I. Project Research

Project 6

PR6 Translational Research on BNCT for Clinical Application

M. Suzuki

Research Reactor Institute, Kyoto University

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 BCNT 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

Six reports could be submitted although KUR has been unavailable since May in 2014.

RS1. Clinical studies on BNCT

No BNCT was carried out since KUR has been unavailable in 2016.

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

Yanagie et al. reported two pre-clinical studies. One was a preclinical study for evaluating ^{10}Boronophenylalanine (BPA) – entrapped water-in-oil in water (WOW) emulsion. Another one was a study for checking.

Fujimoto et al. investigated biodistribution of BPA in metastatic bone of human cancer-bearing animal model.

RS3. Medical physics studies on BNCT

Taketa et al. developed a patient-position-error measuring system and tested the system.

Tanaka K et al. investigated suitable configuration of the converter to combine with the imaging plate.

Sakurai et al. reported the development of the remote-changeable Bonner-sphere spectrometer.

Translational research on BNCT looking toward accelerator-based BNCT era.

For three years when KUR has not worked, clinical trials using AB-BNCT system has made steady progress. Therefore, more strategic translational research leading to clinical application in AB-BNCT may be desired. These researches should be carried out with attention to regulatory science. On the other hand, more innovative or fundamental translational researches are needed looking toward the future 10 or 20 years later.

PR6-1 Preliminary formulation of ^{10}Borono-phenylaranine entrapped WOW emulsion for Neutron Capture Therapy to Hepatocellular Carcinoma

Hironobu Yanagie[1,2,3], Mitsuteru Fujihara[4], Ryuji Mizumachi[5], Yuji Murata[5], Yuriko Sakurai[1,3], Kikue Mouri[1,3], Atsuko Shinohara[6,7], Takehisa Matsukawa[7], Ayano Kubota[7], Yasuyuki Morishita[8], Novriana Dewi[2], Masashi Yanagawa[9], Sho Yui[1,3],Kazuhito Yokoyama[7], Yasumasa Nonaka[1], Hirotaka Sugiyama[1], Yoshitaka Furuya[1], Yoshinori Sakurai[10], Hiroki Tanaka[10], Minoru Suzuki[10], Shinichiro Masunaga[10], Koji Ono[10], Minoru Ono[3,11], Jun Nakajima[3,12], Masazumi Eriguchi[13], and Hiroyuki Takahashi[2,3]

[1]Dept of Innovative Cancer Therapeutics:Alpha particle & Immunotherapeutics, Meiji Pharmaceutical University, [2]Dept of Nuclear Engineering & Management, Graduate School of Engineering, The University of Tokyo, [3]Cooperative Unit of Medicine & Engineering, The University of Tokyo Hospital, [4]SPG Techno Ltd. Co., [5]LSI Medience Ltd Co, [6]The Graduate School of Seisen University, [7]Jyuntendo University, [8]Dept of Human & Molecular Pathology, Graduate School of Medicine, The University of Tokyo, [9]Veterinary Medical Center, Obihiro University of Agriculture & Veterinary Medicine, [10]Research Reactor Institute, Kyoto University, [11]Dept of Cardiac Surgery, The University of Tokyo Hospital, [12]Dept of Thoracic Surgery, The University of Tokyo Hospital, [13]Dept of Surgery, Shin-Yamanote Hospital

INTRODUCTION: Water-in-oil-in-water (WOW) emulsion has been used 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 hepatocellular carcinoma (HCC) by the double emulsification technique [1]. We have previously performed the preclinical BNCT study for VX-2 rabbit tumour model using ^{10}BSH entrapped WOW [2, 3], and we also proceeded clinical BNCT study for HCC using this system [4].

In this study, we prepared ^{10}BPA-entrapped WOW emulsion and evaluated the boron encapsulating activity by measuring the ^{10}B concentrations of WOW using ICP-AES.

EXPERIMENTS: We prepared the ^{10}BPA-entrapped WOW emulsion evaluate the properties by determining boron concentrations of the WOW emulsion was using ICP- AES at Juntendo University.

RESULTS: ^{10}BPA-entrapped WOW emulsion was prepared by mixing 37.5mg of ^{10}BPA, 83.3 mg of Fructose in 8mL of WOW emulsion. ^{10}B concentration of precipitate of WOW emulsion, supernatant, and total homogeneous mixing emulsion, were measured to be 255.5 μg/mL, 93.8 μg/mL, and 222.4±5.2 μg/mL, respectively.

In the case of ^{10}BSH WOW emulsion, the original ^{10}B concentration was found to be 7000~13000 ppm, while in the case of ^{10}BPA, ^{10}B concentration was 250 ppm. The ^{10}B concentration is very low, but ^{10}BPA is incorporated into the tumor cells by LAT-1 transporter. Therefore, it is expected that we could evaluate whether the original concentration is effective or not, in the VX-2 hepatic tumor model.

Figure 1. Formulation of ^{10}BPA WOW emulsion.
Left: Precipitate, Center: Supernatant, Right: Mix

The calculated osmotic pressure of each WOW emulsion were as below:
Epirubicin WOW : 632 mOsm/L
^{10}BSH WOW (BSH 175mg+ D.W. 2.0mL): 909 mOsm/L
^{10}BPA WOW: 641 mOsm/L

The osmolality of ^{10}BPA WOW was the same as epirubicin entrapped WOW emulsion, so it will be easily injected by catheter on the intra-hepatic administration.

We hope to perform toxicity examinations of WOW emulsion to develop the more suitable WOW emulsion for intra-arterial born delivery system.

REFERENCES:

[1] S Higashi S *et al.*, Cancer, **75**(1995):1245–1254.
[2] S Mikado *et al.*, Nucl. Instr. and Meth. A, **605** (2009): 171-174.
[3] H Yanagie *et al.*, Appl Radiat Isot., **69**(2011): 1854-7.
[4] H Yanagie *et al.*, Appl Radiat Isot., **88**(2014):32-7.

PR6-2 Pre-BNCT Biodistribution of *p*-borono-L-phenylalanine in Metastatic Bone of Human Breast Cancer-bearing Animal Model

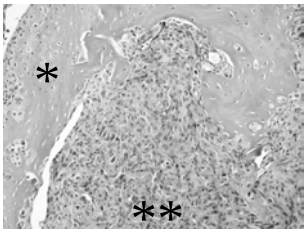
T. Fujimoto[1], T. Andoh[2], Y. Sakurai[3], M. Suzuki[3] and H. Ichikawa[2]

[1]*Hyogo Cancer Center, Department of Orthopaedic Surgery*
[2]*Faculty of Pharmaceutical Sciences and Cooperative Research Center of Life Sciences, Kobe Gakuin University*
[3]*Research Reactor Institute, Kyoto University*

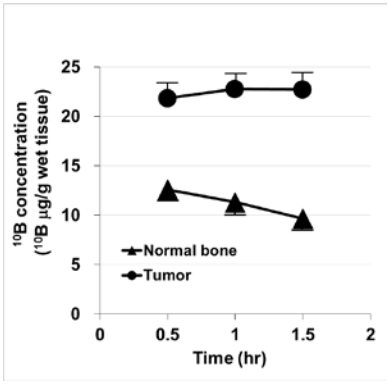
INTRODUCTION: Breast cancer, the most morbid malignancy in women, is frequently encountered in Japan. Although most breast cancer is diagnosed at an early stage, 20-30% of cases turn metastatic [1]. Furthermore, about 70% of such cases metastasize to the bone [2]. When systematic pharmacotherapy is not effective in such cases, the disease is difficult to control. Especially in the case of bone metastasis of lower extremities, there is constant danger of pathological fracture that leads to a lowering of the quality of life. Therefore, mainly surgery with the use of intramedullary nails is carried out to prevent pathological fracture. Nonetheless, this entails not only patient physiological distress, but also the enormous treatment costs of surgery, rehabilitation and postoperative radiotherapy. Here, then, is where BNCT proffers the only option, presently, for resolving these problems. BNCT destroys, by one brief irradiation, individual tumor cells without affecting surrounding normal tissue; therefore, for the management of bone metastasis with BNCT, we evaluated the distribution of ^{10}B in the bone of a newly established human breast cancer-bearing animal model.

EXPERIMENTS: All animal experiments were carried out according to the regulations of the Animal Care and Use Committee.
(1) Tumor cell line: Cells of human breast cancer cell line MDA-MB-231-luc were cultured in Leibovitz's L-15 medium with fetal bovine serum in a 5% CO_2 humidified incubator at 37˚C.
(2) Producing bone metastasis in the human breast cancer-bearing animal model: Cells of MDA-MB-231-luc suspended in Matrigel® were transplanted into the tibia of the left hind leg of the nude mice. Eight weeks thereafter, micro-CT scans disclosed the formation of a tumor in the left tibia. Histological examinations were then carried out by HE staining.
(3) Biodistribution of ^{10}B in the bone-metastasis animal model: *p*-borono-L-phenylalanine (BPA)-Fr (24 mg ^{10}B/kg) was intravenously injected into the tibia of the human breast cancer-bearing animal model and, at predetermined intervals, blood and normal bone samples were collected immediately after the mice were killed. The concentration of boron in the samples was then measured by ICP-AES.

RESULTS: Bone metastasis was successfully produced in the human breast cancer-bearing animal model. The formation of a solid tumor mass in the left tibia was confirmed by macroscopic observation, micro-CT scans and microscopic analysis [Fig. 1]. Biodistribution of ^{10}B: 1.5 hours after the intravenous injection of BPA-Fr into the bone-metastasis animal model, tumor-specific and high-level ^{10}B accumulation at a concentration of 22.7μg ^{10}B/g of wet tumor tissue was identified in the bone tumor compared with normal bone [Fig. 2], with a tumor-to-normal bone ratio of 2.3. These results prognosticated that boron accumulates specifically in the bone tumor and that BNCT destroys tumor cells only at the site of the bone metastasis, preventing bone fracture.



[Fig.1] HE staining. Tumorigenesis within the tibial marrow cavity in the human breast cancer-bearing bone metastasis animal model. *: cortex, **: tumor.



[Fig.2] Biodistribution of ^{10}B in the tumor and the normal bone of the human breast cancer-bearing animal model. ●: Tumor, ▲: Normal bone.

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[2] Clinical management of women with metastatic breast cancer: a descriptive study according to age group. K. Manders *et al*. BMC Cancer, **6**(2006).

PR6-3 Nanoparticle-assisted Boron Neutron Capture Therapeutics: Design of Novel Boron-containing Nanoparticle for ROS Scavenging Ability Improving Therapeutic Efficiency with Low Adverse Effect

Zhenyu Gao[a,b], Yukichi Horiguchi[a], Kei Nakai[b], Akira Matsumura[b],, Minoru Suzuki[c], Koji Ono[c], Yukio Nagasaki[a, b, d*]

[a]*Graduate School of Pure and Applied Sciences, University of Tsukuba,*
[b]*Graduate School of Comprehensive Human Sciences, University of Tsukuba*
[c]*Research Reactor Institute, Kyoto University,*
[d]*WPI-MANA, NIMS*

INTRODUCTION: Boron neutron capture therapy (BNCT) has attracted much attention during recent decades. The success of BNCT is dependent on the boron delivery system to achieve high specific tumor accumulation, keeping low adverse effect. However, the low molecular weight boron compounds currently used in clinical trial of BNCT are excluded rapidly from the blood circulation, which causes non-specific dispersing in whole body. It is confirmed that high-dispersion stable nanoparticle tends to accumulate in tumor environment due to the leaky neovascularization and immature lymphatic systems, which is called enhanced permeability and retention (EPR) effect[1]. Furthermore, during the treatment process, large amount generated reactive oxygen species (ROS) will cause adverse effect such as inflammation. The objective of this study is to design a novel boron nano-delivery-system that enhance the therapeutic efficiency as well as suppress the adverse effect

EXPERIMENTS: The novel boron-containing nanoparticles (BNP) in this study was prepared by mixing a newly synthesized boron-cluster-containing anionic block copolymer (PEG-*b*-PMBSH) and a redox cationic block copolymer (PEG-*b*-PMNT) via the ion complex in phosphate buffered saline (PBS) solution. The BNCT effect was evaluated by using tumor bearing BALB/c mice given BNP at dose of 15 and 5 mg ^{10}B/kg body weight 72 h before irradiation. Mice given boronophenylalanine (BPA)-fructose complex at dose of 40 mg ^{10}B/kg body weight and PBS 2.5 h before irradiation were used as positive and negative control. Tumor volume growing was monitored. White blood cell levels were confirmed 3 d after irradiation.

RESULTS: The size of the BNP was evaluated by dynamic light scattering (DLS), showing average size of 35 nm and neutral surface. In the *in vivo* BNCT effect evaluation study, the tumor volume in PBS treated group grew up to 1.3 cm^3 13 d after irradiation. In contrast, the growth of tumors was effectively suppressed in the BNP treated groups (average size was about 0.4 cm^3, while the doses of ^{10}B were 15 and 5 mg/kg). The suppression of tumor growth was also observed in the mice treated by BPA with dose of ^{10}B at 40 mg/kg, (average size was 0.7 cm^3). By much lower dose, 5 mg ^{10}B/kg (5 ppm boron in tumor tissue), BNP showed better therapeutic effect compared with BPA. Furthermore, we observed high white blood cell (WBC) level in BPA treated group, indicating the inflammation was occurred. However the WBC level in BNP treated group (15 mg/kg) showed almost similar as the non-tumor-bearing healthy mice, probably because of the ROS scavenging ability of BNP. These results strongly indicates that this novel boron-containing nanoparticle is a suitable potential candidate for high performance of BNCT improving the therapeutic efficiency with low adverse effect.

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[1] Y. Matsumura, H. Maeda, Cancer Research 46: 6387–92 (1986)

PR6-4 Toxicity Evaluation of ^{10}BSH entrapped WOW emulsion on intra-arterial delivery in Rabbits for Neutron Capture Therapy to Hepatocellular Carcinoma

Hironobu Yanagie[1,2,3], Tsuyoshi Higuchi[4], Mitsuteru Fujihara[5], Ryoji Mizumachi[4], Yuji Murata[4], Yuriko Sakurai[1,3], Kikue Mouri[1,3], Yasuyuki Morishita[6], Novriana Dewi[1], Masashi Yanagawa[1,7], Yasumasa Nonaka[1], Hirotaka Sugiyama[1], Yoshitaka Furuya[1], Yoshinori Sakurai[8], Hiroki Tanaka[8], Minoru Suzuki[8], Shinichiro Masunaga[8], Koji Ono[8], Minoru Ono[3,9], Jun Nakajima[3,10], Masazumi Eriguchi[11], and Hiroyuki Takahashi[2,3]

[1]Dept of Innovative Cancer Therapeutics:Alpha particle & Immunotherapeutics, Meiji Pharmaceutical University, [2]Dept of Nuclear Engineering & Management, Graduate School of Engineering, The University of Tokyo, [3]Cooperative Unit of Medicine & Engineering, The University of Tokyo Hospital, [4]LSI Medience Ltd Co, [5]SPG Techno Ltd. Co., [6]Dept of Human & Molecular Pathology, Graduate School of Medicine, The University of Tokyo, [7]Veterinary Medical Center, Obihiro University of Agriculture & Veterinary Medicine, [8]Research Reactor Institute, Kyoto University, [9]Dept of Cardiac Surgery, The University of Tokyo Hospital, [10]Dept of Thoracic Surgery, The University of Tokyo Hospital, [11]Dept of Surgery, Shin-Yamanote Hospital

INTRODUCTION: Water-in-oil-in-water (WOW) emulsion has been used 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 by the double emulsification technique to be used in arterial injection therapy to treat patients with hepatocellular carcinoma (HCC) [1]. We previously performed preclinical BNCT study for VX-2 rabbit tumour model using ^{10}BSH-entrapped WOW [2, 3, 4], and we also proceeded clinical BNCT study for HCC using this system [5].

In this study, we prepared ^{10}BSH-entrapped WOW, and evaluated the toxicity by checking survival conditions and biochemical data after intra-hepatic injection of ^{10}BSH entrapped WOW emulsion in healthy rabbits.

EXPERIMENTS: ^{10}BSH-entrapped WOW was administrated with intra-arterial injections via proper hepatic artery on healthy rabbits. As a part of the safety evaluation of ^{10}BSH-entrapped WOW emulsion, the test article was dosed once by hepatic arterial administration to 3 male rabbits at 0.075 and 0.15 mL/kg to investigate its toxicity. The control group was given lactose entrapped WOW emulsion at 0.15 mL/kg.

The investigated items included clinical observation, measurement of body weights and food consumption, blood chemistry, necropsy, and histopathology.

RESULTS: *Body weight*; no statistically significant difference was noted in the 0.075 mL/kg group on Day 3 or 7 compared with the control group. However, decreased body weights were noted in all animals in the control and test article (0.075 and 0.15 mL/kg) groups on Day 3.

Blood chemistry; increases in the α1 globulin, α2 globulin, β globulin, and total cholesterol, as well as decreases in the albumin (g/dL and %) and A/G ratio were noted in 1 male (No. 8) in the 0.15 mL/kg group on Day 7. These were not considered to be attributed to BSH.

Surviving animals; there were no test article-related changes in any of the BSH administration groups. Adhesion was noted between the lobules of the liver in 1 male each of the 0.075 and 0.15 mL/kg groups and between the gallbladder and omental, duodenum, or liver in 2 males of the 0.075 mL/kg group and in 1 male of the 0.15 mL/kg group. All of the changes were treatment-related; however, as they were also noted in the control group or absent in the 0.15 mL/kg group, they were not considered to be attributed to BSH. There were no intergroup differences in their occurrence, so they were not considered to be attributed to BSH.

The minimum dose of WOW emulsion-containing BSH is 3 mL in clinical practice. Based on the assumption that it was given to an individual weighing 50 kg, the minimum dose was calculated to be 0.06 mL/kg (3 mL/50 kg = 0.06 mL/kg). Accordingly, the lowest dose for hepatic artery injection to rabbits was set at 0.075 mL/kg, which is higher than the minimum dose (0.06 mL/kg), and the highest dose at 0.15 mL/kg, which is twice the lowest dose (0.075 mL/kg) in this study.

We hope to refer these results of toxicity examinations to the clinical studies of BNCT to hepatocellular carcinoma with intra-arterial boron delivery using WOW emulsion.

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[1] S Higashi S *et al.*, Cancer, **75**(1995):1245–1254.
[2] S Mikado *et al.*, Nucl. Instr. and Meth. A, **605** (2009): 171-174.
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PR6-5 Exfoliation of Hexagonal Boron Nitride Nanosheet with Chlorin e6 and Application of the Composite to Cancer Photodynamic Therapy

Maruyama Kyouhei, Komatsu Naoki

Graduate School of Human and Environmental Studies, Kyoto University

Recently, we directly fabricated the graphene-based composite from graphite in the presence of chlorin e6 (Ce6) by sonication in aqueous phase.[1] The composite (G/Ce6) was found to deliver the Ce6 into cancer cells and work as a photosensitizer for cancer photodynamic therapy (PDT). In this paper, we used h-BN in place of graphite and realized much higher Ce6 concentration in the composite of h-BN/Ce6 than that of G/Ce6.

Aqueous dispersion of h-BN/Ce6 was prepared by use of commercially available h-BN and Ce6 under the same conditions as those in the preparation of G/Ce6. The formation of h-BN/Ce6 was confirmed by the red shift of Q band in the absorption spectra and quenching of the fluorescence. In comparison of these dispersions shown in Table 1, the contents of Ce6 and the carrier were 10 and 20 times larger in h-BN/Ce6 than G/Ce6, respectively. Since the size of h-BN is much smaller than that of graphite, it is concluded that h-BN was exfoliated much more easily than graphite in the presence of Ce6 in water. This is supported by the phenomenon that the loading capacity of Ce6 on h-BN is half of that on graphene shown in Table 1.

The cytotoxicity of h-BN/Ce6 to HeLa cells was confirmed under irradiation of 660 nm LED light as shown in Fig. 1. While Ce6 without carrier exhibited no cytotoxicity, viability of the cells significantly decreased to less than 20% at the Ce6 concentration of 0.4 mg/mL. This PDT effect by use of h-BN/Ce6 is quite similar to that of G/Ce6, indicating no difference between h-BN and graphene as a drug carrier.

Table 1. Comparison of h-BN/Ce6 with G/Ce6.

	Ce6 (μg/mL)	Carrier (μg/mL)	Loading (%)
h-BN/Ce6	392	438	80
G/Ce6	36	22	160

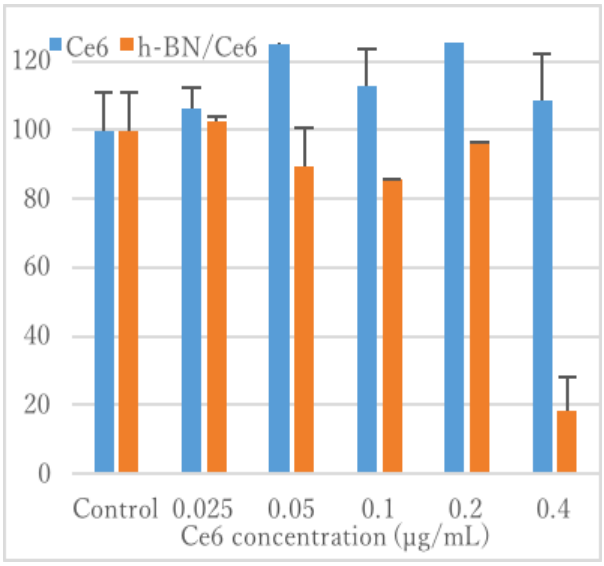

Figure 1. Viability of HeLa cells in presence of h-BN/Ce6 and Ce6 under light irradiation.

REFERENCE:

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Establishment of QA/QC Using Ionization Chamber and Bonner Sphere in BNCT Field (III)

Y. Sakurai, H. Ueda[1], R. Uchida[1], T. Takata, H. Tanaka, K. Okazaki[1], T. Kawamura[1], K. Akita[1,2] and M. Suzuki[1]

Research Reactor Institute, Kyoto University
[1]Graduate School of Engineering, Kyoto University
[2]Osaka Medical School

INTRODUCTION: Research and development into several types of accelerator-based irradiation systems for boron neutron capture therapy (BNCT) is underway [1,2]. In the near future, BNCT using these newly developed irradiation systems may be carried out at multiple facilities across the world. Considering this situation, it is important that the estimations for dose quantity and quality are performed consistently among several irradiation fields, and that the equivalency of BNCT is guaranteed, within and across BNCT systems. Then, we are establishing the quality assurance and quality control (QA/QC) system for BNCT irradiation field. As part of the QA/QC system, we are developing estimation method for neutron energy spectrum using Bonner sphere [3].

METHODS: Liquid such as pure water and/or boric acid solution is used as the moderator. A multi-layer concentric-sphere case with several sphere shells is prepared. The moderator and its diameter are changeable without entering the irradiation room, by the remote supply and drainage of liquid moderator in the several layers. For the detector, activation foils are remotely changed, or online measurement is performed using SOF (scintillator with optical fiber) detector containing boron [4], etc.. The development of this remote-changeable Bonner-sphere spectrometer is reported. The combination of the moderators for boron-10 (B-10) concentration and diameter was optimized by our originally-developed method, "High Independence Selection (HIS)" [5]. The optimized combination was decided among 101 combinations; the combinations of ten B-10 concentrations and ten diameters, additionally the case of manganin foil only without the moderator.

RESULTS: Figure 1 shows the response functions for the selected combinations. The optimized combination was selected by HIS as follows: manganin foil only, 0.7-wt% boron acid solution of 13 cm in diameter, 0.7-wt% boron acid solution of 18 cm in diameter, 0-wt% boron acid solution (namely pure water) of 18 cm in diameter, and 0.028-wt% boron acid solution of 20 cm in diameter. Then, the optimized structure of the spectrometer was decided as follows: three sphere shells such as 13, 18 and 20 cm in diameter, and three liquid moderators such as pure water, 0.028-wt% boron acid solution and 0.7-wt% boron acid solution, as shown in Fig.2.

CONCLUSION: We have a plan to make the remote-changeable Bonner-sphere spectrometer, based on the optimization result. Additionally, we have a plan to perform the spectrometry experiments at Kyoto University Reactor (KUR), etc., in order to confirm the efficacy of this spectrometer.

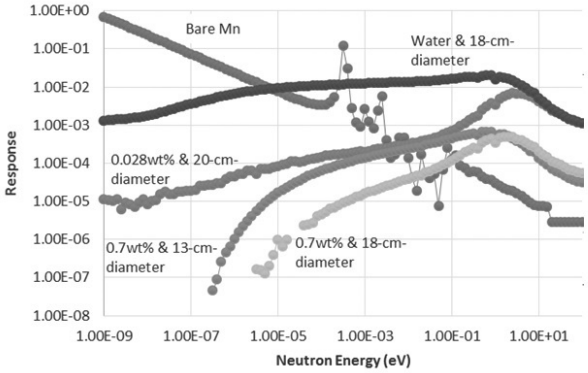

Fig. 1. Response functions for the selected combinations.

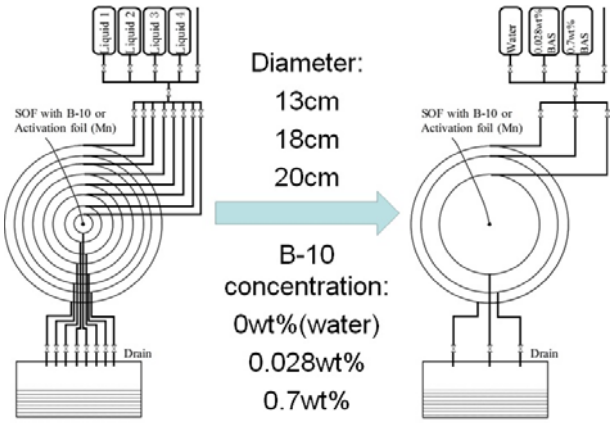

Fig. 2. Optimization for the structure of the remote-changeable Bonner-sphere spectrometer.

REFERENCES:

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[5] H. Ueda, Doctoral Thesis (2016).

PR6-7 Calculational Survey of Converter Configuration for Quality Assurance of Beam Component Distribution at KUR Using Imaging Plate

K. Tanaka, Y. Sakurai[1], T. Kajimoto, H. Tanaka[1], T. Takata[1], M. Suzuki[1] and S. Endo

Graduate School of Engineering, Hiroshima University
[1]Research Reactor Institute, Kyoto University

INTRODUCTION: It is important to check the spatial distributions of neutrons and gamma rays in the quality assurance and quality control of boron neutron capture therapy (BNCT). This study investigates the usage of the imaging plate (IP) for this purpose. The suitable configu-ration of the converter to combine with the IP is investi-gated with calculational survey[1].

METHODS: In order to separate the beam components, the converters to enhance the beam components is sup-posed to be used as follows: thermal and epithermal neu-trons will be enhanced by the secondary particles from (n,α) reactions of the nuclides such as ^{6}Li, which reacts with low-energy neutrons; fast neutrons enhanced by the recoiled protons from the hydrogen-rich material. For gamma rays, carbon is used so that gamma rays are not depressed or neutrons are not enhanced.

The converter configuration in order for the attempted beam component to dominate the IP signal intensity is investigated using PHITS 2.76. The geometry is shown in Fig. 1. The assumed irradiation fields are the standard thermal neutron irradiation mode, mixed neutron irradia-tion mode, and epithermal neutron irradiation mode in KUR-HWNIF, with a power of 5 MW. The IP assumed is "BAS-TR" from Fuji Film Corporation, Japan. The en-ergy deposition at the IP-sensitive region is computed as a representative of the IP signal.

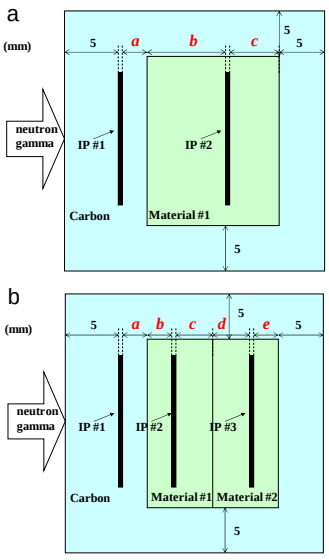

Fig. 1 Calculation geometry.

RESULTS and DISCUSSION: As an example of the results, the energy deposition contribution in IP #2 in 10-wt% ^{6}Li-P.E. for its thickness "b" varied, with a = c = d = e = 1 mm in Fig. 1 (b), is shown in Fig. 2 for standard epithermal neutron irradiation mode. The epithermal neu-tron component is attempted in the IP #2. As "b" in-creased, the contribution of thermal neutrons decreased, which resulted in 1.5% for the thickness at 4 mm. In ad-dition, the contribution of epithermal neutrons slightly increased from 94.4% to 96.7%. As a potential option, b = 4 mm was chosen.

As summary, the converter configuration selected and contribution of attempted beam component to energy deposition in IP is shown in Table 1.

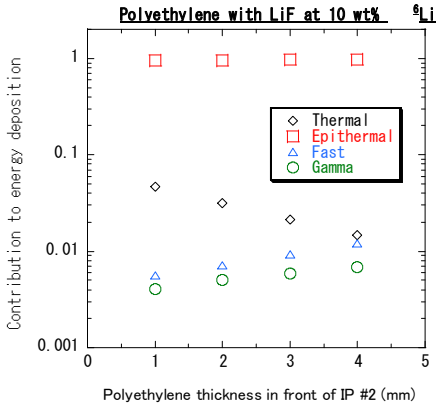

Fig. 2 Energy deposition contribution in IP #2.

Table 1. Converter configuration selected. The attempted beam component is shown in parenthesis.

Mode	Geometry	IP#	Converter matetial	Contribu-tion (%)
Thermal	Fig. 1 (a) with (a, b, c) = (1, 1, 1 mm)	1	Carbon	51.8 (γ)
		2	10-wt% ^{6}Li-P.E.	99.3 (th)
Mixed	Fig. 1 (b) with (a, b, c + d, e) = (1, 1, 5, 1 mm)	1	Carbon	54.9 (γ)
		2	10-wt% ^{6}Li-P.E.	93.2 (th)
		3	10-wt% ^{6}Li-P.E.	48.0 (epi)
Epi-thermal	Fig. 1 (b) with (a, b, c, d, e) = (1, 4, 1, 1, 1 mm)	1	Carbon	69.4 (γ)
		2	10-wt% ^{6}Li-P.E.	96.7 (epi)
		3	P.E. without LiF	30.9 (fast)

REFERENCE:

[1] K. Tanaka *et al.*, Appl. Rad. Isot. **115** (2016) 212-220.

PR6-8 Initial Test Operation of Patient-Position-Error Measuring System for BNCT Irradiation

T. Takata, Y. Sakurai, H. Tanaka and M. Suzuki

Research Reactor Institute, Kyoto University

INTRODUCTION: In boron neutron capture therapy (BNCT) irradiations carried out at Kyoto University Research Reactor, sitting position has been applied in many cases, considering a flexibility of patient positioning and structural restriction of an irradiation facility. In those cases, the patient position is sometimes unstable, resulting in a displacement from an initial set-up position determined by a treatment planning process. The displacement and motion during an irradiation period cause uncertainty in estimation of delivered dose.

Aiming to improve the dose estimation accuracy, we have been preparing a patient-position-error measuring system using a motion sensor [1]. The results of initial test operation of the position measurement are described.

MATERIALS AND METHODS: A MEMS motion sensor module (IMU-Z 2, ZMP Inc., Tokyo) consisting of tri-axial accelerometer, gyroscope and magnetometer was used to track a position and a rotation angle. The sensor module (36×52×11 mm) and a battery box (36×62×15 mm) were fixed to each other, and mounted on the top of the head of a subject as shown in Fig. 1. The data was acquired every 20 ms and registered in the PC by the wireless data transmission function built in the module. The data registered was analyzed to estimate the position and the rotation angle.

At first, the original measured data was smoothed by applying a low-pass filter to remove the high-frequency fluctuation component. Then, each vector data was transformed from the sensor coordinate system to the room coordinate system. After that, the phase of motion, that is, at rest or in motion was determined based on the change rate in magnitude of the acceleration vector. The position displacement was calculated by integrating the accelerometer data twice with respect to time. Also, the rotation angle was calculated by integrating gyroscope data with respect to time in motion phase and by comparing the direction of gravitational acceleration and geomagnetic field to the initial direction in resting phase.

RESULTS: Figure 2 shows an estimation result for the rotation angle around each axis in the case of the head shaking motion from side to side, followed by the nodding motion. The periods of these motions were around 5 seconds. The room coordinate system were defined as the initial sensor coordinate system as illustrated in Fig. 1. The shaking is corresponding to the rotation around Z axis and the nodding to the rotation around Y axis. It was found that the rotation angle could be tracked correctly by this system for the shaking motion during the elapsed time of 5 to 20 seconds and for the nodding motion during the time of 20 to 30 seconds.

Figure 3 shows an estimation result for the position displacement along each axis during the rotation motion described above. The result showed no displacement during the first 20 seconds and then showed large divergence after the beginning of nodding motion while the actual displacement was in a range of several centimeters. It was found that the system could not work correctly in the displacement estimation in this case.

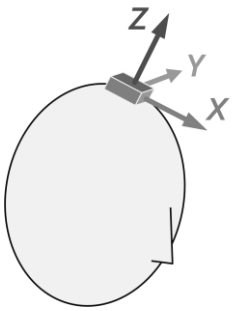

Fig. 1. Mounting of the sensor system and the coordinate system definition.

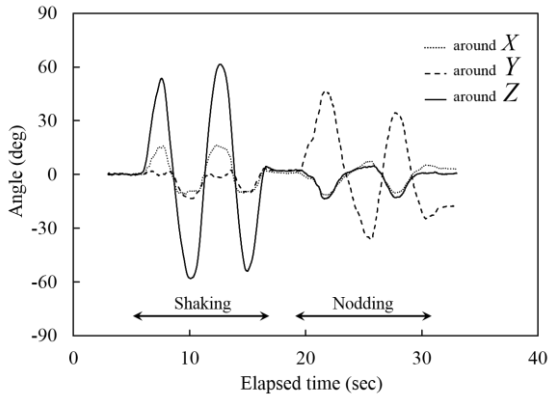

Fig. 2. Estimated rotation angle during head shaking and nodding motion.

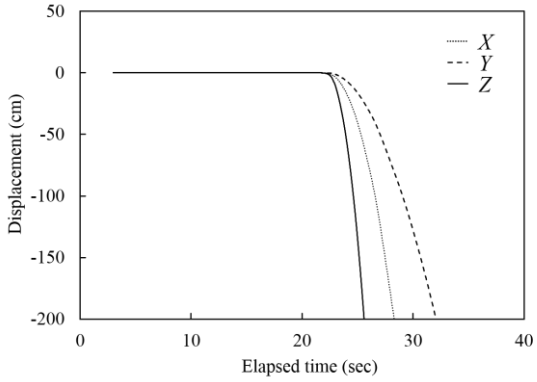

Fig. 3. Estimated position displacement during head shaking and nodding motion.

REFERENCE:

[1] T. Takata *et al.*, KURRI Progress Report 2015 (2016) 49.