# Clinical practice in BNCT to the brain

**Y. Nakagawa**
Department of Neurosurgery,
National Kagawa Children's Hospital,
Kagawa, Japan

**Abstract.** Our concept of Boron Neutron Capture Therapy (BNCT) is to selectively destroy tumour cells using the high LET particles yielded from the 10B(n,α)7Li reactions. The effort of clinical investigators has concentrated on how to escalate the radiation dose at the target point. BNCT in Japan combines thermal neutrons and BSH ($Na_2B_{12}H_{11}SH$). The radiation dose is determined by the neutron fluence at the target point and the boron concentration in the tumour tissue. According to the recent analysis, the ratio of boron concentration (BSH) in tumour tissue and blood is nearly stable at around 1.2 to 1.69. Escalation of the radiation dose was carried out by means of improving the penetration of the thermal neutron beam. Since 1968, 175 patients with glioblastoma (n=83), anaplastic astrocytoma (n=44), low grade astrocytoma (n=16) or other types of tumour (n=32) were treated by BNCT at 5 reactors (HTR n=13, JRR-3 n=1, MuITR n=98, KUR n=30, JRR-2 n=33). The retrospective analysis revealed that the important factors related to the clinical results and QOL of the patients were minimum tumour volume radiation dose, more than 18Gy of physical dose and maximum vascular radiation dose (less than 15Gy) in the normal cortex. We have planned several trials to escalate the target radiation dose. One trial makes use of a cavity in the cortex following debulking surgery of the tumour tissue to improve neutron penetration. The other trial is introduction of epithermal neutron. KUR and JRR-4 were reconstructed and developed to be able to irradiate using epithermal neutrons. The new combination of surgical procedure and irradiation using epithermal neutrons should remarkably improve the target volume dose compared to the radiation dose treated by thermal neutrons.

## 1. INTRODUCTION

Glioblastoma is a poorly differentiated glioma and considered the most malignant tumour of the brain. It occurs in the white matter of the cerebrum and rapidly grows and invades the normal brain tissue from multiple directions before the time of diagnosis. Most of the patients with such an invasive glioma, not only glioblastoma but also anaplastic astrocytoma and low-grade astrocytoma are beyond the point of curative treatments such as surgery, chemotherapy, and conventional radiotherapy. The proton beam therapy & heavy-ion therapy with Bragg peak have high risk of damage to the surrounding normal brain tissue in the same way with surgical excision. Recent trials using high dose radiation (60-70Gy) therapy show constantly efficient results. However, radiotherapy of the whole brain produced extensive radiation damage. From the viewpoint of the radiation effect and good quality of life after treatment, boron neutron capture therapy (BNCT) is an ideal treatment for malignant brain tumours. [1,2]

## 2. BASIC PRINCIPLE OF BNCT

We consider BNCT an intercellular internal radiation therapy. Alpha particles ($^4He$) and recoiling lithium-7 ($^7Li$) nuclei yielded from the nuclear reaction between boron-10 and thermal neutron have a high linear energy transfer (LET) and an associated high relative biological effectiveness (RBE). Furthermore, the two particles have a short path length (5–10 mm) which is approximately equal to the diameter of the tumour cells. Selective accumulation of $^{10}B$ in the tumour cells and corrective irradiation with suitable thermal neutron beam can realise cell levelled destruction of tumour tissue without significant damage to the surrounding brain tissue. It is well known that for a successful treatment in patients with malignant brain tumour, it is essential to secure a sufficient radiation dose (enough alpha

particles & recoiling lithium-7). This depends on the boron compounds that adequately accumulate in the tumour tissue and improvement of neutron penetration in the brain. [3]

## 3. HISTORY OF BNCT

Clinical trials of BNCT were initiated in 1951 at Brookhaven National Laboratory by Farr et al and developed by Sweet and Sweet et al. at Massachusetts General Hospital/ Massachusetts Institute of Technology. However, after several trials, it was discontinued in 1961 because of the discouraging clinical results. The renewal of BNCT was organised in 1968 by H. Hatanaka in Japan using a new boron compound, BSH ($Na_2B_{12}H_{11}SH$) at HTR (Hitachi training reactor) in Japan. Successively, four reactors (JRR-3; Reactor of Japan Atomic Energy Research Institute, MuITR; Reactor of Musashi Institute of Technology, KUR; Research Reactor Institute of Kyoto University, JRR-2; Reactor of Japan Atomic Energy Research Institute) were authorised for medical use. Besides facilities, evolutionary procedures and new ideal instruments were introduced into the clinical trials. One was the diagnostic procedure such as CT scan and MRI, which made it possible to determine the size and the depth of the tumour with greater accuracy. The other ideal instrument was prompt gamma ray spectrometry developed by Drs. Kobayashi and Kanda· Prompt gamma ray spectrometry has given us more accurate data on the boron concentration in tumour tissue and blood before a decision on the radiation time is made. As various improvements progressed, a more correct radiation plan was made and dose escalation has been tried.

## 4. RECENT STANDARD TECHNIQUE OF BNCT

In order to improve the neutron penetration of the brain tissue, we de-bulk the brain tumour and make a cavity during a preliminary operation one to two weeks before BNCT. Partial excision of the tumour also minimises the bulk of future narcotised tissue after BNCT. The skin flap must be large enough to allow a large aperture for the neutron beam (12 cm x12 cm). According to the MRI findings, we insert a few gold wires in the tumour or around the tumour for measurement of neutron flux. The tip of the wire must be around the target point. After the operation, we identify the location of the gold wires by CT and/or skull X ray. The day before BNCT, about fifteen hours before neutron irradiation, BSH diluted in 500-ml saline is intravenously infused for 60 minutes by drip infusion. (60~80 mg BSH/kg body weight). The following morning the patient is taken to the reactor. Under general anaesthesia, the patient's skin flap is reopened and the bone flap is removed. After the opening of the dura mater, a piece of the tumour tissue is obtained for boron-10 analysis. We place an additional two or three gold wires on the surface of the brain to measure the neutron fluence on the irradiation field. A thin silastic rubber balloon filled with air is placed into the cavity. The procedure maintains the size of the cavity during neutron irradiation and improves the neutron penetration. Following the closure of the dura matter, a heat-malleable plate of a plastic material containing $^6$Li-F is applied to the patient's head to protect the skin from the thermal neutron irradiation. This "helmet" has a hole in the center to allow the neutron beam into the tumour-harbouring area of the brain. The beam should be as free as possible from fast neutrons and gamma rays to avoid indiscriminate radiation to the brain. The entire head is covered with sterile plastic drapes to prevent infection. Simultaneous neutron beam monitoring devices are attached on the surface of the brain. Gamma rays are measured by TLD at several points of the body. The patient is moved into the irradiation chamber. Under remote-control general anaesthesia, the head is fixed towards the neutron port and neutrons are delivered. Blood is intermittently drawn from the patient before and after neutron irradiation for boron-10 analysis. Boron concentration in the brain tumour and blood is

measured by prompt gamma ray spectrometry during the irradiation. In order to measure the exact neutron flux at each point of interest, gold wires inserted in the tumour tissue are pulled out at 15–30 minute intervals after the full power operation of the reactor. It is possible to assess the exact neutron fluence at each point of interest. The plan for the remainder of the irradiation is then based on this up-to-the-minute data regarding boron concentration and neutron flux.

## 5. TIMING OF THE NEUTRON IRRADIATION

Neutron irradiation was designed according to the clinical analysis in our series. T. Kageji et al. reported detailed pharmacokinetics and boron uptake of BSH in a recently issued report.. Neutron irradiation was started between 10 to 20 hours after a single infusion of BSH in consecutive trials. [4] The mean boron concentration before the neutron irradiation in the tumour tissue was 25.8 ppm. The tumour to blood ratio (T/B) was nearly stable at around 1.2 to 1.69 in successful cases. The study showed a significant statistical correlation between boron uptake and time interval from the infusion of BSH. Within the first 10 hours after BSH infusion, malignant glioma tissue contained high level of boron (30–60 ppm), however; the boron concentration in blood showed a higher level than that in the tumour tissue. Hence the T/B ratio was below one. In the 12–24 hours following BSH infusion, the boron concentration in the tumour was above 20 ppm in 56% of malignant glioma patients. The T/B ratio was more than one in 69% and two in 38% of them. These data indicated that the neutron irradiation should be done around 15–18 hours after the BSH infusion. A positive tumour-to-blood ratio and a uniform tumour concentration around 10–40 mg/g $^{10}B$ are needed for successful BNCT.

## 6. CASE REPORTS

*Case 1.* A 50-year-old man developed speech disturbance and right hemiparesis. Cerebral angiography demonstrated tumour stain in the left front-parietal area. He underwent craniotomy and the tumour was subtotally removed. Histological diagnosis was glioblastoma. He received BNCT at MuITR in June 1972. After craniotomy under general anaesthesia, a ping pong ball was inserted into the cavity to improve the neutron penetration. Neutron flux was measured on the surface of the ping-pong ball and on the bottom of the cavity using gold foils. It was 8.8E + 12n/cm$^2$ and 5.3E + 12n/cm$^2$ respectively. Boron concentration in the tumour tissue was 15.3pp. and 27.3 ppm in the blood (Fig. 1-a). Retrospective analysis of the radiation dose of boron n-alpha reaction was 7.5-16.8 Gy (physical dose). A follow up CT scan studied 11 years after BNCT demonstrated porencephalic cyst, however, there was no recurrence of the tumour. After 20 years the man was still active as a farmer and holds a driving license at the age of 70 (Fig. 1-b).

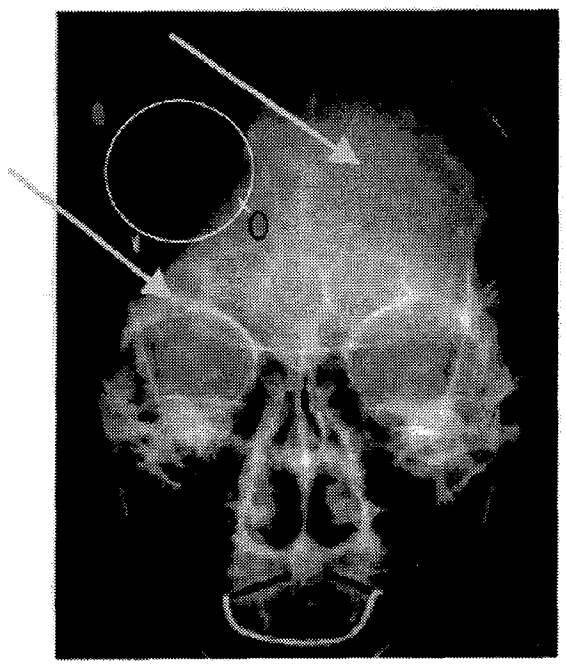

*Fig. 1.a. Radiation planning*

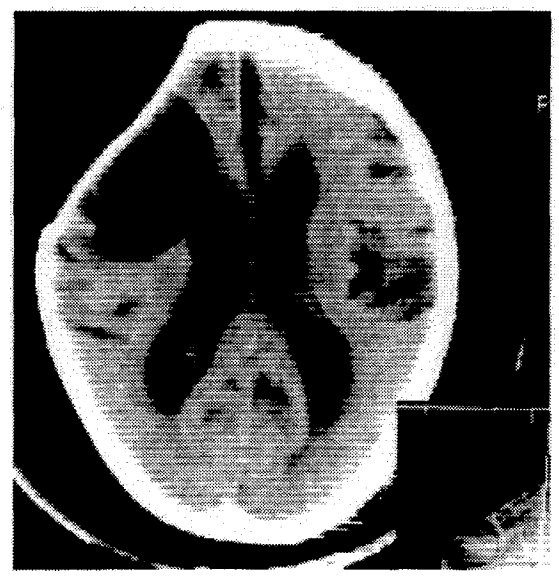

*Fig. 1.b. Follow up CT 15 years after BNCT*

*Case 2.* A 60-year-old woman with glioblastoma underwent BNCT at MuITR in July 1977. A ping pong ball was inserted into the cavity and neutron flux was measured on the surface of the ping pong ball and on the bottom of the cavity. It was 1.45E + 13n/cm$^2$ and 7.5E + 12n/cm$^2$ respectively. Boron concentration in the tumour tissue was 14.0ppm and 13.3ppm in the blood. According to the retrospective analysis of the radiation dose of boron n-alpha reaction, tumour volume dose was 15.9 Gy (physical dose). Follow up MRI studied 16 years after BNCT demonstrated multi cystic lesion, however, there was no recurrence of the tumour (Fig. 2).

*Case 3.* An 11-year-old girl had a huge tumour in the right frontal lobe. Histological diagnosis was grade 3 oligo-astrocytoma. BNCT was performed at MuITR in Oct. 1981. Neutron flux measured on the surface of the ping pong ball and on the bottom of the cavity using gold foils was 1.46E + 13n/cm$^2$ and 6.72E + 12n/cm$^2$ respectively. Boron concentration in the tumour tissue was 22.1ppm and 11.2ppm in the blood. Tumour volume radiation dose was 23.0 Gy (physical dose). Follow up MRI studied in 1994 demonstrated porencephalic cyst, however, there was no recurrence of the tumour (Fig. 3).

*Case 4.* A 41-year-old female suffered from headache epileptic seizure and right hemiparesis. A magnetic resonance image (MRI) showed an enhanced mass in the left parietal lobe. She underwent craniotomy and partial resection of the tumour. Histological diagnosis was glioblastoma. BNCT was performed at KUR in Aug. 1992. Two gold wires were inserted around the tumour. Neutron flux was measured on the surface of the brain and at the target point. It was 1.6E + 13n/cm$^2$ and 4.1E + 12n/cm$^2$ respectively. Boron concentration in the tumour tissue was 20.0ppm and 11.2ppm in the blood. Retrospective analysis of the radiation dose of boron n-alpha reaction was 13.0 Gy (tumour volume dose). Follow up MRI demonstrated marked decrease of the enhanced lesion (Fig 4).

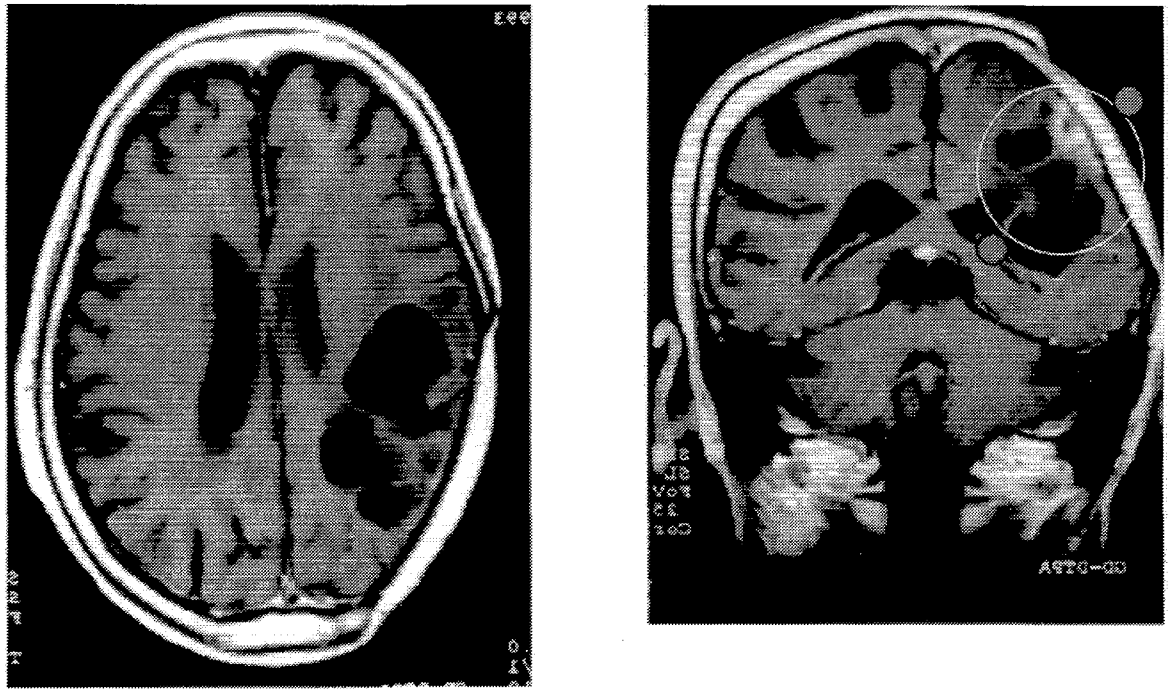

*Fig. 2. Follow up MRA after 16 years after BNCT. Boron concentration :14.0 ppm in tumor tissue, 13.3 ppm on blood Radiation time : 140 min . Radiation dose:15.9 Gy (B-10 n-a)*

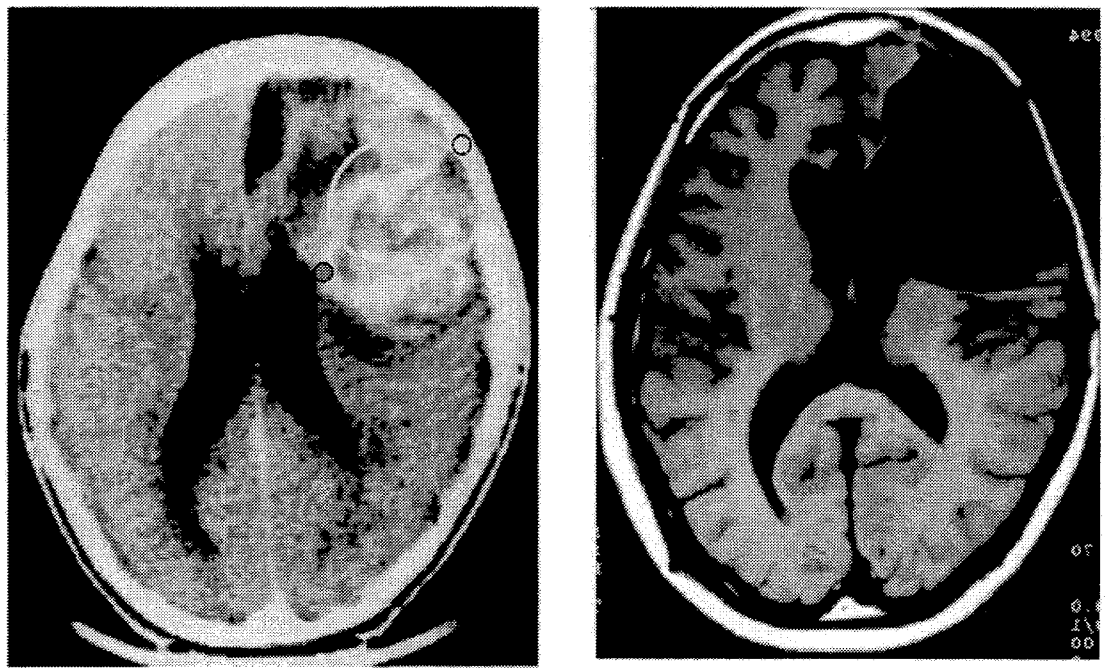

*Fig. 3. 11F, Oligo-astrocytoma (G3). Planning (left) Oct. 1981 at MuITR. Follow up MRI (right) in 1994. Radiation dose at target pint was 23Gy.*

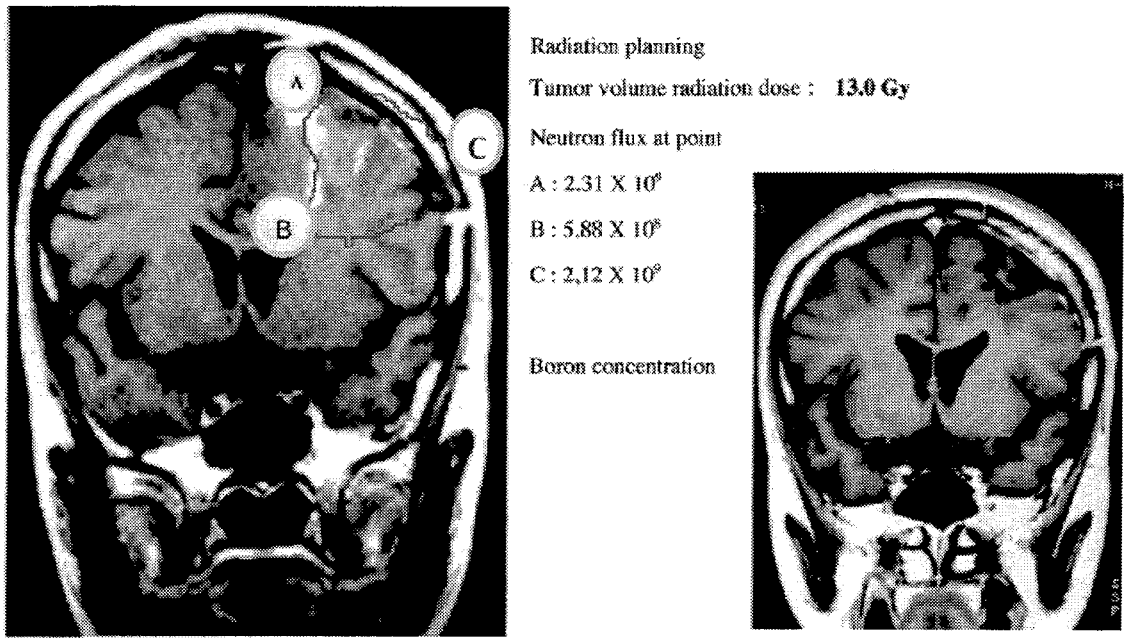


*Fig. 4. A 41-year-old female with glioblastoma.. Planning (left) Aug. 1992 at KUR. Follow up MRI (right) 2 years after BNCT. Radiation dose at target pint "B "was 13Gy.*

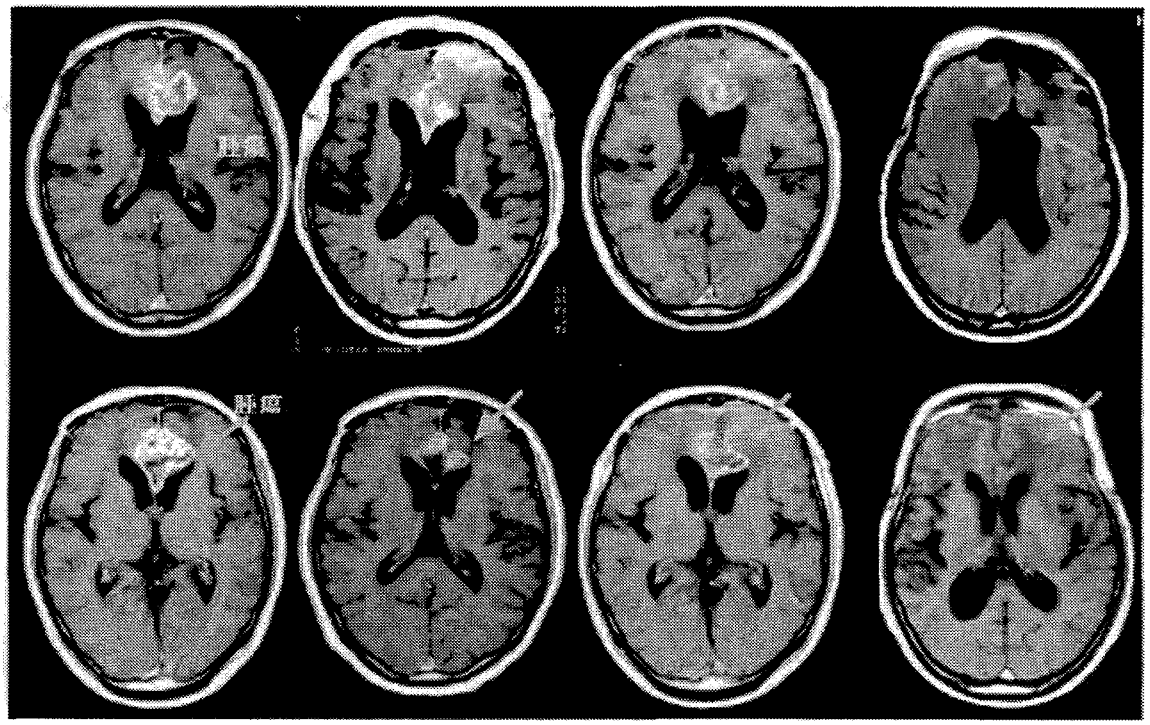

*Fig. 5. A 65-year-old man with glioblastoma was underwent in March, 1995 at JRR-2. Follow up MRI BNCT (from leftto right ; pre BNCT, 2weeks, 1 month, 6 months after BNCT ) Radiation dose at target pint was 11Gy. Abnormally enhanced lesion gradually decreased (arrow).*

*Case 5.* A 65-year-old man had glioblastoma in the bilateral frontal lobe. He underwent craniotomy and partial resection of the tumour. Histological diagnosis was glioblastoma. BNCT was performed at IRR-2 in March, 1995. Neutron flux was measured using gold wires which were inserted around the tumour. It was 4.2E + 12n/cm$^2$ at the target point. Boron concentration in the tumour tissue was 31.0ppm and 25.0ppm in the blood. Retrospective analysis of the radiation dose of boron n-alpha reaction was 11.0 Gy (tumour volume dose). Follow up MRI demonstrated a gradual decreasing of the enhanced lesion (Fig 5).

## 7. CLINICAL OUTCOME

Since 1968, we have treated 175 patients and performed boron-neutron capture therapy (BNCT) using 5 reactors in Japan. There were 83 patients with glioblastoma, 44 patients with anaplastic astrocytoma and 16 patients with low grade astrocytoma (grade 1 or 2). There were 32 patients with other types of tumour. Most of the patients were followed by CT or MRI to study the efficacy of BNCT. Retrospectively we divided the patients into two groups to investigate the prognostic factors. One group (group 1): the patients who lived more than 3 years. The other group (group 2): the patients who lived less than 3 years. We analyzed histology of the tumours, age of the patients, radiation time, boron concentration in the blood, neutron fluences on the surface of the brain at the target point target depth and tumour volume dose in each group.

Table I. Clinical outcome of the patients who lived more than 10 years

| Patient | Age | Sex | Histology | T/B ratio | 10B in tumour | Tumour volume dose |
|---|---|---|---|---|---|---|
| M.T. | 50 | M | Glioblastoma | 0.56 | 15.3 | 13.5 |
| R.N. | 60 | F | Glioblastoma | 1.05 | 13.3 | 18.9 |
| T.T. | 30 | M | Chondrosarcoma | 1.07 | 27.1 | 11.6 |
| C.U. | 47 | F | Meningioma | 8.95 | 90.4 | 13.8 |
| C.Y. | 58 | F | Meningioma | N.D | N.D | 12.5 |
| K.N. | 25 | M | An. Astrocytoma | 1.15 | 35.2 | 23.1 |
| T.M. | 11 | f | An. Astrocytoma | 1.43 | 11.2 | 14.2 |
| Y.T. | 38 | F | Glioblastoma | 1.42 | 13.9 | 15.9 |
| R.K. | 56 | M | Glioblastoma | 1.89 | 21.6 | 20.3 |
| M.I. | 22 | M | Malig. Ependymoma | N.D. | N.D. | 14.8 |
| K.K. | 39 | M | An. Astrocytoma | N.D. | N.D. | 15.2 |
| E.M. | 48 | F | Meningioma | N.D. | N.D. | 9.3 |

CT or MRI demonstrated marked response in 3 to 6 months after BNCT in 60% of the patients with glioma. Twelve patients (four glioblastomas and four anaplastic astrocytomas three meningioma, one chondrosarcoma) lived more than 10 years. Seventeen patients lived more than 5 years. There were two patients with glioblastoma, 10 patients with anaplastic astrocytoma and one with low grade astrocytoma. Out of 143 patients with glial tumours treated by BNCT, 27 lived or have lived longer than 3 years after BNCT. As prognostic factors, grading of the tumour, ages of the patients and target depth were proved as important

factors. However, the most important factor was tumour volume radiation dose demonstrated by boron n-alpha reaction. The tumour volume was calculated on CT or MRI findings. Twenty-eight patients were treated before the induction of CT, therefore the patients were excluded in this study. [5.6]. The tumour volume radiation dose in the patients with grade 2 glioma were 11.5Gy (group 1) vs. 6.7Gy (group 2), 15.6Gy (group 1) vs. 11.8 (group 2) in grade 3 glioma and 18.2Gy (group 1) vs. 9.8Gy (group 2) in glioblastoma patients (table 2).

## 8. RADIATION NECROSIS

Radiation necrosis was diagnosed by CT and/or MRI; however, it is still considered controversial to diagnose the radiation necrosis after BNCT. Radiation necrosis was determined as follows: low intensity on MRI T-1 weighted image with contrast enhancement (+) and high intensity on T-2 weighted image. Low density area with contract enhancement (+) on CE-CT. Radiation necrosis was found in 19 patients (19/175 10.9%). Fourteen of those 19 patients had clinical symptoms and radiographic change. Nine of the 14 had neurological deficits such as motor weakness and speech disturbance. The patients were treated with a high dose of steroid therapy ( Dexamethasone 32-64mg/day was tapered for one to two weeks and changed to prednisolone 10-30mg / day per os). Of these 9, 3 patients' symptoms gradually disappeared after using the steroid treatment. The remaining six patients had permanent mild to slight neurological deficits. The other 5 out of 14 patients had only epileptic seizure within 1 week after BNCT. The remaining five patients had only radiographic change without neurological deterioration. Radiation necrosis demonstrated by CT or MRI was noticed in two months to two years after BNCT. The age of the patients with radiation necrosis is 38.5±19.0 y.o., and the age of the patients without radiation necrosis is 41.8± 18.6 y.o. The radiation time of the patients with radiation necrosis was 254 ± 99 min., as opposed to the radiation time of the patients without radiation necrosis, which was 218 ± 103 min. The boron concentration in the blood of the patients with radiation necrosis was 28± 9 ppm, while the boron concentration in the blood of the patients without radiation necrosis was 22± 10 ppm. The maximum neutron fluence of the patients with radiation necrosis was $2.1x10^{13}\pm 0.6x10^{13}$ n/cm$^2$; however, the neutron fluence of the patients without radiation necrosis was $1.7x10^{13}\pm 0.8x10^{13}$ n/cm$^2$. Vascular radiation dose was calculated according to the report by Kitao and Rydin. Only one-third of the $^{10}B$ (n, a)$^7Li$ radiation occurring in vascular lumen will be absorbed by the vascular endothelium. Lastly, the vascular radiation dose of the patients with radiation necrosis was 21± 8.1 Gy, while the vascular dose of the patients without radiation necrosis was 9.4 ± 5.1 Gy. These data indicated that the maximum vascular dose should be less than 15 Gy.

Table II. Patients surviving more than 5 years after BNCT

| Patient | Age | Sex | Histology | T/B ratio | 10B in tumour | Tumour volume dose |
|---|---|---|---|---|---|---|
| P.C. | 50 | M | Glioblastoma | 0.75 | 15.3 | 13 |
| I.M. | 15 | F | Rhabdomiosarcoma | 3.8 | 28 | 11.1 |
| R.T.. | 4 | F | Pontine glioma | N.D | N.D. | 10.6 |
| Y.A. | 44 | M | An. Astrocytoma | 1.7 | 13.4 | 16.7 |
| Y.S. | 37 | M | An. Astrocytoma | 1.9 | 25.8 | 10.1 |

Table II. (cont.)

| | | | | | | |
|---|---|---|---|---|---|---|
| T.Y.. | 39 | F | An. Astrocytoma | 1.9 | 30.1 | 18.3 |
| K.Y.. | 52 | F | Meningioma | N.D. | N.D. | 10.3 |
| P.J. | 40 | F | An. Astrocytoma | 1.1 | 12.8 | 13.3 |
| K.O.. | 33 | M | An. Astrocytoma | 1.3 | 18.4 | 17.2 |
| Y.M. | 27 | M | An. Astrocytoma | N.D. | N.D. | 11.5 |
| M.F. | 42 | F | Meningioma | N.D. | N.D | 10.3 |
| N.M. | 1.4 | F | An. Astrocytoma | 1.6 | 28.6 | 8.5 |
| R.T | 41 | F | Glioblastoma | 0.8 | 11.6 | 16.6 |
| K.Y. | 7 | M | An. Astrocytoma | N.D. | N.D | 7.9 |
| I.O. | 8 | F | An. Astrocytoma | N.D. | N.D | 9.7 |
| T.S. | 31 | M | An. Astrocytoma | N.D.. | N.D | 13.8 |
| H.M. | 17 | M | An. Astrocytoma | 2.6 | 56.1 | 15.2 |

Table III. Radiation necrosis and related factors

| | Necrosis (+) | Necrosis (-) |
|---|---|---|
| Age | 38.5 ± 19.0 | 41.8 ± 18.6 |
| Radiation time | 254 ± 99 | 218 ± 108 (min) |
| B-10 in blood | 28.9 ± 9 | 22 ± 10 (ppm) |
| Neutron fluences | 21.E ± 0.6 | 1.7E ± 0.8 (13n/cm$^2$) |
| Maximum | | |
| Vascular dose | 21.8 ± 8.1 | 9.4 ± 5.1 (Gy) |

## 9. NEW PROTOCOL

The tumour volume radiation dose of the last protocol was 10Gy but increased up to 15Gy in the new protocol. Surgical procedures and making a cavity played an important role not only to irradiate with sufficient neutron fluence, but also to avoid radiation side effect. Radiation side effect or radiation necrosis was observed in 10.9 % of our series. The factors related to radiation necrosis were maximum thermal neutron fluence on the brain surface and vascular dose. Therefore, we decided the maximum thermal neutron fluence on the surface of the brain should be below 2.0 + E13 n/cm$^2$. Vascular dose in the brain tissue near the surface of the brain or maximum vascular dose must be controlled below 15 Gy. To improve the neutron penetration, we decided to utilize epithermal neutron beams. KUR was reconstructed in 1997. Following the shutdown of the JRR-2, JRR-4 was renewed for medical use in 1998. Both reactors have the capacity to yield thermal neutron beam, epithermal neutron beam and

mixed beams. We compared the neutron fluences at the target point and on the surface of the cavity between a case treated by thermal neutron and one by mixed beam (Fig. 3). Thanks to the cavity, neutron penetration was improved ca. 30% even if irradiated by thermal neutron. The new combination of surgical procedure and irradiation using epithermal neutrons should remarkably improve the target volume dose compared to the radiation dose treated by thermal neutrons, seven times without cavity and 3.5 times with cavity.

### 9.1. Proposed protocol for malignant brain tumours in Japan in 1998

*Patient selection*
- Patients with glioma grade 3-4
- Less than 70 years of age
- No serious systemic disease
- Good general condition (KPS>70)
- Radiation dose
- Minimum Tumour Volume Dose: 18Gy*
- Target Volume Dose: 15Gy*
- Maximum Vascular Dose < 15Gy

*Physical dose of boron n-alpha reaction
Neutron irradiation using mixed beam of thermal neutron or epithermal neutron beam
Radiation time is decided according to the data of boron concentration in the blood or tumour tissue and neutron flux at the target point and surface of the brain.

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