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### Background and Objective

Using Kyoto University Research Reactor (KUR), patients with malignant tumors greater than 500 have been treated with boron neutron capture therapy (BNCT). Malignant brain tumors and head and neck cancers have been main malignancies treated with BNCT. Our laboratory (Division of Particle Radiation Oncology) has investigated the possibilities for new applications for BNCT. According to promising results in pre-clinical study, we have already treated some patients with liver cancers with BNCT and carried out clinical study on phase I study on BNCT for malignant pleural mesothelioma (MPM).

Promising clinical results of BNCT using the research reactor encouraged us to go to further stage of BNCT using an accelerator-based (AB) BNCT system. Co-operation of Kyoto University Research Reactor Institute and Sumitomo Heavy Industry have developed AB BNCT system with compact cyclotron as an accelerator. In 2012 and 2014, clinical studies on BNCT for recurrent malignant brain tumors and head and neck tumors to get an approval as a medical device from the Pharmaceuticals and Medical Devices Agency (PMDA), a Japanese regulatory agency. In a transition period from reactor-based (RB) BNCT into AB-based BNCT, many research issues should be dissolved from impending and long-term viewpoints.

Main objectives of our project is to dissolve many impending clinical issues to perform BNCT safely in AB-BNCT system and to investigate many research projects for many patients with cancer to be treated with AB-BNCT system.

### Research Subjects

To advance RB-BNCT into AB-BNCT, a lot of researchers in various research fields such as clinical radiation oncology, medical physics, pharmacology, boron chemistry, and accelerator engineering are needed to be involved in our research projects. In this viewpoint, this research project consists of three research subjects (RS) as follows,

RS1. Clinical studies on BNCT

RS2. Pre-clinical studies on physiological and pharmacological aspects of BNCT

RS3. Medical physics studies on BNCT.

### Main Results

Unfortunately, KUR has been unavailable since May in 2014. Many research subjects could not be performed.

#### RS1. Clinical studies on BNCT

Two research groups reported case reports treated with BNCT using KUR. Miyatake et al. reported a very important case report from a clinical viewpoint of new application of BNCT. In this report, radiation-induced osteosarcoma in the skull was successfully treated with BNCT. Kat et al, reported case reports of six patients with head and neck cancer.

Yanagie et al. reported the result of <sup>18</sup>F-boronophenylalanine (BPA) – positron emission tomography (PET) study which was taken by breast cancer patient with right supraclavicular lymph node metastasis and treatment planning study.

#### RS2. Pre-clinical studies on physiological and pharmacological aspects of BNCT

Nakamura et al. studied the effects of the counter cations of boron clusters on liposome formation to develop high boron content liposomes for BNCT by overcoming osmotic pressure limitations.

Gao et al. studied the therapeutic efficiency and suppression of the adverse effects of a novel boron-containing nanoparticles which were prepared by mixing a newly synthesized boron-cluster-containing anionic block copolymer and a redox cationic block copolymer.

Fujimoto et al. studied the efficiency and potential of BNCT for lung metastasis using the human clear cell sarcoma lung metastasis mouse model.

Tada et al. studied the feasibility of a boron-rich boron carbide (B<sub>4</sub>C) as a boron-including drug in BNCT for oral cancer using xenograft nude cancer-bearing mice.

Yanagie et al. performed preclinical BNCT study for VX-2 rabbit liver tumor model using borocaptate sodium (BSH) entrapped water-in-oil-in-water (WOW).

#### RS3. Medical physics studies on BNCT

Hayashi et al. studied the NMR response of the standard methacrylic-acid-based polymer gel (MAGAT) with and without boron and examined its availability to measure the depth-dose responses in the irradiation of neutron beams with different energy spectra from nuclear reactor.

Tanaka K et al. reported a calculational approach for measurement of the beam components such as thermal, epithermal, fast neutrons and gamma rays separately using twin imaging plate system.

Sakurai et al. studied the QA/QC in BNCT using ionization chamber and Bonner sphere in BNCT irradiation field.

Tanaka H et al. studied the prototype system of real-time boron concentration monitor.

## PR14-1 Boron Neutron Capture Therapy for Radiation-induced Osteosarcoma from the Skull

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**INTRODUCTION:** From March 2014 to May 2014, we applied boron neutron capture therapy (BNCT) for 11 lesions in KUR. The lesions were composed of 3 recurrent glioblastomas, 2 recurrent anaplastic astrocytomas, 4 high-grade meningiomas, 1 head and neck cancer and 1 recurrent osteosarcoma from the skull. We have already reported the effectiveness of BNCT for malignant gliomas, high-grade meningiomas and head and neck cancers, however, that for osteosarcoma is extremely rare and no report of BNCT was found for radiation-induced osteosarcoma. Therefore we introduce here the successful treatment of BNCT for radiation-induced osteosarcoma from the skull.

### Clinical Presentation:

A 54-year-old female was referred to our institute for treatment by BNCT of a recurrent radiation-induced osteosarcoma involving the left occipital bone. Ten years earlier, she was diagnosed with cancer of the uterine body and underwent resection surgery. Two years after that surgery, she underwent chemotherapy and whole-brain radiation therapy (WBRT, total 30 Gy with 10 fractions) including the cerebellum for brain metastasis. Six years after the WBRT, she was diagnosed with a radiation-induced osteosarcoma involving the left occipital bone, and she underwent resection surgery and successive chemotherapy using methotrexate. One year after that surgery and chemotherapy, the subcutaneous tumor appeared again in the left occipital region and rapidly enlarged over a period of only 3 months (Figure 1 A). Magnetic resonance images (MRI) showed the epidural tumor invasion (Figure 2 A and A'). Eventually, the patient could not walk because of acutely developing cerebellar ataxia. This tumor was diagnosed as a recurrence of the radiation-induced osteosarcoma. We performed BNCT for this radiation-induced osteosarcoma.

At one day after the BNCT, the patient's gait disturbance was aggravated. Computed tomography at that time showed aggravation of peri-lesional edema (data not shown). Remarkably, the MRI taken 4 days after the BNCT demonstrated the definitive shrinkage of the mass, but the left cerebellar edema was still there (Figure 2 B and B'). We then treated the edema with dehydrators and steroids. The symptoms gradually

improved.

At only 3 weeks after the BNCT, the patient was able to walk again stably without aid. The subcutaneous tumor was reduced dramatically without radiation injury of the scalp, with time after BNCT, as shown in Figure 1 B and C. The only adverse effect was hair loss in neutron-irradiation field, as shown in Figure 1 C. MRI showed the further reduction of tumor and the disappearance of the cerebellar edema (Figure 2 C and C'), 3 months after BNCT.

We experienced only a case of successful treatment of BNCT for radiation-induced osteosarcoma. Hopefully these potential therapeutic effects will be applicable for non-radiation-induced osteosarcomas which are generally refractory for other treatment modalities.

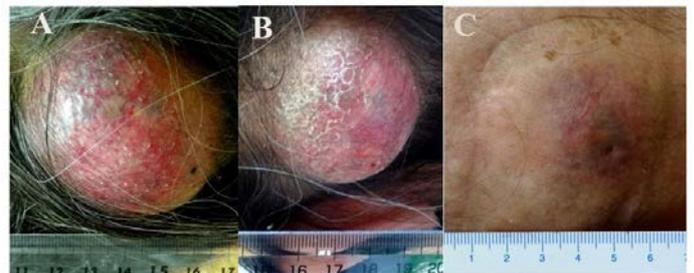


Figure 1. Marked improvement of the subcutaneous tumor at 3 weeks after the application of BNCT.

A: Just prior to the BNCT; B: Seven days after the BNCT; C: At 2 months after the BNCT,

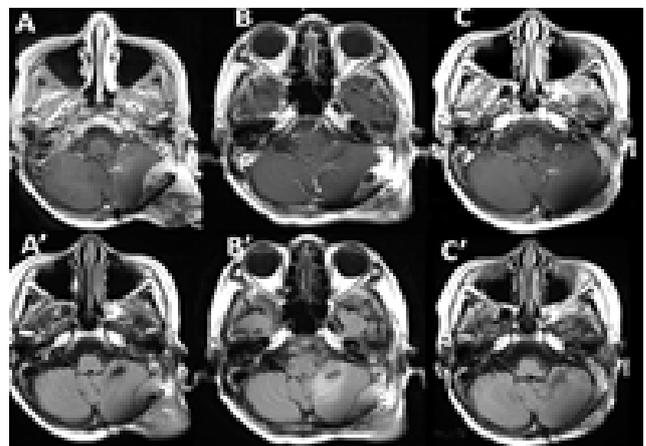


Figure 2. MRI of the patient's brain before and after the BNCT.

A,A':Just prior to BNCT

B,B':4 days after BNCT

C,C': 3 months after BNCT

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**INTRODUCTION:** We had first reported that six patients with head and neck cancer (HNC) had been treated with BNCT [1]. We also report long term (more than 5-year) clinical outcomes of our 26 patients with recurrent HNC treated with BNCT [2]. We summarized here the latest 6 patients with HNC who had treated with BNCT at KUR in last year in Table 1.

**PURPOSES:** The purpose of this study was to estimate safety and effectiveness of BNCT for patients with advanced/ recurrent HNC for which there were no other treatment options.

**RESULTS:** We also report here the latest clinical outcomes of 37 patients with recurrent HNC

All cases are advanced such as 18 (49%) out of 37 patients had developed regional lymph node metastases. Distant metastases were developed in 10 cases (27%) during treatment. (1) Regression rates were CR:19cases (51%), PR: 14 cases (38%), PD: 3cases (8%), NE (not evaluated):1case (3%). Response rate was 89%. (2) Mean Survival time was 26.3months. 4-year overall survival

rate (OS) and 9-year OS were 42% and 31%, respectively. (3)BNCT improved QOL, PS and survival periods. (4)Survival periods after BNCT were 1-105 months. (5) Adverse events were brain necrosis, osteomyelitis and transient mucositis and alopecia and so on.

**Case 4:** A 56-year old man with SCC at the left margin of tongue (T2N0M0) had got interstitial radiation therapy (60Gy) at the Osaka University Hospital in July 2013, with rejection against his doctor's recommendation of the surgery (tongue hemi-section). About 6 months after the interstitial radiotherapy, he had developed the left lymph node metastasis at upper neck region (level II). However, he had again rejected to the surgery of radical neck dissection against his doctor. During his rejection of the surgery, the lymph node had rapidly grown more than 7cm in diameter, involving carotid vein and artery. He had referred to our department in March 2014. FBPA-PET study resulted that T/B ratio=4.2. The left upper neck lymph node had treated with BNCT in May, 2014. About 3 month later, the huge lymph node had completely disappeared under the CT scan. Then 6-month after BNCT, he had complaint of dyspnea. He had seen his general practitioner and his doctor advised him to see specialist. He had found the left lung lesions which were seemed to be distant metastasis under the CT scan. He had got chemotherapy for treatment of lung lesions at a hospital in his home town.

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- [1] I. Kato, *et al.*, Appl. Radiat. Isot., **61** (2004) 1069-1073.  
[2] R. Barth, *et al.*, Radiat. Oncol., **7** (2012) 146-166

**Table 1. Treatment Summary of 6 Cases**

(Dec, 2014)

Case No.	Pt's Initial (Age)	Clinical Diag. (Histopathol. Diag.)	10B-conc. Blood(ppm)	T/B ratio	T-max of thermal neutron (D)		Total-RBE-Dose Eq (Gy-Eq)			Irradiation time(min.)	% Reduction (Period) Prognosis (Survival)
					Fluence (E+11n/cm <sup>2</sup> )	History of RT: (Gy)	T-Peak Gy-Eq	T-deepest Gy-E	Skin/Mu cosa		
1	K·M(28)	Rec.of Lt-ZK (SCC)	1st 16.7 2nd 15.0	2.9	1.5(Left-P) 1.4(Left-A)	48	23 20	12 15	5.7/11	1st 66 min. 2nd 46 min.	PR·Alive(6M)
2	K·M(63)	Rt-op.OKK, RND, Lt-LN meta	33.3	3.9	2.8	50	45(2.1 cm)	21(5.8 cm)	4.4/13	52	PD(2M)Alive(9M)
3	A·H(51)	Rt-op.ZK,RND,BNCT, lung meta	23	2.8	1.8	63	26(1.6 cm)	8.8(6 cm)	2.6spine	80	PR(2M),DOC(8M)
4	I·T(56)	Post RT of Lt-ZK, Lt-LN meta	22	4.2	2.52	60(interstitial)	50	18	7.9/12	70	CR(7M),Lung meta
5	S·K(69)	Rt-OGK(SCC)after Proton T.	26.5	2.1	3.79	70(Proton T.)	30	12	8.3/12	44	PD, DOC(3M)
6	S·M(69)	Rec.of Rt-op.UGK, RND,	20.0	2.0	3.36	60	34	13	12/14	63	CR, Lung meta,DOC(6M)

採択課題番号26 P14-5 頭頸部悪性腫瘍におけるホウ素中性子捕捉療法の臨床的研究 プロジェクト  
(阪大2口外) 加藤 逸郎、岩井 聡一、墨 哲郎、中澤 光博、由良 義明 (阪大工) 村田 勲  
(慶大) 岡本 正人 (長崎大) 梅田 博昭、柳本 惣市 (りんくう医療セ) 大前 政利 (東大阪総合)  
千足 浩久 (市立池田) 大西 徹郎 (田中クリニック) 田中 善 (山口大) 上山 吉哉、内田 堅一郎  
(京大炉) 田中 浩基、鈴木 実、櫻井 良憲、増永 慎一郎、丸橋 晃、小野 公二

## PR14-3 Boron Uptake in Tumour of Local Recurrent Breast Cancer by $^{18}\text{F}$ -BPA Positron Emission Tomography for Application to Boron Neutron Capture Therapy

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**INTRODUCTION:** Boron neutron capture therapy (BNCT) is a targeted radiation approach, because tumour cells can be selectively irradiated according to the accumulation of boron compounds. The cytotoxic effect of BNCT is due to the nuclear reaction between  $^{10}\text{B}$  and thermal neutrons. The resulting lithium ions and  $\alpha$ -particles have high linear energy transfer and produce significant biological effects. Their short range in tissue (5 – 9  $\mu\text{m}$ ) restricts radiation damage to cells containing boron atoms at the time of neutron irradiation. If sufficient boron compound can be targeted accurately to the tumour, BNCT can be applied to locally recurrent gastrointestinal cancers, and breast cancers.

Recently, positron emission tomography (PET) is developed for primary detection and metastasis of cancers.  $^{18}\text{F}$  labeled borono-phenylalanine (BPA)-PET are applied to evaluate the accumulation of boron atoms to tumours and the activity of cancer cells in the fields of BNCT.

**CASE REPORT:** We had experienced the  $^{18}\text{F}$ -BPA PET for the case of breast cancer patient who had metastasized to right supraclavicular lymph node. The patient who had been performed modified radical mastectomy with lymph node dissection (Patey's method) and adjuvant chemotherapies, had been occurred right cervical LN metastasis after 3 years. The high accumulating images of metastasized to right supraclavicular lymph node was acquired by  $^{18}\text{F}$ -BPA PET. The tumour / blood ratio was 2.26 (Figure 1). There was no other active images in the body.

**EXPERIMENTS:** In this case of advanced breast cancer, we performed the feasibility estimation of 3D construction of tumour according to the PET-CT imaging of a patient with epithermal neutron mode at Japan

Atomic Research Reactor 4. This simulation was performed optimizing modification to detect the minimum thermal neutron fluence.

**RESULTS:** The blood boron concentration (ppm) and tumour/normal tissue ratio are estimated to 24, 2.26, respectively. Skin RBE dose is restricted to 10 Gy-Eq, the maximum tumour RBE dose, minimum tumour RBE dose, and mean tumour RBE dose are 38.5, 19.9, and 30.6 Gy-Eq, respectively, in 40 minutes irradiation (Figure 2). In this study, we showed the possibility to apply BNCT to local recurrent advanced breast cancer with the estimation of boron accumulation using  $^{18}\text{F}$ -BPA Positron Emission Tomography.

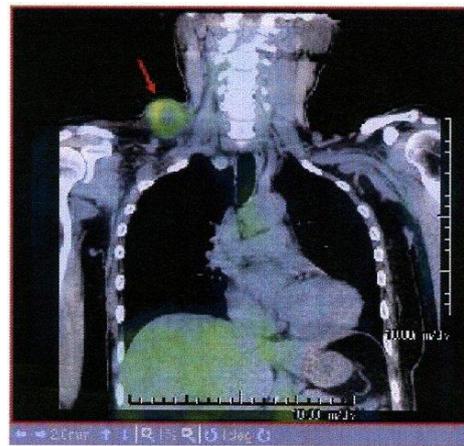


Figure 1.  $^{18}\text{F}$ -BPA PET image of rt cervical LN metastasis.

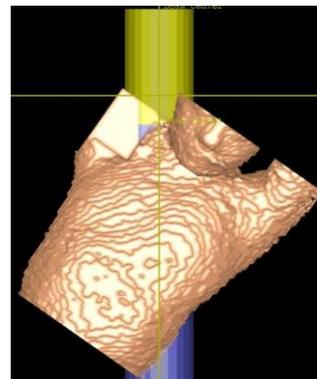


Figure 2. Image of Patient View from frontal side

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- [1] Y Imahori *et al.*, Clin Cancer Res. 4(1998)1833-41.
- [2] Y Imahori *et al.*, Clin Cancer Res. 4(1998)1825-32.
- [3] H Yanagie *et al.*, Applied Radiation & Isotopes, 67(2009) S63-66.

採択課題番号26P14-8 中性子捕捉療法的一般外科領域難治性癌への展開に向けた臨床的研究 プロジェクト (明薬大) 柳衛宏宣、野中泰政 (結核予防会新山手病院) 江里口正純、小山和行、大野烈士、丸山正二、波多江 亮 (宏仁会メディカルシティ東部病院) 東 秀史、瀬口浩司 (京大・原子炉) 小野公二、増永慎一郎、鈴木 実、櫻井良憲

## PR14-4 High Boron-Accumulated Liposomes as Efficient Boron Carriers for Neutron Capture Therapy

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**INTRODUCTION:** Boron neutron capture therapy (BNCT) has been attracting growing interest as one of the minimally invasive cancer therapies. The accelerator-based BNCT is now undergoing phase I clinical study for the treatment of brain tumor and head and neck cancer patients using L-BPA in Japan. We previously developed Na<sub>2</sub>BSH-encapsulating 10% distearoyl boron lipid (DSBL) liposomes that have high boron content with excellent boron delivery efficacy to tumors.[1] In this report, we studied the effects of the counter cations of boron clusters on liposome formation to develop high boron content liposomes for BNCT by overcoming osmotic pressure limitations.

**EXPERIMENTS:** An aqueous solution of various ammonium chloride salts (1,4-diaminobutane, spermidine, and spermine) of *closo*-dodecaborates Na<sub>2</sub>[B<sub>12</sub>H<sub>12</sub>], Na<sub>2</sub>[B<sub>12</sub>H<sub>11</sub>OH] and Na[B<sub>12</sub>H<sub>11</sub>NH<sub>3</sub>] in addition to Na<sub>2</sub>BSH (Fig. 1), were prepared by adding sodium *closo*-dodecaborates to a mixture of each amine and aqueous 1N HCl solution. Liposomes encapsulated with these ammonium *closo*-dodecaborates were prepared from DSPC, cholesterol and DSPE-PEG (1:1:0.11, molar ratio) by the reverse-phase evaporation method. B/P (boron concentration / phosphorus concentration) ratio was calculated from data obtained by the simultaneous measurement of boron and phosphorus concentrations by inductively coupled plasma atomic emission spectroscopy (ICP-AES, HORIBA, Japan).

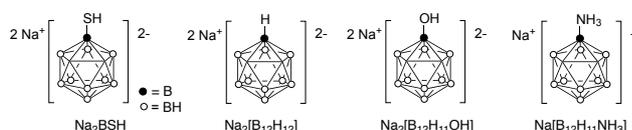


Fig. 1. Structures of *closo*-dodecaborates used for encapsulation in liposomes.

**RESULTS:** Various ammonium salts of *closo*-dodecaborates were prepared and examined their encapsulation into liposomes. Interestingly, the B/P ratio dramatically increased to 3.4 when spermidinium (spd) cation was employed. In addition, liposome yield was markedly increased to 98% and final boron concentration of the liposome solution reached 13,867 ppm. Transmis-

sion electron microscopy analysis of spd-BSH-encapsulating liposomes and Na<sub>2</sub>BSH-encapsulating liposomes was also carried out with Cryo-TEM (Fig. 2). It is notable that the liposomes interacted with each other in the case of Na<sub>2</sub>BSH-encapsulating liposomes, whereas the liposomes dispersed in solution without interacting with each other in the case of spd-BSH-encapsulating liposomes.

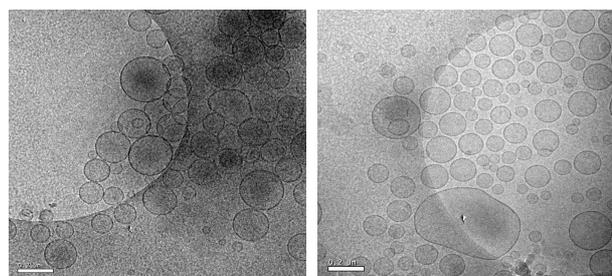


Fig. 2. TEM images of Na<sub>2</sub>BSH-encapsulating liposomes (left) and spd-BSH-encapsulating liposomes (right). Scale bar represents 200 nm.

Fig. 3 shows the survival curve of tumor-bearing mice after thermal neutron irradiation. Thermal neutron irradiation enhanced mouse survival and all mice exposed to thermal neutron irradiation died within 78 days. Remarkable antitumor effect was observed in the mice treated with spd-[<sup>10</sup>BSH]-encapsulating liposomes at the dose of 30 mg [<sup>10</sup>B]/kg; 100% of the mice survived up to 100 days after the thermal neutron irradiation.[2]

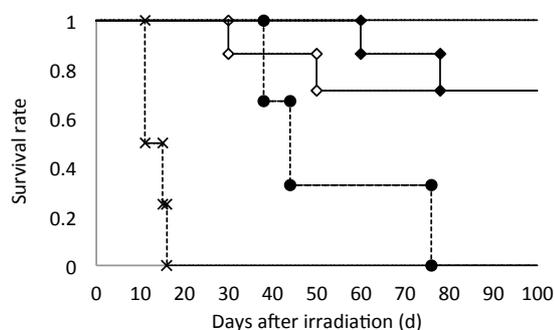


Fig. 3. Survival curve of tumor-bearing mice after thermal neutron irradiation. The irradiation was performed 36 h after injection of *closo*-dodecaborates (–, spd-BSH: 30 mg [<sup>10</sup>B]/kg; ◆, spd-BSH: 15 mg [<sup>10</sup>B]/kg; ◇, spd-<sup>10</sup>B<sub>12</sub>H<sub>11</sub>NH<sub>3</sub>: 15 mg [<sup>10</sup>B]/kg) for 50 min (1.3–2.2 × 10<sup>12</sup> neutrons/cm<sup>2</sup>). ×, Cold control; ●, Hot control.

### REFERENCES:

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採択課題番号 26P14-16 中性子捕捉療法のための新規ホウ素薬剤の開発 プロジェクト  
(東工大・資源研) 中村浩之、菊地俊介 (学習院大・理) 立川将士 (京大・原子炉) 小野公二、鈴木実

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**INTRODUCTION:** We determined whether a boron-rich boron carbide (B4C) nanoparticle could be used for BNCT for oral squamous cell carcinoma (SCC) xenografts in nude mice.

**EXPERIMENTS:** B4C nanoparticles were obtained by the laser fragmentation of boron particles in ethyl acetate and dissolved in PBS. To generate tumors, SAS cells derived from oral SCC were inoculated subcutaneously into the back of the leg of female Balb/c nude mice. Fifty microliters of B4C solution containing 12.5 $\mu$ g B4C particles was infiltrated into tumors. 10B concentrations in these tissues were measured by prompt gamma-ray spectrometry at the Kyoto University Research Reactor (KUR). After injection of B4C solution, tumors were exposed to thermal neutrons. Control tumors were left untreated. Experimental groups included untreated control, neutron only, and B4C-mediated BNCT groups. Neutron irradiation was delivered via a neutron beam at the KUR.

**RESULTS:** Injecting B4C particles into the oral SCC xenografts of nude mice increased the concentration of 10B in the tumors, but not in the kidney, liver, or spleen. Ten minutes after injection of B4C particles the 10B concentration was 18.57 ppm in the tumor. SAS tumor-bearing animals received an intratumoral injection of B4C solution followed by neutron irradiation. No significant differences were observed in body weight among these groups during the experimental period (Figure 1). In control animals, tumors continued to grow and were 5867 mm<sup>3</sup> 42 days after the start of the experiment. When tumors were subjected to B4C-mediated BNCT, tumor volume decreased from 7 days after neutron irradiation. A significant difference was observed between the B4C-mediated BNCT and neutron only groups 42 days after BNCT ( $P < 0.01$ ) (Figure 2).

**CONCLUSION:** These results indicate that B4C particles can be used locally as a boron compound in BNCT for oral SCC in vivo.

Figure 1

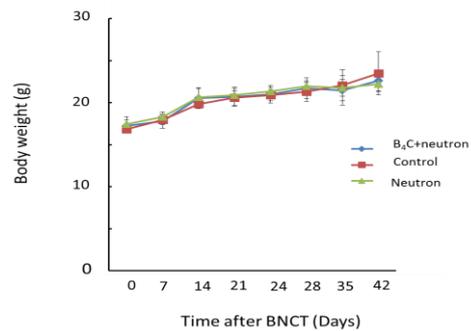


Figure 1: Nude mice carrying SAS tumors received 50  $\mu$ l of 250 ppm B4C solution intratumorally. Ten minutes later, tumors were exposed to thermal neutrons. The experimental groups were as follows: untreated control, neutron only, and B4C-mediated BNCT. n=5

Figure 2

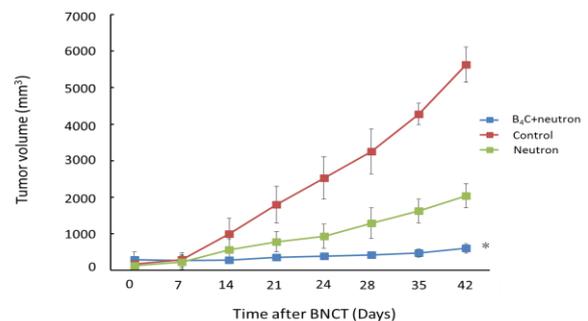


Figure 2: Nude mice carrying SAS tumors were treated as described in Figure 1. After BNCT, tumor size was measured and tumor volume was determined. \* $P < 0.01$  significantly different from neutrons only. n=5

#### References

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## PR14-6 Boron Neutron Capture Therapy Selectively Destroys Human Clear Cell Sarcoma (CCS) Metastasis to Lung in CCS-bearing Animal Model

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**INTRODUCTION:** Sarcoma metastasis to the lung is almost the final status for the treatment of sarcoma, and palliative therapy is recommended for reducing severe patient symptoms. Since neither chemotherapy nor radiation therapy is effective for most sarcomas, new therapeutic strategies are required. Clear cell sarcoma (CCS) of tendons and aponeuroses is one such with poor prognosis [1]. We have, however, demonstrated the effectiveness of boron neutron capture therapy (BNCT) for tumors in the limbs of the human CCS-bearing nude mouse model with the use of p-boronophenylalanine (BPA) [2, 3]. Here, therefore, we first created a new model of sarcoma metastasizing to the lung in the human CCS-bearing animal model, and then evaluated the efficacy and potential of BNCT after measuring the distribution of BPA in the lung.

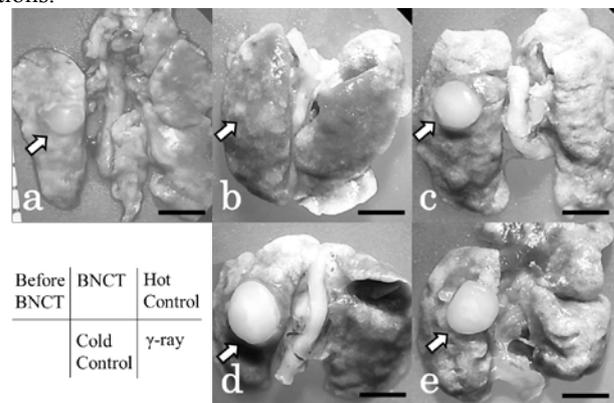
**EXPERIMENTS:** (1) *Creating the lung metastasis model of human CCS-bearing animal model:* All animal experiments were carried out according to the regulations of the Animal Care and Use Committee. Lung metastasis in the human CCS-bearing animal model was created by transplanting cells of CCS cell line (MP-CCS-SY [4]) suspended in Matrigel® into the parenchyma of the left lung of nude mice. After 8 weeks, tumor formation in the lung was confirmed by micro CT scans, and the tumor mass was measured through CT image analysis.

(2) In BNCT trials, the animals were divided into four groups of 4 each, and, under anesthesia, BPA-Fr (24 mg <sup>10</sup>B/kg) was intravenously administered to the BNCT group (A) and to the Cold control group (C), and saline to the Hot control group (B) on day 0. Groups A and B were then irradiated two times with a thermal neutron beam (1MW) to the whole lung at KURRI, once anteriorly between 60 and 80 minutes and once posteriorly between 100 minutes and 120 minutes. The  $\gamma$ -ray group (D) was irradiated with cobalt-60  $\gamma$ -ray at a dose of 0.3 Gy/min. On day 21, the tumor mass was resected from each mouse under anesthesia, routinely formalin-fixed,

paraffin-embedded, and HE stained according to standard protocols for histological examination.

**RESULTS:** The irradiation doses (Gy) absorbed by the CCS-bearing mice were 5.2 (Group A, BNCT), 0.7 (Group B, Hot control) and 0.9 (Group D,  $\gamma$ -ray). In the three control groups, no significant anti-tumor effect was observed; the tumor mass simply increased time-dependently. By contrast, the volume of the tumor mass in the BNCT groups decreased with time [Fig. 1].

**CONCLUSION:** BNCT selectively destroyed CCS cells in the lung of the human CCS-bearing animal model by irradiating the whole lung, without significant complications.



**[Fig.1]** BNCT for the lung metastasis model of CCS-bearing animal model. a: Before neutron irradiation. A well-defined solid tumor mass about 2 mm in diameter was detected in the left lung. b, c and d: three weeks after the neutron irradiation. b: Group A. BNCT. Tumor mass shrank and was hardly discernible. c: Group B. Hot control. Neutron irradiation without administration of BPA. Tumor mass was almost 3 mm in diameter. d: Group C. Cold control. Without neutron irradiation. Tumor mass was almost 4 mm in diameter. e: Group D. Three weeks after the  $\gamma$ -ray irradiation. Tumor mass was almost 4 mm in diameter. Bar = 2.5 mm.

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採択課題番号 26P14-19

悪性末梢性神経鞘腫および明細胞肉腫

プロジェクト

に対するホウ素中性子捕捉療法 of 検討

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## PR14-8 Evaluation of Component in WOW Emulsion as Intra-arterial Boron Delivery Carrier for Neutron Capture Therapy to Hepatocellular Carcinoma

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**INTRODUCTION:** We has been used water-in-oil-in-water emulsion (WOW) as the carrier of anti-cancer agents by modifying of IPSO on intra-arterial injections in clinical. Higashi et al prepared a long term inseparable, WOW for use in arterial injection therapy to treat patients with HCC [1]. We performed preclinical BNCT study for VX-2 rabbit tumour model using <sup>10</sup>BSH entrapped WOW [2, 3]. In order to improve the WOW for application to BNCT, we prepared <sup>10</sup>BSH entrapped WOW in verifying the component of surfactant, and evaluated the boron delivery activity to measure the <sup>10</sup>B concentrations of organs in VX-2 hepatic tumour model on time course after intra-arterial injection.

**EXPERIMENTS:** <sup>10</sup>BSH entrapped WOW were administered with intra-arterial injections via proper he-

patric artery (<sup>10</sup>BSH : 75 mg/kg rabbit) on VX-2 rabbit hepatic tumour models. One and three days after arterial injections, the boron concentrations of the tumor nodules and normal liver tissues were determined by ICP- Mass Spectroscopy of Jyuntendo University.

**RESULTS:** VX-2-bearing rabbits (n = 3) were given intra-arterial injection with 2 ml of <sup>10</sup>BSH WOW emulsion consist with surfactant HCO40, or PGCR. We prepared <sup>10</sup>BSH entrapped WOW. The mean <sup>10</sup>B concentration prepared in <sup>10</sup>BSH-WOW was 10000 ppm in this experiment. The size of WOW was controlled to 70 μm. The <sup>10</sup>B concentration in VX-2 tumour was 170.8 ppm, 58.3 ppm by WOW with HCO40 after day1, day3 intra-arterial injection, respectively. The <sup>10</sup>B concentration of tumour was 186.0ppm, 40.4ppm by WOW with PGCR after day1, day3 same injection, respectively. <sup>10</sup>B concentration in normal liver tissue / blood were 8.0 / 0.3 ppm in HCO40 group, and 15.1 / 0.1 ppm in PGCR group at day 3, respectively in the same procedures of WOW. We also perform Oil-O Red staining to detect the lipid components in WOW. We had showed the staining of cytoplasm in the tumours 3 day after intra-arterial injections (Figure 1). These means that the WOW accumulated selectively to the tumours by intra-arterial injections.

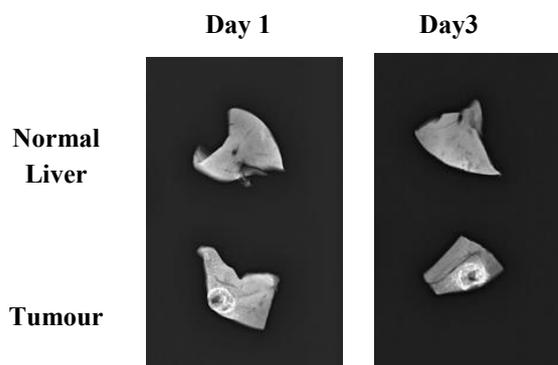


Figure1: IPSO component in WOW was accumulated in the VX-2 tumour by intra-arterial injection of <sup>10</sup>BSH entrapped WOW with HCO40 surfactant by Soft X ray radiography.

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**INTRODUCTION:** After the restart of the operation of Kyoto University Reactor (KUR) in May 2010, 235 clinical studies of boron neutron capture therapy (BNCT) have already been carried out as of May 2015 [1]. Also, the BNCT clinical trial using Cyclotron-based BNCT Epi-thermal Neutron Source (C-BENS) started in November 2012 [2]. In the while, the research and development into several types of accelerator-based irradiation systems are underway by several research groups in the world at present time. With this situation in mind, it is important that the physical and biological estimations for dose quantity and quality are performed consistently among several irradiation fields, and that the equivalency of BNCT is guaranteed, even across BNCT systems. The aim of this research is the establishment of quality assurance and quality control (QA/QC) using ionization chamber and Bonner sphere in BNCT irradiation field. In 2014, the improvement of the energy resolution in epi-thermal neutron region was studied for the Bonner sphere using boric acid solution moderator.

**METHODS:** The Bonner sphere in this research consists of a spherical neutron moderator shell and activation foils placed in the sphere center as thermal neutron detector. The boric acid solution of  $^{10}\text{B}$  0.14wt% was used as the moderator material. Manganin ( $^{55}\text{Mn}$ ) and gold ( $^{197}\text{Au}$ ) were used as activation foil material. The specific saturated activities per neutron flux for each energy group were calculated as the response function of Bonner spheres. The calculations were performed for the sphere diameter of 10, 15 and 20 cm, using the MCNP-5 radiation transport code [3]. The calculated activities were unfolded into the estimated spectrum by UMG unfolding package [4]. The influence of the uncertainty for the moderator concentration and the detector placement to the spectrum estimation, were investigated. The spectrum estimation was performed for the epi-thermal neutron irradiation mode in Heavy Water Neutron Irradiation Facility (HWNIF) of KUR was studied.

**RESULTS:** Figure 1 shows the results in the case that the activation detector displacement of 3 mm occurs on the 10-cm diameter of Bonner sphere. The error was not considered in the unfolding procedure. Figure 2 shows the unfolding results in the same condition as Fig. 1, except the error was considered. In Fig. 1, the neutron energy spectrum is estimated wrongly. In Fig. 2, the neutron energy spectrum is estimated more adequately, but the errors of the estimated spectrum become larger.

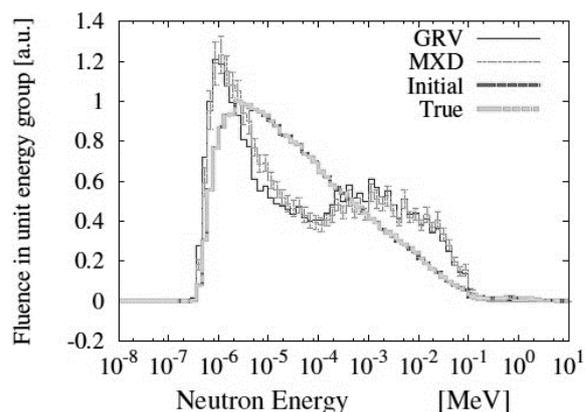


Fig. 1. Unfolding results in the case that the activation detector displacement of 3 mm occurs on the 10-cm diameter Bonner sphere and the error is not considered in the unfolding procedure.

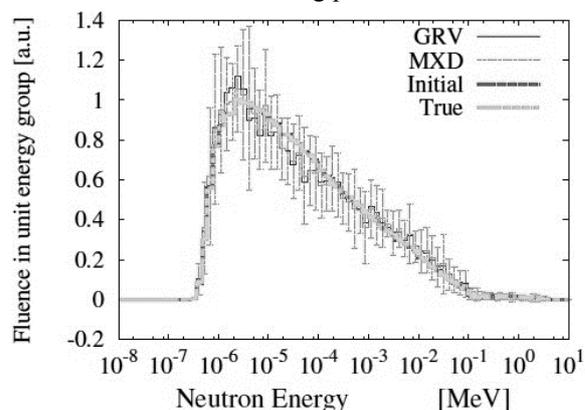


Fig. 2. Unfolding results in the same case as Fig. 1 except the error is considered.

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# PR14-10 Study on the Real-time dose Monitor System Using Prompt Gamma Rays for Boron Neutron Capture Therapy

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**INTRODUCTION:** Over 500 clinical studies of boron neutron capture therapy (BNCT) have been performed using Kyoto University Research Reactor (KUR). The information of neutron flux and boron concentration during the irradiation is needed for the determination of irradiation time. The boron concentration is determined by the prompt gamma rays from the blood sample using thermal neutron guide tube at KUR. On the other hand, neutron flux is measured by the activation material, which is irradiated by the treatment beam and picked up after 10 minutes from the irradiation start. However, the information of boron concentration and neutron flux is not able to be obtained during the irradiation. In order to determine precise dose information, it is important to detect real-time boron concentration and neutron flux. Recently, the real-time neutron flux monitor have been developed using the combination of tiny scintillator and optical fiber. The real-time boron concentration monitor have been studied using SPECT system for BNCT[1]. However, the actual level system have not realized, because the background of gamma rays at the BNCT irradiation field is quite high. The aims of this study are to clarify the gamma rays dose level at the BNCT irradiation field and the development of the prototype system of real-time boron concentration monitor. The measured gamma rays dose during BNCT clinical studies is shown in this report.

**EXPERIMENTS:** The BeO thermoluminescence dosimeters (TLDs) were used for the measurement of gamma rays dose. BeO powder was enclosed in quartz tube to reduce the neutron sensitivity. The TLDs were set at the position that was assumed to set the real-time boron concentration monitor. Figure 1 shows the schematic layout of irradiation field and the TLDs setting positions. The TLDs were set from the center of collimator for the lateral and beam direction with the 20 cm interval. The height of TLDs setting position was the 60 cm, corresponding to beam center height. The irradiation was performed for head and neck tumor. The irradiation time was 63 minutes. After the irradiation, TLDs were processed by the TLD reader and the gamma rays dose were derived with the correction.

**RESULTS:** Figure 2 shows the gamma rays dose rate distribution for lateral and beam direction. For the beam

direction, the patient was set between 0 cm and 60cm. The background of gamma rays were produced by the  $^1\text{H}(n,\gamma)^2\text{D}$  reactions with the energy of 2.22MeV, the annihilation gamma rays of 0.511 MeV, and the decay gamma rays of  $^{41}\text{Ar}$ . The gamma rays at the near the collimator center are almost of 2.22 MeV produced in the human body. For the lateral direction, the level of gamma rays were rapidly reduced. On the other hand, at the distance from the center of 60 cm, the dose rate of beam direction was two times higher than that of lateral direction. This was caused by the  $^{41}\text{Ar}$  or annihilation gamma rays produced by the reaction between thermal neutron and the component of irradiation bed. Therefore, for the beam direction, the level of gamma rays was slowly decreased. If the real-time boron concentration monitor is set at the BNCT field, it is recommended to set at the behind of collimator for the lateral direction.

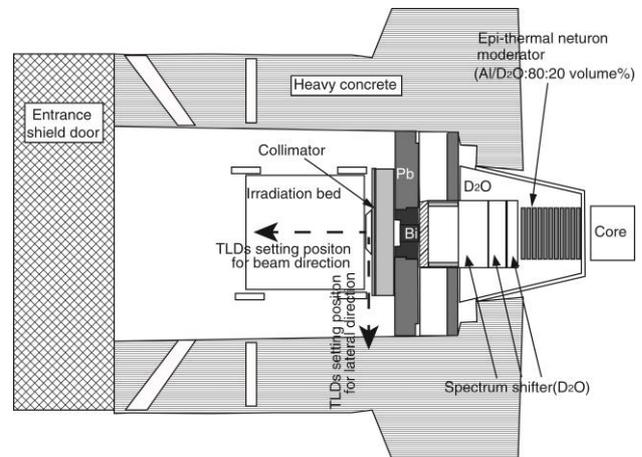


Fig. 1. Schematic layout of BNCT irradiation field of KUR and the setting position of TLDs.

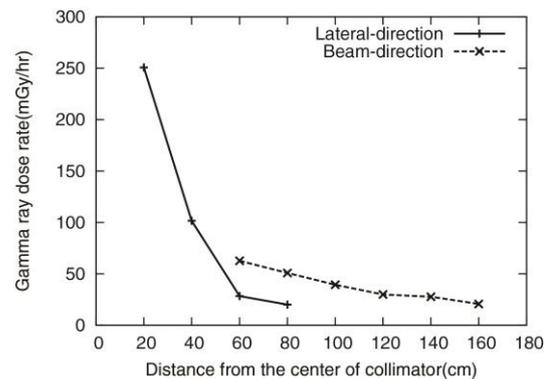


Fig. 2. The relationship between gamma rays dose rate and the distance from the center of collimator.

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採択課題番号 26P14-27 BNCT のための即発ガンマ線によるリアルタイム線量評価システムに関する研究

プロジェクト

(京大・原子炉) 田中浩基、櫻井良憲、藤本望、高田卓志、増永慎一郎、小野公二、丸橋晃、鈴木実

## PR14-11 Quality Assurance of Irradiation Field for BNCT Using Twin Imaging Plate System

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**INTRODUCTION:** Measurement of the spatial distributions of neutrons and gamma rays is one of the potential and essential options for the quality assurance and quality control for boron neutron capture therapy (BNCT). It is desirable to measure the beam components such as thermal, epithermal, fast neutrons ( $n_{th}$ ,  $n_{epi}$ ,  $n_f$ ) and gamma rays ( $\gamma$ ), separately. This study investigates using the twin imaging plate (IP) system for this purpose. A calculational approach is reported here.

**CALCULATIONS:** The twin IP system consists of the converters to enhance the components, and IPs. The principle is: thermal and epithermal neutrons will be enhanced with the secondary particles of the  $^{10}\text{B}(n,\alpha)^7\text{Li}$  reaction in the epoxy resin doped with boron, fast neutrons with the recoiled protons from the epoxy resin, gamma rays with Graphite, then enhanced components will be detected with the IPs. By comparing two IPs, intensity of a beam component is to be estimated<sup>[1,2]</sup>.

The configuration of the converters was surveyed using Monte Carlo calculations with PHITS 2.52<sup>[3]</sup>. The irradiation field assumed was that by the  $^7\text{Li}(p,n)$  reaction by 2.5 MeV protons moderated with 20 cm thick  $\text{D}_2\text{O}$ . The calculation geometry consisted of an IP (Fujifilm corporation, BAS-TR) and a converter. The IP in dimension of 20 X 20 mm was assumed to be covered with 1 mm thick converter<sup>[1]</sup> in every direction of the IP. Each beam component was separately impinged on the converter as a parallel beam perpendicular to the IP. The epoxy resin assumed was its compound with  $\text{B}_4\text{C}$ , where boron was enriched  $^{10}\text{B}$  with abundance of 100 %. The  $^{10}\text{B}$  concentration in epoxy resin (wt%) was varied in calculations.

**RESULTS:** The energy deposition in IP is shown in Fig. 1. Those for Graphite converter is 425, 546, 1570, and 13300 MeV/sec/mA for  $n_{th}$ ,  $n_{epi}$ ,  $n_f$ , and  $\gamma$ , respectively. The contribution of each beam component to total of the energy deposition is shown in Fig. 2. Again, those for Graphite is 0.3, 0.4, 1.2, 98.1 % for  $n_{th}$ ,  $n_{epi}$ ,  $n_f$ , and  $\gamma$ . In usage in twin IP system, it is desirable that only one beam component has different energy deposition among two IPs while other components have identical values, respectively. In this viewpoint, Epoxy converters with 1 to 50 wt% of  $^{10}\text{B}$  will be potential options for detecting  $n_{th}$ ,  $n_{epi}$ .

Consequently, potential combinations of twin IPs are listed in table 1. The values shown are the contribution of

the beam component to the total of the energy deposition. Here, the configuration “A-B” means that the energy deposition for the converter ‘B’ is subtracted from that for ‘A’. “50% B – 10% B” or “Epoxy – Graphite” is not suitable to use since some of the components have negative value in contribution.

In using two IPs, “50% B – Epoxy or Graphite” is potential for  $n_{epi}$ , while 20 % of the energy deposition is by unintended component,  $n_{th}$ . On the other hand, combining “10% B – Epoxy or Graphite” and “10% B – 1% B”, *i.e.* using triple IP in Epoxy converters at 0, 1, 10 wt % of  $^{10}\text{B}$ , will work in estimating  $n_{th}$  and  $n_{epi}$ .

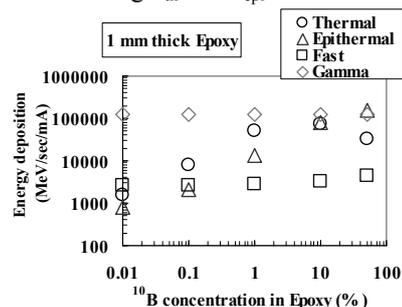


Fig. 1. Energy deposition for Epoxy at varied  $^{10}\text{B}$  concentration.

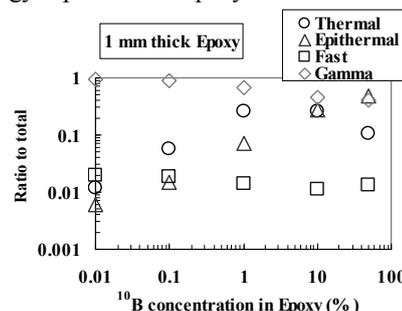


Fig. 2. Beam component contribution to energy deposition.

Table 1 Energy deposition ratio (%) to total for subtraction among two IPs in converters.

Configuration	Contribution (%)			
	$n_{th}$	$n_{epi}$	$n_f$	$\gamma$
10% B – Epoxy or Graphite	50	50	0	0
50% B – Epoxy or Graphite	20	80	0	0
10% B – 1% B	28	72	0	0
50% B – 10% B	-100	200	0	0
Epoxy – Graphite	-14	-5	-43	162

“x %B” specifies the epoxy resin with  $\text{B}_4\text{C}$  at x wt% of  $^{10}\text{B}$  to total weight of the converter.

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**INTRODUCTION:** Polymer gel dosimeters have been investigated for the three-dimensional (3D) dose measurement of the complex conformal dose distributions in the clinical applications [1]. These devices utilize radiation-induced polymerization reactions of vinyl monomer in the gel to preserve information about the radiation dose. The 3D absorbed dose distribution is deduced from the polymer distribution measured by imaging modalities, such as MRI. The applications to neutron irradiation have been investigated, and the potential as a 3D dosimeter has been suggested [1].

In this work, the NMR response of the standard methacrylic-acid-based polymer gel (MAGAT) with and without boron was examined its availability to measure the depth-dose responses in the irradiation of neutron beams with different energy spectra from nuclear reactor.

**EXPERIMENTS:** Boric acid,  $B(OH)_3$ , containing  $^{10}B$  of 20% naturally was added into the standard gel. The concentration in the gel is the same order (approximately 50 ppm) as the clinical use. The resulting solution was subdivided by pouring into quartz tall beakers (65 mm diameter and 135 mm length, 400 mL).

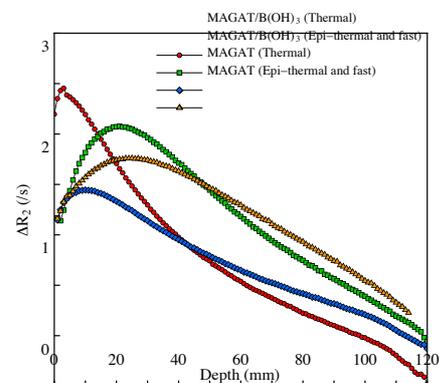
The neutron irradiations were performed using Heavy Water Neutron Irradiation Facility (HWNIF) of Kyoto University Research Reactor (KUR, power of 1 MW). The samples were irradiated from the bottom direction through the axis with the field size of almost 50 cm diameter in air at room temperature. The three different modes (thermal neutron rich, epi-thermal and fast neutron rich, and the mixed modes) of neutron beams made by heavy water spectrum shifter and cadmium thermal-neutron filters were applied to each sample.

MRI measurements were performed using a 1.5 T scanner (Siemens). A multiple spin-echo sequence was applied and the transverse relaxation rate ( $R_2 = 1/T_2$ ) was estimated.

**RESULTS:** Figure 1 shows the depth- $R_2$  profiles obtained from our polymer gel dosimeters exposed to neu-

tron beams of the different energy spectrum modes. In the thermal neutron mode, both profiles of the gels with and without boron show monotonically decreasing with depth after the peak near the surface. It seems that the decrease for the gels with boron corresponds to decreasing of thermal neutron in tissue and the peak shifts to near the surface significantly due to the reaction with boron. In the epi-thermal and fast neutron mode, broad peaks are observed at deeper position, around from 20 to 25 mm of depth. It is suggested that the  $R_2$  profile for the gel with boron corresponds to the distribution of the thermal neutron due to the moderation of epi-thermal neutron. But for the gels without boron, it seems that the decreases correspond to decreasing of gamma ray. As same as the profiles in thermal mode, the peak shift due to boron was also observed. The depth profiles of the mixed mode (not shown) were similar to that of thermal neutron. It is suggested that the contributions of epi-thermal and fast neutrons are small compared to that of thermal neutron. These results indicate both MAGAT gel dosimeters with and without boron have the effective sensitivity on the thermal neutron rather than on fast neutron.

(These results were presented at 8<sup>th</sup> International Conference on 3D Radiation Dosimetry : IC3DDose 2014 in Ystad, Sweden. [2])



**Figure 1** The depth from phantom surface vs.  $\Delta R_2$  [ $=R_2 - R_{2,bg}$ ] responses in different energy spectra.

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