J, Auterinen I, Savolainen S: A tale of two beam-comparison of the radiation fields at the BMRR and FiR 1 epithermalBNCT facilities. Med Biol Eng Comput 37(suppl 1) 396–397, 1999
9. Tanner, Auterinen I, Helin J, Kosunen A, Savolainen S: On-line neutron beam monitoring of the Finnish BNCT facility. Nucl Instrum Meth Phys Res A 422: 101–105, 1999
10. Savolainen S, Auterinen I, Aschan C, Hiismäki P, Kortesniemi M, Kosunen A, Kotiluoto P, Lampinen J, Seppälä T, Serén T, Tanner V, Toivonen M: Dosimetry chain for the treatments of glioma patients in the epithermal neutron beam at the Finnish BNCT facility (FiR 1). Med Biol Eng Comp 37: 388–389, 1999
11. Vähätalo J, Tuominen J, Kokkonen J, Kriz O, Karonen SL, Kallio M: Trace impurities identified by high performance liquid chromatography/electrospray mass spectrometry in two different synthetic batches of 4-boronophenylalanne. Rapid Commun Mass Spectrom 12: 1118–1122, 1998
12. Laakso J, Kulvik M, Ruokonen I, Vähätalo J, Zilliacus R, Färkkilä M, Kallio M: Atomic emission method for total boron in blood during neutron-capture therapy. Clin Chem 47: 1796–1803, 2001
13. Ryynänen PM, Kortesniemi M, Coderre JA, Diaz AZ, Hiismäki P, Savolainen SE: Models for estimation of the (10)B concentration after BPA-fructose complex infusion in patients during epithermal neutron irradiation in BNCT. Int J Radiat Oncol Biol Phys 48: 1145–1154, 2000
14. ICRU: ICRU Report 46, Photon, electron, proton, and neutron interaction data for body tissues, International Committee on Radiation Units and Measurements, Bethesda, MD, 1992
15. Seppälä T, Kotiluoto P, Savolainen S, Auterinen I, Hiismäki P, Seren T, Kosunen A, Aschan C, Kortesniemi M, Toivonen M: Determining and reporting the doses in the treatment of glioma patients in the epithermal neutron beam at the Finnish BNCT facility (FIR 1), IAEA-TECDOC-1223. Current status of neutron capture therapy. International Atomic Energy Agency IAEA, pp 275–288, 2001
16. Chadha M, Capala J, Coderre JA, Elowitz EH, Iwai J, Joel DD, Liu HB, Wielopolski L, Chanana AD: Boron

Neutron-Capture Therapy (BNCT) for Glioblastoma Multiforme (GBM) Using the Epithermal Neutron Beam at the Brookhaven National Laboratory. Int J Radiat Oncol Biol Phys 40: 829–834, 1998
17. Coderre JA, Morris GM: Review: the radiation biology of boron neutron capture therapy. Rad Res 151: 1–18, 1999
18. Brooks RA, DiChiro G, Keller MR: Explanation of cerebral white-gray contrast in computed tomography. J Comp Assist Tomog 4, 489–491, 1980
19. Ryynänen P, Kangasmäki A, Hiismäki P, Coderre J, Diaz A, Kallio M, Laakso J, Kulvik M, Savolainen S: Non-linear models for kinetics 10B in blood after BPA-fructose complex infusion. Phys Med Biol 47: 737–745, 2002
20. Smith DR, Chandra S, Barth RF, Yang W, Joel DD, Coderre JA: Quantitative imaging and microlocalization of boron-10 in brain tumors and infiltrating tumor cells by SIMS ion microscopy: relevance to neutron capture therapy. Cancer Res 61: 8179–8187, 2001
21. Yang W, Barth RF, Bartus RT, Rotaru JH, Moeschberger ML, Ferketich AK, Nawrocky MM, Coderre JA, Goodman JH: Improved survival after boron neutron capture therapy of brain tumors by Cereport-mediated blood–brain barrier modulation to enhance delivery of boronophenylalanine. Neurosurgery 47: 189–1997, 2000
22. Morris GM, Micca PL, Rezvani M, Hopewell JW, Coderre JA: Boron neutron capture therapy: effects of split dose and overall treatment time. J Neuro-Oncol 52: 101–110, 2001
23. Kabalka GW, Smith GT, Dyke JP, Reid WS, Longford CPD, Roberts TG, Reddy NK, Buonocore E, Hübner KF: Evaluation of fluorine-18-BPA-fructose for boron neutron capture therapy treatment planning. J Nucl Med 38: 1762–1767, 1997
24. Imahori Y, Ueda S, Ohmori Y, Kusuki T, Ono K, Fujii R, Ido T: Fluorine-18-labeled fluoroboronophenylalanine PET in patients with glioma. J Nucl Med 39: 325–333, 1998
25. Imahori Y, Ueda S, Ohmori Y, Sakae K, Kusuki T, Kobayashi T, Takagaki M, Ono K, Ido T, Fujii R: Positron emission tomography-based boron neutron capture therapy using boronophenylalanine for high-grade gliomas: part I & II. Clin Cancer Res 4: 1825–1841, 1998
26. Zuo CS, Prasad PV, Busse P, Tang L, Zamenhof RG: Proton nuclear magnetic resonance measurement of p-boronophenylalanine (BPA): a therapeutic agent for boron neutron capture therapy. Med Phys 26: 1230–1236, 1999
27. Yung WK, Albright RE, Olson J, Fredericks R, Fink K, Prados MD, Brada M, Spence A, Hohl RJ, Shapiro W, Glantz M, Greenberg H, Selker RG, Vick NA, Rampling R, Friedman H, Phillips P, Bruner J, Yue N, Osoba D, Zaknoen S, Levin VA: A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse. Br J Cancer 83: 588–593, 2000
28. Ang KK, Price RE, Stephens LC, Jiang GL, Feng Y, Schultheiss TE, Peters LJ: The tolerance of primate spinal cord to re-irradiation. Int J Radiat Oncol Biol Phys 25: 459–464, 1993
29. Morris GM, Coderre JA, Hopewell JW, Micca PL, Wielopolski L: Boron neutron capture therapy: re-irradiation response of the rat spinal cord. Radiother Oncol 48: 313–317, 1998
30. Veninga T, Lagendijk HA, Slotman BJ, Rutten EHJM, van der Kogel AJ, Prick MJJ, Keyser A, van der Maazen RWM: Reirradiation of primary brain tumours: survival, clinical response and prognostic factors. Radiother Oncol 59: 127–137, 2001
31. Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, Shank B, Solin LJ, Wesson M: Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 21: 109–122, 1991

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