XA0101253

Annex 8
CLINICAL

Medical set-up of boron neutron capture therapy (BNCT) for malignant glioma at the Japan research reactor (JRR)-4

T. Yamamoto, A. Matsumura, T Nose, Y. Shibata, K. Nakai
Department of Neurosurgery,
Institute of Clinical Medicine,
University of Tsukuba

F. Sakurai, T. Kishi, H. Kumada, K. Yamamoto, Y. Torii
Department of Research Reactor,
Tokai Research Establishment,
Japan Atomic Energy Research Institute,
Ibaraki

Japan

Abstract. The University of Tsukuba project for boron neutron capture therapy (BNCT) was initiated at the Japan Atomic Energy Research Institute (JAERI) in 1992. The clinical study for BNCT began at the Japan Research Reactor (JRR)-2 of the JAERI in November 1995. By the end of 1998, a new medical irradiation facility had been installed in JRR-4 of that included a new medical treatment room and patient-monitoring area adjacent to the irradiation room. The medical treatment room was built to reflect a hospital-type operation room that includes an operating table with a carbon head frame, anesthesia apparatus with several cardiopulmonary monitors, etc. Following craniotomy in the treatment room, a patient under anesthesia is transported into the irradiation room for BNCT. The boron concentration in tissue is measured with prompt gamma ray analysis (PGA) and simultaneously by inductively coupled plasma atomic emission spectroscopy (ICP-AES) methods. For the immediate pre- and post-BNCT care, a collaborating neurosurgical department of the University of Tsukuba was prepared in the vicinity of the JAERI. The long term follow-up is done at the University of Tsukuba Hospital. Epithermal neutron beam also became available at the new JRR-4. By changing the thickness and/or the configuration of heavy water, a cadmium plate, and a graphite reflector, the JRR-4 provides a variety of neutron beams, including three typical beams (Epithermal mode and Thermal modes I and II). Intraoperative BNCT using the thermal beam is planned to study at the beginning of the clinical trial. The ongoing development of the JAERI Computational Dosimetry System (JCDS) and radiobiological studies have focused in the application of the epithermal beam for BNCT. After obtaining these basic data, we are planning to use the epithermal beam for intraoperative BNCT.

1. INTRODUCTION

A new medical irradiation facility was completed at the Japan Research Reactor (JRR)-4 in the Japan Atomic Energy Research Institute (JAERI) in September 1998. The research project on boron neutron capture therapy (BNCT) for malignant glioma will begin at the JRR-4 in July 1999. The University of Tsukuba project for the clinical study of BNCT was proposed in 1992 in collaboration with Hatanaka and colleagues [1]. The first clinical study, BNCT with a thermal neutron beam and $Na_2{}^{10}B_{12}H_{11}SH$ (BSH), took place from November 1995 to the end of 1996 at JRR-2 in JAERI [2]. The new JRR-4 facility is capable of providing both epithermal and thermal beams, and it has a medical treatment room being prepared for intraoperative BNCT.

2. MEDICAL IRRADIATION FACILITY

2.1. The medical treatment room and the patient-monitoring area

The general arrangement of the medical irradiation facility is shown in FIG.1. The irradiation room, the patient-monitoring area, the laboratory, and the medical treatment (operating) room are located in the basement. The medical treatment room was built to reflect a hospital-type operating room, with the following features: (1) an operating table that can move patient in all three orthogonal directions and in the vertical and horizontal directions; (2) a carbon head frame for use in the irradiation room; (3) an anesthesia apparatus with cardiopulmonary monitors; (4) a washbasin plus sterilized warm water; (5) sterilamps; and (6) on-line TV monitors. Following craniotomy, a patient on the operating table is moved from the medical treatment room into the irradiation room. In the patient-monitoring area, the drip infusion bottles and an urinary bag are observed via TV monitor by the anesthesiologist. The anesthesiologist can observe all the monitors and anesthetic machine used during the craniotomy.

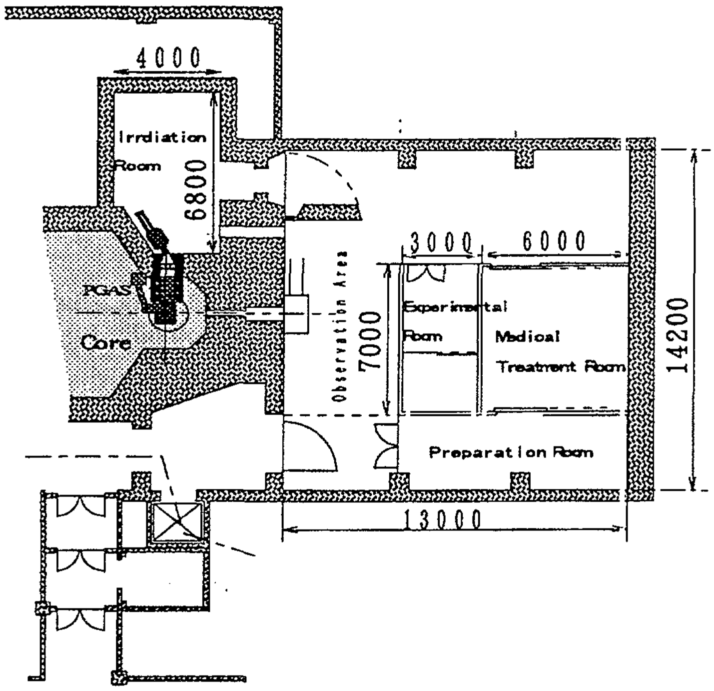

FIG. 1. General arrangement of medical irradiation facility.

2.2. Boron concentration measurement

A prompt gamma ray analysis (PGA) device has been installed on the second floor of the JRR-4. An inductively coupled plasma atomic emission spectroscopy (ICP-AES) device has been installed in the laboratory in the basement. To estimate the irradiation time during the intraoperative BNCT procedure, the measurement of the boron concentration of specimens must be complete within half an hour by using PGA and/or ICP-AES in the JRR-4.

2.3. Beam performance of in the facility at the JRR-4

The JRR-4 irradiation facility can provide a variety of neutron beams by changing the thickness and/or configurations of heavy water, a cadmium shutter, and a graphite reflector (FIG.2). However, three typical beam settings for BNCT have been proposed (TABLE 1). Among the three typical beams, the use of mode II results in similar irradiation time and dose distribution to the beam used at the JRR-2 that had been utilized in a part of the clinical trial by Hatanaka and Nakagawa [1] and also in the first clinical experiences by the University of Tsukuba group [2].

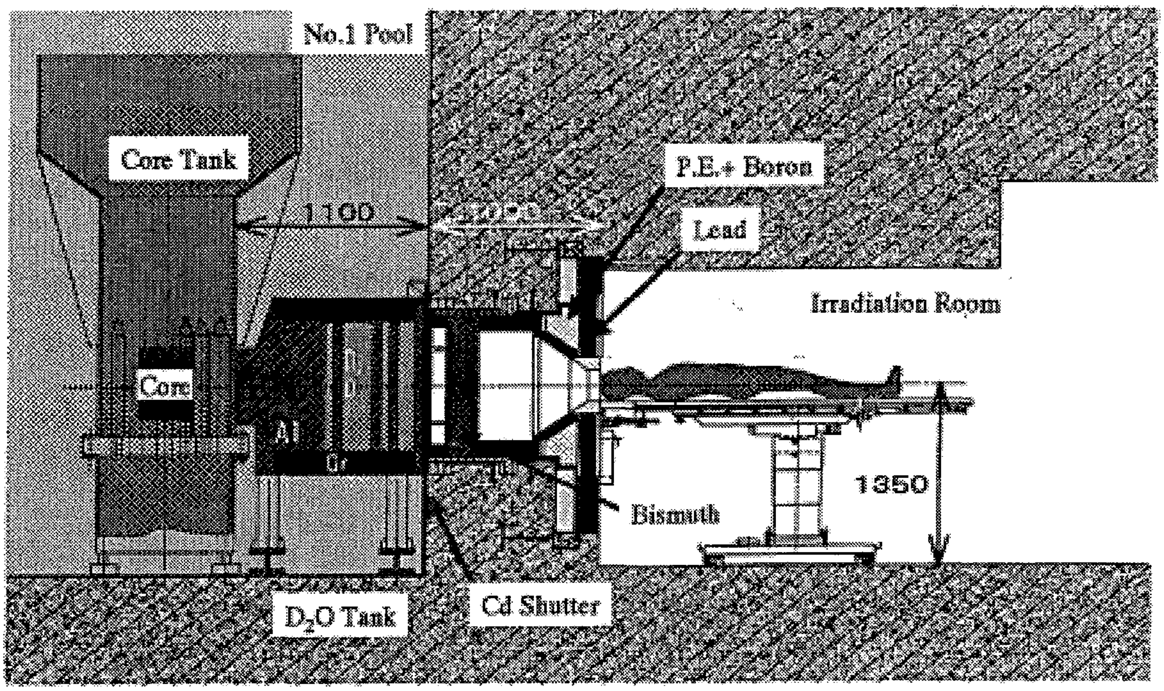

FIG. 2. Cross-section of the medical irradiation facility.

TABLE 1. Beam performance of typical modes of JRR-4

Items		Unit	Epitherma l mode	Thermal Mode I	Thermal Mode II	JRR-2
Heavy water		cm	8	12	33	-
Cadmium shutter			on	off	off	-
Bi filter		cm	18	18	18	-
Carbon lining		(7cm)	Yes	Yes	Yes	-
Collimator*		cmcm	15	15	15	-
Neutron flux	Thermal < 0.53eV	n/cm^2sec	$3.6 x10^8$	$2.0 x10^9$	$6.5x10^8$	$1.1 x10^9$
	Epithermal 0.53-10keV	n/cm^2sec	$2.2 x10^9$	$9.0 x10^8$	$3.2 x10^7$	-
	Fast > 2.6MeV	n/cm^2sec	$4.7 x10^5$	$3.6 x10^5$	$5.0 x10^4$	-
Cadmium ratio			1.15	2.5	13.5	64
Gamma dose rate		Sv/h	2.4	3.6	0.7	0.48

*Collimators in 10 cm and 20-cm diameter are also available

2.4. Dose planning system (JAERI Computational Dosimetry System: JCDS)

A software-based dose planning system is under development for the purpose of precise dose simulation and further investigation of BNCT with an epithermal beam. By the end of May 1999, the beta version of the JAERI Computational Dosimetry System (JCDS) for BNCT became available. This JCDS not only allows dosimetry of the usual non-surgical BNCT, but it also enables physicians to plan the dosimetry for intra-operative BNCT using skin reflection and air void.

2.5. Peri-BNCT care of patients

The initial debulking surgery and boron distribution study are performed at the University of Tsukuba Hospital. The immediate pre- and post-BNCT care is given at Naka Central Hospital, which is located in the vicinity of JRR-4, and long term follow-up is done again at the University of Tsukuba Hospital.

3. PROTOCOL

The new research protocol on boron neutron capture therapy (BNCT) for malignant glioma will begin at the JRR-4 in October 1999. The primary goals of this project are: (1) establishment of the treatment facility, including the treatment room and anesthesia apparatus, for the performance of intraoperative BNCT; (2) establishment of the safety and efficacy of BNCT with BSH and the thermal beams; (3) cross-calibration of the JCDS data with actual measurement results during intraoperative BNCT for optimizing the JCDS; (4) preparation for possible use of the epithermal beam.

3.1. Patient criteria

All patients entered into this study will be seen at the University of Tsukuba Hospital. To be eligible, patients have to fulfill the following criteria [2]:

(1) Histologic proof of anaplastic astrocytoma or glioblastoma and its variants [3]
(2) Karnofsky performance score ≥ 70
(3) Age 18 to 70 years
(4) Supratentorial unilateral tumor no deeper than 6 cm from brain surface
(5) Adequate cardiopulmonary, hepatic, renal, and bone marrow functions:
(6) - SGOT<60 IU/ml, Bilirubin<1.5 mg%
(7) - BUN<30 mg/dl, Cr<1.5 mg%
(8) - WBC>2500/mm3, Plt>75000/mm3, no severe anemia
(9) No previous chemotherapy or radiotherapy
(10) No double cancer and no previous therapy for any other cancers
(11) No allergy to BSH
(12) Signed informed consent

3.2. BNCT treatment conditions

Intraoperative BNCT is comprised of: (1) BSH biodistribution study at the first operation for tumor removal, and (2) a second craniotomy and BNCT approximately 2 to 4 weeks following the first operation. In the BSH biodistribution study, 1 g of BSH 12 h before the first operation, then blood is taken up serially for boron concentration analyses. Specimens from various parts of the brain tumor are kept for the measurement of boron level. For BNCT, 100 mg/kg BW of BSH is given with 500 ml of saline for 1 h via intravenous drip infusion. The infusion is initiated 12 h before planned irradiation. The calculation of irradiation time is based on the tumor and blood boron level and the thermal neutron dose that is measured intraoperatively using gold wire and/or foils.

4. DISCUSSION

Malignant gliomas are refractory to all current therapeutic modalities, including surgery, chemotherapy, and radiation therapy. The difficulties of using postoperative radiation therapy to cure patients with malignant gliomas are caused by the low intrinsic radiosensitivity and the diffuse microinvasion within the brain parenchyma around the tumor [4,5]. BNCT, the emerging therapeutic modality for high-grade gliomas, is based on neutron capture reaction between the cold isotope of boron (^{10}B) and the thermal neutron. On capture reaction, ^{10}B atoms disintegrate into high-LET alpha (^{4}He) and Lithium (^{7}Li) particles. Theoretically, tumor affinity of boron compounds and a short path length (-10Lim) would result in selective tumor cell killing with minimum damage to circumscribing normal tissue.

Several years after the early clinical trials of BNCT by Farr et al. [6,7] and Sweet et al. [8,9], Hatanaka and Nakagawa had treated more than 150 patients using intraoperative BNCT with BSH [1]. Recently, American and European clinical trials were initiated using BNCT with epithermal neutrons, which can overcome the steep attenuation of thermal neutrons in the brain [10,11]. Epithermal neutrons can pass through the scalp, the temporal muscle, and the cranial bone and convert to thermal neutrons in tissue. Therefore, epithermal neutrons would improve the amount of thermal neutrons delivered to deep-seated lesions. In the American and European clinical trials, BNCT is performed in a rather non-invasive fashion in which patients are irradiated without skin reflection and general anesthesia. Treatment planning and the assessment of BNCT dose are based on software-based treatment planning systems [12] and/or the accumulated knowledge from clinical biodistribution studies, and animal experiments [13,14]. In intraoperative BNCT, the BNCT dose would be planned based on the previous clinical data of JRR-2, especially with regard to preventing radiation damage. Irradiation time would be decided by calculating the BNCT dose from the actual boron content of the residual tumor and the blood boron level, and the measurement of the withdrawn gold wire. Regarding the validity of the estimated irradiation time (dose) with JCDS, JCDS data should be compared to the intraoperative measurement results, which are calculated from gold wires placed in the surgical field.

It is empirically known that an air balloon placed in a surgical defect of the brain plays a role of being the void for neutron beams and leads to increased dose delivery at the bottom of the surgical defect. Experimentally, an improvement of thermal neutron flux is observed not only in the direction of the beam axis but also in the vertical and horizontal directions (unpublished data). The improvement of dose distribution in deep-seated lesion caused by skin reflection and the void effect is thought to be essential to BNCT with thermal neutrons. Similarly, improved dose distribution would be a considerable gain for future intraoperative BNCT with an epithermal beam. Since intraoperative radiation therapy (IORT) has demonstrated some advantages [15], for example single high-dose targeting radiation, avoids unwanted radiation damage to normal tissues, we think that intraoperative BNCT with an epithermal beam could play an important role in improved clinical results. For that reason we have designed studies that focus on intraoperative BNCT with an epithermal beam to enter the next phase of clinical trials.

5. CONCLUSION

A medical irradiation facility for intraoperative BNCT has been installed in JRR-4. The University of Tsukuba group is preparing for a clinical study to assess the safety of intraoperative BNCT with BSH and a thermal beam at the brand-new facility. Following this clinical study, we are planning to initiate intraoperative BNCT with an epithermal beam.

ACKNOWLDGEMENTS

This project was supported by the University of Tsukuba research projects, by Charitable Trust: The Matsuoka Memorial Fund for Medical Aid to the Citizens in Ibaraki Prefecture and by the Fund-in Trust for Cancer Research from the Governor of Ibaraki Prefecture, Japan.

REFERENCES

[1] NAKAGAWA Y, HATANAKA H: Boron neutron capture therapy: Clinical brain tumor studies. *J Neurooncol* 33: 105–115, 1997.

[2] MATSUMURA A, SHIBATA Y, YAMAMOTO T, YAMADA T, FUJIMORI H, NAKAI K, NAKAGAWA K, HAYAKAWA Y, ISSIKI M, NOSE T.: The University of Tsukuba BNCT research group; first clinical experiences at JAERI, in Larsson B, Crawford J, Weinreich R (eds): *Advances in Neutron capture Therapy: Medicine and physics.* Amsterdam, Elsevier, 1997, Vol 1, pp46–50.

[3] Histological classification of CNS tumours, in Kleihues P, Burger PC, Scheithauer BW (eds): *Histological typing of tumuors of the central nervous system* (WHO), Springer-Verlag, 2nd edn, 1993.

[4] YAES, RJ: Tumor heterogeneity, tumor size, and radioresistance. *Int J Radiat Oncol Biol Phys.*17: 993–1005, 1989

[5] CHICOINE MR, SILBERGELD DL: Assessment of brain tumor cell motility *in vivo* and *in vitro*. *J Neurosurg* 82: 615–622,1995.

[6] FARR LE, HAYMAKER W, KONIKOWSKI T, LIPPINCOTT SW: Effects of alpha particles randomly induced in the brain in the neutron-capture treatment of intracranial neoplasm. *Int J Neurol* 3: 564–576, 1962.

[7] FARR LE, SWEET WH, ROBERTSON JS, FOSTER CG, LOCKSLEY HB, SUTHERLAND L, MENDELSOHN ML, STICKLEY EE: Neutron capture therapy with boron in the treatment of glioblastoma multiforme. *Am J Roentgenol* 71: 279–293, 1954.

[8] SWEET WH: Early history of development of boron neutron capture therapy of tumors. *J Neurooncol* 33: 19–26, 1997

[9] SWEET WH, SOLOWAY AH, BROWNELL GL: Boron-slow neutron capture therapy of gliomas. *Acta Radiol* 1: 114–121, 1963.

[10] CODERRE JA, ELOWITZ EH, CHADHA M, BERGLAND R, CAPALA J, JOEL DD, LIU HB, SLATKIN DN, CHANANA AD: Boron neutron capture therapy for glioblastoma multiforme using *p*-boronophenylalanine and epithermal neutrons: Trial design and early clinical results. *J Neurooncol* 33:141–152, 1997.

[11] SAUERWEIN W: The clinical project at HFR Petten: A status report, in Larsson B, Crawford J, Weinreich R (eds): *Advances in Neutron capture Therapy: Medicine and physics.* Amsterdam, Elsevier, 1997, Vol 1, pp 77–84.

[12] NIG DW, WHEELER FJ, WESSOL DE, CAPALA J, CHADHA M: Computational desimetry and treatment planning for boron neutron capture therapy. *J Neurooncol* 33: 93–104, 1997.
[13] ELOWITZ EH, BERGLAND RM, CODERRE JA, JOEL DD, CHADHA M, CHANANA AD: Biodistribution of *p*-boronophenylalanine in patients with glioblastoma multiforme for use in boron neutron capture therapy. *Neurosurgery* 42: 463–469, 1998.
[14] GAVIN PR, KRAFT SL, HUISKAMP R, CODERRE JA: A review: CNS effects and normal tissue tolerance in dogs. *J Neurooncol* 33: 71–80, 1997.
[15] HARRISON LB, MINSKY BD, ENKER WE, MYCHALCZAK B, GUILLEM J, PATY PB, ANDERSON L, WHITE C, COHEN AM: High dose rate intraoperative radiation therapy (HDR-IORT) as part of the management strategy for locally advanced primary and recurrent rectal cancer. *Int J Radiat Oncol Biol Phys* 42: 325–330,1998.